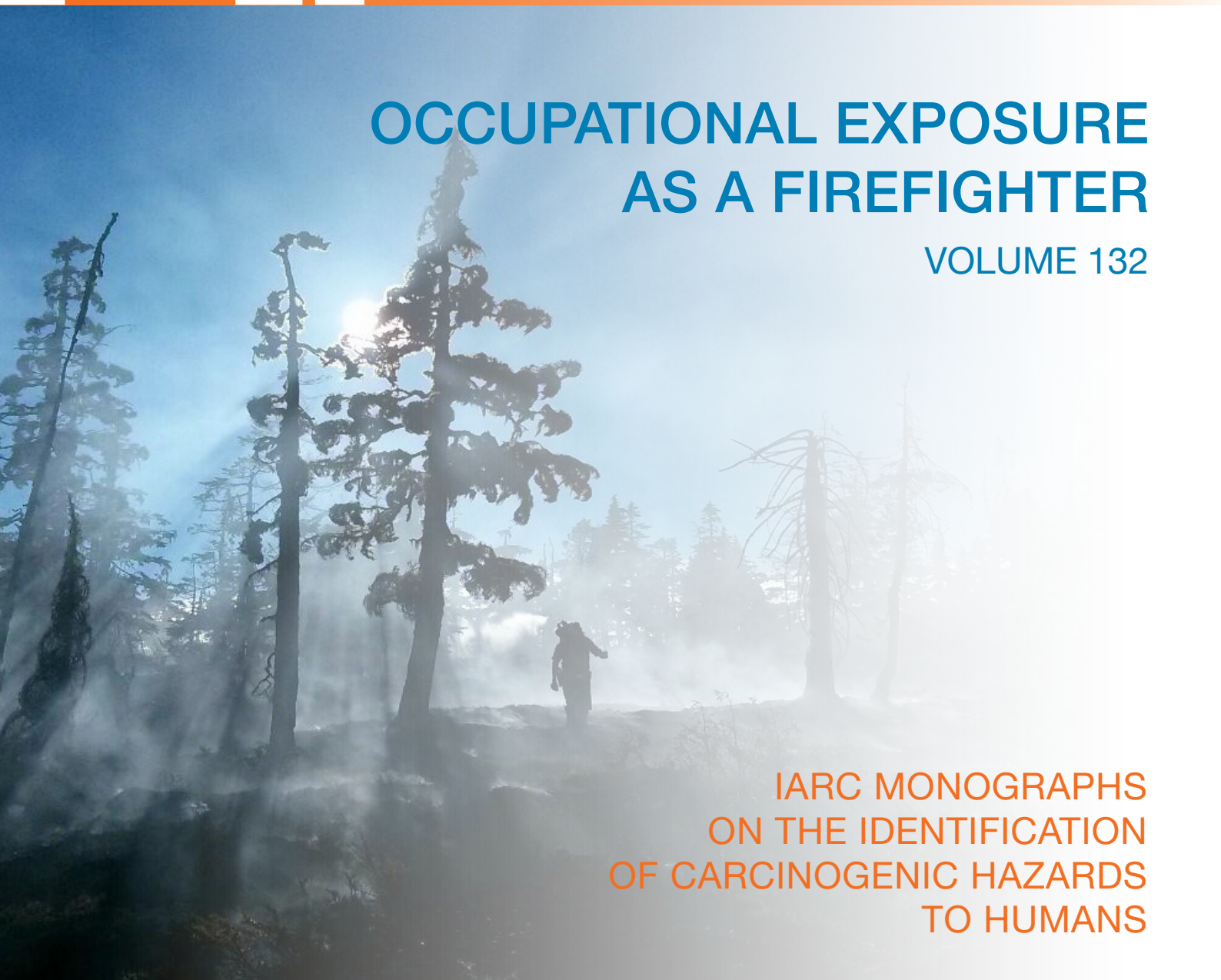
IARC MONOGRAPHS



OCCUPATIONAL EXPOSURE AS A FIREFIGHTER

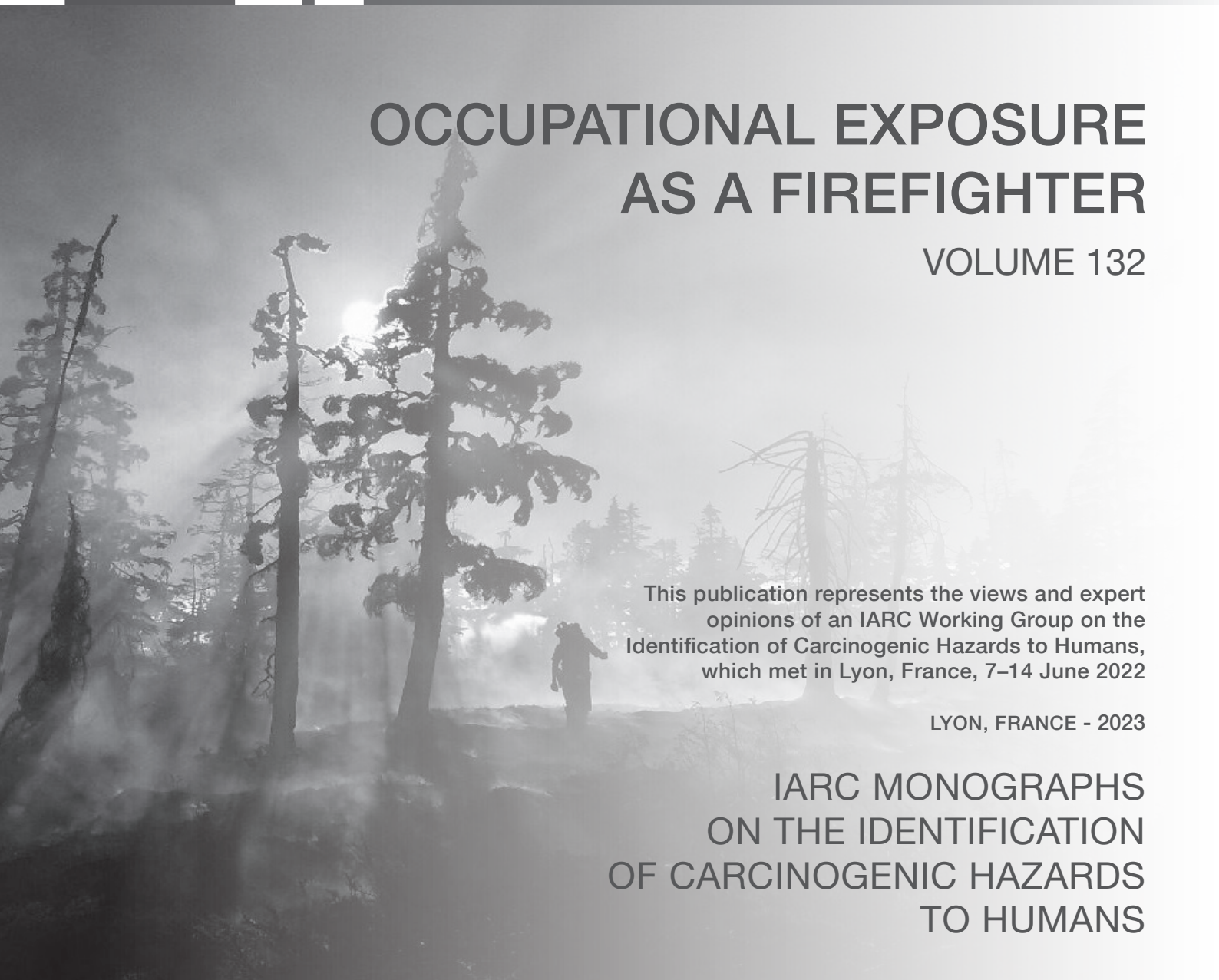
VOLUME 132

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS



OCCUPATIONAL EXPOSURE AS A FIREFIGHTER

VOLUME 132

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 7–14 June 2022

LYON, FRANCE - 2023

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic hazard of chemicals to humans, involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic hazards associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of cancer hazard to humans with the help of international working groups of experts in carcinogenesis and related fields; and to identify gaps in evidence. The lists of IARC evaluations are regularly updated and are available on the internet at https://monographs.iarc.who.int/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (for further information please consult: https://ec.europa.eu/social/easi). Support has also been provided since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

Co-funded by the European Union

Published by the International Agency for Research on Cancer,
25 avenue Tony Garnier, CS 90627, 69366 Lyon Cedex 07, France

Online publication, July 2023

IARC Monographs (and Corrigenda) are published online at https://publications.iarc.fr.
To report an error, please contact: imo@iarc.who.int.

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; website: https://apps.who.int/bookorders; email: bookorders@who.int).

About the cover: Firefighter at a wildland fire near Woss Lake, Vancouver Island, Canada. The photo illustrates the "mop-up" stage, when the active fire had been extinguished and firefighters from the British Columbia Wildfire Services had rappelled from a helicopter to the combat site.

Source: © Matthew Park

How to cite: IARC (2023). Occupational exposure as a firefighter. *IARC Monogr Identif Carcinog Hazards Hum*. 132:1–730.

IARC Library Cataloguing-in-Publication Data

Names: IARC Working Group on the Identification of Carcinogenic Hazards to Humans.

Title: Occupational exposure as a firefighter.

Description: Lyon: International Agency for Research on Cancer, 2023. | Series: IARC monographs on the identification of carcinogenic hazards to humans, ISSN 1017-1606; v. 132. | "This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 7–14 June 2022." | Includes bibliographical references.

Identifiers: ISBN 9789283201311 (pbk.) | ISBN 9789283201991 (ebook)

Subjects: MESH: Neoplasms--etiology. | Firefighters. | Air Pollutants, Occupational. | Occupational Exposure. | Occupational Diseases. | Smoke Inhalation Injury. | Risk Factors.

Classification: NLM W1

The *IARC Monographs* Working Group and Secretariat for Volume 132, Occupational Exposure as a Firefighter, which met in Lyon, France, on 7–14 June 2022.

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NOTE TO THE READER

The evaluations of carcinogenic hazard in the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* series are made by international working groups of independent scientists. The *IARC Monographs* classifications do not indicate the level of risk associated with a given level or circumstance of exposure. The *IARC Monographs* do not make recommendations for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic hazard of an agent to humans is encouraged to make this information available to the *IARC Monographs* programme, International Agency for Research on Cancer, 25 avenue Tony Garnier, CS 90627, 69366 Lyon Cedex 07, or via email at imo@iarc.who.int, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the *IARC Monographs* programme. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: https://publications.iarc.fr/).

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[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only. Invited Specialists do not serve as Meeting Chair or Subgroup Chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. Each participant was asked to declare potentially relevant research, employment, and financial interests that are current or that have occurred during the past 4 years. Minimal interests are not disclosed here, and include stock valued at no more than US$ 1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All other non-publicly funded grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are disclosed as potentially significant conflicts of interests.

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[2] Dr Graber reported having received personal consultancy fees from the Lung Ambition Alliance (LAA), which does not represent a potential conflict of interest for the present activity because the LAA and its founders do not have a competing interest in the topic of the meeting.

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[3] Dr Burgess reported receiving recent funding from the International Association of Fire Fighters.
[4] Dr Stec reported that her research unit received research funding from the Fire Brigades Union.
[5] Dr White reported receiving past funding from the International Association of Fire Fighters.

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[6] Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft any part of a monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

[7] Mr Forrest reported being an elected representative of, and receiving payments of less than US$ 5000 from, the International Association of Fire Fighters; providing expert opinion representing firefighters diagnosed with Occupational Cancer for Workers Compensation Purposes; and having received support for travel from United Fire Fighters of Winnipeg. He noted that the IARC classification may benefit his professional colleagues.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, general principles and procedures, and scientific review and evaluations. The *IARC Monographs* embody principles of scientific rigour, impartial evaluation, transparency, and consistency. The Preamble should be consulted when reading a *Monograph* or a summary of a *Monograph*'s evaluations. Separate Instructions for Authors describe the operational procedures for the preparation and publication of a volume of the *Monographs*.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after the International Agency for Research on Cancer (IARC) was established in 1965, it started to receive frequent requests for advice on the carcinogenicity of chemicals, including requests for lists of established and suspected human carcinogens. In 1970, an IARC Advisory Committee on Environmental Carcinogenesis recommended "that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented." The next year, the IARC Governing Council adopted a resolution that IARC should prepare "monographs on the evaluation of carcinogenic risk of chemicals to man", which became the initial title of the series.

In succeeding years, the scope of the programme broadened as *Monographs* were developed for complex mixtures, occupational exposures, physical agents, biological organisms, pharmaceuticals, and other exposures. In 1988, "of chemicals" was dropped from the title, and in 2019, "evaluation of carcinogenic risks" became "identification of carcinogenic hazards", in line with the objective of the programme.

Identifying the causes of human cancer is the first step in cancer prevention. The identification of a cancer hazard may have broad and profound implications. National and international authorities and organizations can and do use information on causes of cancer in support of actions to reduce exposure to carcinogens in the workplace, in the environment, and elsewhere. Cancer prevention is needed as much today as it was when IARC was established, because the global burden of cancer is high and continues to increase as a result of population growth and ageing and upward trends in some exposures, especially in low- and middle-income countries (https://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports).

IARC's process for developing *Monographs*, which has evolved over several decades, involves

the engagement of international, interdisciplinary Working Groups of expert scientists, the transparent synthesis of different streams of evidence (exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis), and the integration of these streams of evidence into an overall evaluation and classification according to criteria developed and refined by IARC. Since the *Monographs* programme was established, the understanding of carcinogenesis has greatly deepened. Scientific advances are incorporated into the evaluation methodology. In particular, strong mechanistic evidence has had an increasing role in the overall evaluations since 1991.

The Preamble is primarily a statement of the general principles and procedures used in developing a *Monograph*, to promote transparency and consistency across *Monographs* evaluations. In addition, IARC provides Instructions for Authors (https://monographs.iarc.who.int/preamble-instructions-for-authors/), which specify more detailed working procedures. IARC routinely updates these Instructions for Authors to reflect advances in methods for cancer hazard identification and accumulated experience, including input from experts.

2. Objective and scope

The objective of the programme is to prepare, with the engagement of international, interdisciplinary Working Groups of experts, scientific reviews and evaluations of evidence on the carcinogenicity of a wide range of agents.

The *Monographs* assess the strength of the available evidence that an agent can cause cancer in humans, based on three streams of evidence: on cancer in humans (see Part B, Section 2), on cancer in experimental animals (see Part B, Section 3), and on mechanistic evidence (see Part B, Section 4). In addition, the exposure to each agent is characterized (see Part B, Section 1). In this Preamble, the term "agent" refers to any chemical, physical, or biological entity or exposure circumstance (e.g. occupation as a painter) for which evidence on the carcinogenicity is evaluated.

A cancer *hazard* is an agent that is capable of causing cancer, whereas a cancer *risk* is an estimate of the probability that cancer will occur given some level of exposure to a cancer hazard. The *Monographs* assess the strength of evidence that an agent is a cancer hazard. The distinction between hazard and risk is fundamental. The *Monographs* identify cancer hazards even when risks appear to be low in some exposure scenarios. This is because the exposure may be widespread at low levels, and because exposure levels in many populations are not known or documented.

Although the *Monographs* programme has focused on hazard identification, some epidemiological studies used to identify a cancer hazard are also used to estimate an exposure–response relationship within the range of the available data. However, extrapolating exposure–response relationships beyond the available data (e.g. to lower exposures, or from experimental animals to humans) is outside the scope of *Monographs* Working Groups (IARC, 2014). In addition, the *Monographs* programme does not review quantitative risk characterizations developed by other health agencies.

The identification of a cancer hazard should trigger some action to protect public health, either directly as a result of the hazard identification or through the conduct of a risk assessment. Although such actions are outside the scope of the programme, the *Monographs* are used by national and international authorities and organizations to inform risk assessments, formulate decisions about preventive measures, motivate effective cancer control programmes, and choose among options for public health decisions. *Monographs* evaluations are only one part of the body of information on which decisions to control exposure to carcinogens may be based.

Options to prevent cancer vary from one situation to another and across geographical regions and take many factors into account, including different national priorities. Therefore, no recommendations are given in the *Monographs* with regard to regulation, legislation, or other policy approaches, which are the responsibility of individual governments or organizations. The *Monographs* programme also does not make research recommendations. However, it is important to note that *Monographs* contribute significantly to the science of carcinogenesis by synthesizing and integrating streams of evidence about carcinogenicity and pointing to critical gaps in knowledge.

3. Selection of agents for review

Since 1984, about every five years IARC convenes an international, interdisciplinary Advisory Group to recommend agents for review by the *Monographs* programme. IARC selects Advisory Group members who are knowledgeable about current research on carcinogens and public health priorities. Before an Advisory Group meets, IARC solicits nominations of agents from scientists and government agencies worldwide. Since 2003, IARC also invites nominations from the public. IARC charges each Advisory Group with reviewing nominations, evaluating exposure and hazard potential, and preparing a report that documents the Advisory Group's process for these activities and its rationale for the recommendations.

For each new volume of the *Monographs*, IARC selects the agents for review from those recommended by the most recent Advisory Group, considering the availability of pertinent research studies and current public health priorities. On occasion, IARC may select other agents if there is a need to rapidly evaluate an emerging carcinogenic hazard or an urgent need to re-evaluate a previous classification. All evaluations consider the full body of available evidence, not just information published after a previous review.

A *Monograph* may review:

(a) An agent not reviewed in a previous *Monograph*, if there is potential human exposure and there is evidence for assessing its carcinogenicity. A group of related agents (e.g. metal compounds) may be reviewed together if there is evidence for assessing carcinogenicity for one or more members of the group.

(b) An agent reviewed in a previous *Monograph*, if there is new evidence of cancer in humans or in experimental animals, or mechanistic evidence to warrant re-evaluation of the classification. In the interests of efficiency, the literature searches may build on previous comprehensive searches.

(c) An agent that has been established to be carcinogenic to humans and has been reviewed in a previous *Monograph*, if there is new evidence of cancer in humans that indicates new tumour sites where there might be a causal association. In the interests of efficiency, the review may focus on these new tumour sites.

4. The Working Group and other meeting participants

Five categories of participants can be present at *Monographs* meetings:

(i) *Working Group* members are responsible for all scientific reviews and evaluations developed in the volume of the *Monographs*. The Working Group is interdisciplinary and comprises subgroups of experts in the fields of (a) exposure characterization, (b) cancer in humans, (c) cancer in experimental animals, and (d) mechanistic evidence. IARC selects Working Group members on the basis of expertise related to the subject matter and relevant methodologies, and absence

of conflicts of interest. Consideration is also given to diversity in scientific approaches and views, as well as demographic composition. Working Group members generally have published research related to the exposure or carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Since 2006, IARC also has encouraged public nominations through its Call for Experts. IARC's reliance on experts with knowledge of the subject matter and/or expertise in methodological assessment is confirmed by decades of experience documenting that there is value in specialized expertise and that the overwhelming majority of Working Group members are committed to the objective evaluation of scientific evidence and not to the narrow advancement of their own research results or a pre-determined outcome (Wild & Cogliano, 2011). Working Group members are expected to serve the public health mission of IARC, and should refrain from consulting and other activities for financial gain that are related to the agents under review, or the use of inside information from the meeting, until the full volume of the *Monographs* is published.

IARC identifies, from among Working Group members, individuals to serve as Meeting Chair and Subgroup Chairs. At the opening of the meeting, the Working Group is asked to endorse the selection of the Meeting Chair, with the opportunity to propose alternatives. The Meeting Chair and Subgroup Chairs take a leading role at all stages of the review process (see Part A, Section 7), promote open scientific discussions that involve all Working Group members in accordance with normal committee procedures, and ensure adherence to the Preamble.

(ii) *Invited Specialists* are experts who have critical knowledge and experience but who also have a conflict of interest that warrants exclusion from developing or influencing the evaluations of carcinogenicity. Invited Specialists do not draft any section of the *Monograph* that pertains to the description or interpretation of cancer data, and they do not participate in the evaluations. These experts are invited in limited numbers when necessary to assist the Working Group by contributing their unique knowledge and experience to the discussions.

(iii) *Representatives of national and international health agencies* may attend because their agencies are interested in the subject of the meeting. They do not draft any section of the *Monograph* or participate in the evaluations.

(iv) *Observers* with relevant scientific credentials may be admitted in limited numbers. Attention is given to the balance of Observers from constituencies with differing perspectives. Observers are invited to observe the meeting and should not attempt to influence it, and they agree to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers do not draft any section of the *Monograph* or participate in the evaluations.

(v) The *IARC Secretariat* consists of scientists who are designated by IARC and who have relevant expertise. The IARC Secretariat coordinates and facilitates all aspects of the evaluation and ensures adherence to the Preamble throughout development of the scientific reviews and classifications (see Part A, Sections 5 and 6). The IARC Secretariat organizes and announces the meeting, identifies and recruits the Working Group members, and assesses the declared interests of all meeting participants. The IARC Secretariat supports the activities of the Working Group (see Part A, Section 7) by searching the literature and performing title and abstract screening, organizing conference calls to coordinate the development of pre-meeting

Table 1 Roles of participants at *IARC Monographs* meetings

Category of participant	Role			
	Prepare text, tables, and analyses	Participate in discussions	Participate in evaluations	Eligible to serve as Chair
Working Group members	✓	✓	✓	✓
Invited Specialists	✓[a]	✓		
Representatives of health agencies		✓[b]		
Observers		✓[b]		
IARC Secretariat	✓[c]	✓	✓[d]	

[a] Only for the section on exposure characterization.
[b] Only at times designated by the Meeting Chair and Subgroup Chairs.
[c] When needed or requested by the Meeting Chair and Subgroup Chairs.
[d] Only for clarifying or interpreting the Preamble.

drafts and discuss cross-cutting issues, and reviewing drafts before and during the meeting. Members of the IARC Secretariat serve as meeting rapporteurs, assist the Meeting Chair and Subgroup Chairs in facilitating all discussions, and may draft text or tables when designated by the Meeting Chair and Subgroup Chairs. Their participation in the evaluations is restricted to the role of clarifying or interpreting the Preamble.

All participants are listed, with their principal affiliations, in the front matter of the published volume of the *Monographs*. Working Group members and Invited Specialists serve as individual scientists and not as representatives of any organization, government, or industry (Cogliano et al., 2004).

The roles of the meeting participants are summarized in Table 1.

5. Working procedures

A separate Working Group is responsible for developing each volume of the *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year before the meeting of a Working Group, a preliminary list of agents to be reviewed, together with a Call for Data and a Call for Experts, is announced on the *Monographs* programme website (https://monographs.iarc.who.int/).

Before a meeting invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests form to report financial interests, employment and consulting (including remuneration for serving as an expert witness), individual and institutional research support, and non-financial interests such as public statements and positions related to the subject of the meeting. IARC assesses the declared interests to determine whether there is a conflict that warrants any limitation on participation (see Table 2).

Approximately two months before a *Monographs* meeting, IARC publishes the names and affiliations of all meeting participants together with a summary of declared interests, in the interests of transparency and to provide an opportunity for undeclared conflicts of interest to be brought to IARC's attention. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

The Working Group meets at IARC for approximately eight days to discuss and finalize the scientific review and to develop summaries

Table 2 Public engagement during *Monographs* development

Approximate timeframe	Engagement
Every 5 years	IARC convenes an Advisory Group to recommend high-priority agents for future review
~1 year before a *Monographs* meeting	IARC selects agents for review in a new volume of the *Monographs* IARC posts on its website: Preliminary List of Agents to be reviewed Call for Data and Call for Experts Request for Observer Status WHO Declaration of Interests form
~8 months before a *Monographs* meeting	Call for Experts closes
~4 months before a *Monographs* meeting	Request for Observer Status closes
~2 months before a *Monographs* meeting	IARC posts the names of all meeting participants together with a summary of declared interests, and a statement discouraging contact of the Working Group by interested parties
~1 month before a *Monographs* meeting	Call for Data closes
~2–4 weeks after a *Monographs* meeting	IARC publishes a summary of evaluations and key supporting evidence
~9 months after a *Monographs* meeting	IARC Secretariat publishes the verified and edited master copy of plenary drafts as a *Monographs* volume

and evaluations. At the opening of the meeting, all participants update their Declaration of Interests forms, which are then reviewed by IARC. Declared interests related to the subject of the meeting are disclosed to the meeting participants during the meeting and in the published volume (Cogliano et al., 2004). The objectives of the meeting are peer review and consensus. During the first part of the meeting, subgroup sessions (covering exposure characterization, cancer in humans, cancer in experimental animals, and mechanistic evidence) review the pre-meeting drafts, develop a joint subgroup draft, and draft subgroup summaries. During the last part of the meeting, the Working Group meets in plenary session to review the subgroup drafts and summaries and to develop the consensus evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections. After the meeting, the master copy is verified by the IARC Secretariat and is then edited and prepared for publication. The aim is to publish the volume within approximately nine months of the Working Group meeting. A summary of the evaluations and key supporting evidence is prepared for publication in a scientific journal or is made available on the *Monographs* programme website soon after the meeting.

In the interests of transparency, IARC engages with the public throughout the process, as summarized in Table 2.

6. Overview of the scientific review and evaluation process

The Working Group considers all pertinent epidemiological studies, cancer bioassays in experimental animals, and mechanistic evidence, as well as pertinent information on exposure in humans. In general, for cancer in humans, cancer in experimental animals, and mechanistic evidence, only studies that have been published or accepted for publication in the openly available scientific literature are reviewed. Under some circumstances, materials that are publicly available and whose content is final may be reviewed if there is sufficient information to permit an evaluation of the quality of the methods and results of the studies (see Step 1,

below). Such materials may include reports and databases publicly available from government agencies, as well as doctoral theses. The reliance on published and publicly available studies promotes transparency and protects against citation of premature information.

The principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence related to cancer in humans, cancer in experimental animals, and mechanistic evidence (as described in Part B, Sections 2–4 and as detailed in the Instructions for Authors). Each *Monograph* specifies or references information on the conduct of the literature searches, including search terms and inclusion/exclusion criteria that were used for each stream of evidence.

In brief, the steps of the review process are as follows:

Step 1. Comprehensive and transparent identification of the relevant information: The IARC Secretariat identifies relevant studies through initial comprehensive searches of literature contained in authoritative biomedical databases (e.g. PubMed, PubChem) and through a Call for Data. These literature searches, designed in consultation with a librarian and other technical experts, address whether the agent causes cancer in humans, causes cancer in experimental systems, and/or exhibits key characteristics of established human carcinogens (in humans or in experimental systems). The Working Group provides input and advice to IARC to refine the search strategies, and identifies literature through other searches (e.g. from reference lists of past *Monographs*, retrieved articles, and other authoritative reviews).

For certain types of agents (e.g. regulated pesticides and pharmaceuticals), IARC also provides an opportunity to relevant regulatory authorities, and regulated parties through such authorities, to make pertinent unpublished studies publicly available by the date specified in the Call for Data. Consideration of such studies by the Working Group is dependent on the public availability of sufficient information to permit an independent evaluation of (a) whether there has been selective reporting (e.g. on outcomes, or from a larger set of conducted studies); (b) study quality (e.g. design, methodology, and reporting of results), and (c) study results.

Step 2. Screening, selection, and organization of the studies: The IARC Secretariat screens the retrieved literature for inclusion based on title and abstract review, according to pre-defined exclusion criteria. For instance, studies may be excluded if they were not about the agent (or a metabolite of the agent), or if they reported no original data on epidemiological or toxicological end-points (e.g. review articles). The Working Group reviews the title and abstract screening done by IARC, and performs full-text review. Any reasons for exclusion are recorded, and included studies are organized according to factors pertinent to the considerations described in Part B, Sections 2–4 (e.g. design, species, and endpoint). Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results.

Step 3. Evaluation of study quality: The Working Group evaluates the quality of the included studies based on the considerations (e.g. design, methodology, and reporting of results) described in Part B, Sections 2–4. Based on these considerations, the Working Group may accord greater weight to some of the included studies. Interpretation of the results and the strengths and limitations of a study are clearly outlined in square brackets at the end of study descriptions (see Part B).

Step 4: *Report characteristics of included studies, including assessment of study*

quality: Pertinent characteristics and results of included studies are reviewed and succinctly described, as detailed in Part B, Sections 1–4. Tabulation of data may facilitate this reporting. This step may be iterative with Step 3.

Step 5: *Synthesis and evaluation of strength of evidence*: The Working Group summarizes the overall strengths and limitations of the evidence from the individual streams of evidence (cancer in humans, cancer in experimental animals, and mechanistic evidence; see Part B, Section 5). The Working Group then evaluates the strength of evidence from each stream of evidence by using the transparent methods and defined descriptive terms given in Part B, Sections 6a–c. The Working Group then develops, and describes the rationale for, the consensus classification of carcinogenicity that integrates the conclusions about the strength of evidence from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic evidence (see Part B, Section 6d).

7. Responsibilities of the Working Group

The Working Group is responsible for identifying and evaluating the relevant studies and developing the scientific reviews and evaluations for a volume of the *Monographs*. The IARC Secretariat supports these activities of the Working Group (see Part A, Section 4). Briefly, the Working Group's tasks in developing the evaluation are, in sequence:

(i) Before the meeting, the Working Group ascertains that all appropriate studies have been identified and selected, and assesses the methods and quality of each individual study, as outlined above (see Part A, Section 6). The Working Group members prepare pre-meeting working drafts that present accurate tabular or textual summaries of informative studies by extracting key elements of the study design and results, and highlighting notable strengths and limitations. They participate in conference calls organized by IARC to coordinate the development of working drafts and to discuss cross-cutting issues. Pre-meeting reviews of all working drafts are generally performed by two or more subgroup members who did not participate in study identification, data extraction, or study review for the draft. Each study summary is written or reviewed by someone who is not associated with the study.

(ii) At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. Subgroup Chairs ensure that someone who is not associated with the study leads the discussion of each study summary. A proposed classification of the strength of the evidence reviewed in the subgroup using the *IARC Monographs* criteria (see Part B, Sections 6a–c) is then developed from the consensus subgroup drafts of the evidence summaries (see Part B, Section 5).

(iii) During the plenary session, each subgroup presents its drafts for scientific review and discussion to the other Working Group members, who did not participate in study identification, data extraction, or study review for the drafts. Subgroup Chairs ensure that someone who is not associated with the study leads the discussion of each study summary. After review, discussion, and revisions as needed, the subgroup drafts are adopted as a consensus Working Group product. The summaries and classifications of the strength of the evidence, developed in the subgroup in line with the *IARC Monographs* criteria

(see Part B, Sections 6a–c), are considered, revised as needed, and adopted by the full Working Group. The Meeting Chair proposes an overall evaluation using the guidance provided in Part B, Section 6d.

The Working Group strives to achieve consensus evaluations. Consensus reflects broad agreement among the Working Group, but not necessarily unanimity. The Meeting Chair may poll the Working Group to determine the diversity of scientific opinion on issues where consensus is not apparent.

Only the final product of the plenary session represents the views and expert opinions of the Working Group. The entire *Monographs* volume is the joint product of the Working Group and represents an extensive and thorough peer review of the body of evidence (individual studies, synthesis, and evaluation) by an interdisciplinary expert group. Initial working papers and subsequent revisions are not released, because they would give an incomplete and possibly misleading impression of the consensus developed by the Working Group over a full week of deliberation.

B. SCIENTIFIC REVIEW AND EVALUATION

This part of the Preamble discusses the types of evidence that are considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations. In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and any key issues encountered during the meeting.

1. Exposure characterization

This section identifies the agent and describes its occurrence, main uses, and production locations and volumes, where relevant. It also summarizes the prevalence, concentrations in relevant studies, and relevant routes of exposure in humans worldwide. Methods of exposure measurement and analysis are described, and methods of exposure assessment used in key epidemiological studies reviewed by the Working Group are described and evaluated.

Over the course of the *Monographs* programme, concepts of exposure and dose have evolved substantially with deepening understanding of the interactions of agents and biological systems. The concept of exposure has broadened and become more holistic, extending beyond chemical, physical, and biological agents to stressors as construed generally, including psychosocial stressors (National Research Council, 2012; National Academies of Sciences, Engineering, and Medicine, 2017). Overall, this broader conceptualization supports greater integration between exposure characterization and other sections of the *Monographs*. Concepts of absorption, distribution, metabolism, and excretion are considered in the first subsection of mechanistic evidence (see Part B, Section 4a), whereas validated biomarkers of internal exposure or metabolites that are routinely used for exposure assessment are reported on in this section (see Part B, Section 1b).

(a) Identification of the agent

The agent being evaluated is unambiguously identified. Details will vary depending on the type of agent but will generally include physical and chemical properties relevant to the agent's identification, occurrence, and biological activity. If the material that has been tested in experimental animals or in vitro systems is different from that to which humans are exposed, these differences are noted.

For chemical agents, the Chemical Abstracts Service Registry Number is provided, as well as the latest primary name and other names in common use, including important trade names,

along with available information on the composition of common mixtures or products containing the agent, and potentially toxic and/or carcinogenic impurities. Physical properties relevant to understanding the potential for human exposure and measures of exposure used in studies in humans are summarized. These might include physical state, volatility, aqueous and fat solubility, and half-life in the environment and/or in human tissues.

For biological agents, taxonomy and structure are described. Mode of replication, life-cycle, target cells, persistence, latency, and host responses, including morbidity and mortality through pathologies other than cancer, are also presented.

For foreign bodies, fibres and particles, composition, size range, relative dimensions, and accumulation, persistence, and clearance in target organs are summarized. Physical agents that are forms of radiation are described in terms of frequency spectrum and energy transmission.

Exposures may result from, or be influenced by, a diverse range of social and environmental factors, including components of diet, sleep, and physical activity patterns. In these instances, this section will include a description of the agent, its variability across human populations, and its composition or characteristics relevant to understanding its potential carcinogenic hazard to humans and to evaluating exposure assessments in epidemiological studies.

(b) Detection and analysis

Key methods of detection and quantification of the agent are presented, with an emphasis on those used most widely in surveillance, regulation, and epidemiological studies. Measurement methods for sample matrices that are deemed important sources of human exposure (e.g. air, drinking-water, food, residential dust) and for validated exposure biomarkers (e.g. the agent or its metabolites in human blood, urine, or saliva) are described. Information on detection and quantification limits is provided when it is available and is useful for interpreting studies in humans and in experimental animals. This is not an exhaustive treatise but is meant to help readers understand the strengths and limitations of the available exposure data and of the epidemiological studies that rely on these measurements.

(c) Production and use

Historical and geographical patterns and trends in production and use are included when they are available, to help readers understand the contexts in which exposures may occur, both within key epidemiological studies reviewed by the Working Group and in human populations generally. Industries that produce, use, or dispose of the agent are described, including their global distribution, when available. National or international listing as a high-production-volume chemical or similar classification may be included. Production processes with significant potential for occupational exposure or environmental pollution are indicated. Trends in global production volumes, technologies, and other data relevant to understanding exposure potential are summarized. Minor or historical uses with significant exposure potential or with particular relevance to key epidemiological studies are included. Particular effort may be directed towards finding data on production in low- and middle-income countries, where rapid economic development may lead to higher exposures than those in high-income countries.

(d) Exposure

A concise overview of quantitative information on sources, prevalence, and levels of exposure in humans is provided. Representative data from research studies, government reports and websites, online databases, and other citable, publicly available sources are tabulated. Data

from low- and middle-income countries are sought and included to the extent feasible; information gaps for key regions are noted. Naturally occurring sources of exposure, if any, are noted. Primary exposure routes (e.g. inhalation, ingestion, skin uptake) and other considerations relevant to understanding the potential for cancer hazard from exposure to the agent are reported.

For occupational settings, information on exposure prevalence and levels (e.g. in air or human tissues) is reported by industry, occupation, region, and other characteristics (e.g. process, task) where feasible. Information on historical exposure trends, protection measures to limit exposure, and potential co-exposures to other carcinogenic agents in workplaces is provided when available.

For non-occupational settings, the occurrence of the agent is described with environmental monitoring or surveillance data. Information on exposure prevalence and levels (e.g. concentrations in human tissues) as well as exposure from and/or concentrations in food and beverages, consumer products, consumption practices, and personal microenvironments is reported by region and other relevant characteristics. Particular importance is placed on describing exposures in life stages or in states of disease or nutrition that may involve greater exposure or susceptibility.

Current exposures are of primary interest; however, information on historical exposure trends is provided when available. Historical exposures may be relevant for interpreting epidemiological studies, and when agents are persistent or have long-term effects. Information gaps for important time periods are noted. Exposure data that are not deemed to have high relevance to human exposure are generally not considered.

(e) Regulations and guidelines

Regulations or guidelines that have been established for the agent (e.g. occupational exposure limits, maximum permitted levels in foods and water, pesticide registrations) are described in brief to provide context about government efforts to limit exposure; these may be tabulated if they are informative for the interpretation of existing or historical exposure levels. Information on applicable populations, specific agents concerned, basis for regulation (e.g. human health risk, environmental considerations), and timing of implementation may be noted. National and international bans on production, use, and trade are also indicated.

This section aims to include major or illustrative regulations and may not be comprehensive, because of the complexity and range of regulatory processes worldwide. An absence of information on regulatory status should not be taken to imply that a given country or region lacks exposure to, or regulations on exposure to, the agent.

(f) Critical review of exposure assessment in key epidemiological studies

Epidemiological studies evaluate cancer hazard by comparing outcomes across differently exposed groups. Therefore, the type and quality of the exposure assessment methods used are key considerations when interpreting study findings for hazard identification. This section summarizes and critically reviews the exposure assessment methods used in the individual epidemiological studies that contribute data relevant to the *Monographs* evaluation.

Although there is no standard set of criteria for evaluating the quality of exposure assessment methods across all possible agents, some concepts are universally relevant. Regardless of the agent, all exposures have two principal dimensions: intensity (sometimes defined as concentration or dose) and time. Time considerations include

duration (time from first to last exposure), pattern or frequency (whether continuous or intermittent), and windows of susceptibility. This section considers how each of the key epidemiological studies characterizes these dimensions. Interpretation of exposure information may also be informed by consideration of mechanistic evidence (e.g. as described in Part B, Section 4a), including the processes of absorption, distribution, metabolism, and excretion.

Exposure intensity and time in epidemiological studies can be characterized by using environmental or biological monitoring data, records from workplaces or other sources, expert assessments, modelled exposures, job-exposure matrices, and subject or proxy reports via questionnaires or interviews. Investigators use these data sources and methods individually or in combination to assign levels or values of an exposure metric (which may be quantitative, semi-quantitative, or qualitative) to members of the population under study.

In collaboration with the Working Group members reviewing human studies (of cancer and of mechanisms), key epidemiological studies are identified. For each selected study, the exposure assessment approach, along with its strengths and limitations, is summarized using text and tables. Working Group members identify concerns about exposure assessment methods and their impacts on overall quality for each study reviewed (see Part B, Sections 2d and 4d). In situations where the information provided in the study is inadequate to properly consider the exposure assessment, this is indicated. When adequate information is available, the likely direction of bias due to error in exposure measurement, including misclassification (overestimated effects, underestimated effects, or unknown) is discussed.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part B, Section 2b) that include cancer as an outcome. These studies encompass certain types of biomarker studies, for example, studies with biomarkers as exposure metrics (see Part B, Section 2) or those evaluating histological or tumour subtypes and molecular signatures in tumours consistent with a given exposure (Alexandrov et al., 2016). Studies that evaluate early biological effect biomarkers are reviewed in Part B, Section 4.

(a) Types of study considered

Several types of epidemiological studies contribute to the assessment of carcinogenicity in humans; they typically include cohort studies (including variants such as case–cohort and nested case–control studies), case–control studies, ecological studies, and intervention studies. Rarely, results from randomized trials may be available. Exceptionally, case reports and case series of cancer in humans may also be reviewed. In addition to these designs, innovations in epidemiology allow for many other variants that may be considered in any given *Monographs* evaluation.

Cohort and case–control studies typically have the capacity to relate individual exposures under study to the occurrence of cancer in individuals, and provide an estimate of effect (such as relative risk) as the main measure of association. Well-conducted cohort and case–control studies provide most of the evidence of cancer in humans evaluated by Working Groups. Intervention studies are much less common, but when available can provide strong evidence for making causal inferences.

In ecological studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary

measure of the exposure in the population under study. In ecological studies, data on individual exposure and outcome are not available, which renders this type of study more prone to confounding and exposure misclassification. In some circumstances, however, ecological studies may be informative, especially when the unit of exposure is most accurately measured at the population level (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

Exceptionally, case reports and case series may provide compelling evidence about the carcinogenicity of an agent. In fact, many of the early discoveries of occupational cancer hazards came about because of observations by workers and their clinicians, who noted a high frequency of cancer in workers who share a common occupation or exposure. Such observations may be the starting point for more structured investigations, but in exceptional circumstances, when the risk is high enough, the case series may in itself provide compelling evidence. This would be especially warranted in situations where the exposure circumstance is fairly unusual, as it was in the example of plants containing aristolochic acid (IARC, 2012a).

The uncertainties that surround the interpretation of case reports, case series, and ecological studies typically make them inadequate, except in rare instances as described above, to form the sole basis for inferring a causal relationship. However, when considered together with cohort and case–control studies, these types of study may support the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, pre-neoplastic lesions, malignant precursors, and other end-points are also reviewed when they relate to the agents reviewed. On occasion they can strengthen inferences drawn from studies of cancer itself. For example, benign brain tumours may share common risk factors with those that are malignant, and benign neoplasms (or those of uncertain behaviour) may be part of the causal path to malignancies (e.g. myelodysplastic syndromes, which may progress to acute myeloid leukaemia).

(b) Identification of eligible studies of cancer in humans

Relevant studies of cancer in humans are identified by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below. Eligible studies include all studies in humans of exposure to the agent of interest with cancer as an outcome. Multiple publications on the same study population are identified so that the number of independent studies is accurately represented. Multiple publications may result, for example, from successive follow-ups of a single cohort, from analyses focused on different aspects of an exposure–disease association, or from inclusion of overlapping populations. Usually in such situations, only the most recent, most comprehensive, or most informative report is reviewed in detail.

(c) Assessment of study quality and informativeness

Epidemiological studies are potentially susceptible to several different sources of error, summarized briefly below. Qualities of individual studies that address these issues are also described below.

Study quality is assessed as part of the structured expert review process undertaken by the Working Group. A key aspect of quality assessment is consideration of the possible roles of chance and bias in the interpretation of epidemiological studies. Chance, which is also called random variation, can produce misleading study results. This variability in study results is strongly influenced by the sample size: smaller studies are more likely than larger studies to have effect estimates that are imprecise. Confidence intervals

around a study's point estimate of effect are used routinely to indicate the range of values of the estimate that could easily be produced by chance alone.

Bias is the effect of factors in study design or conduct that lead an association to erroneously appear stronger or weaker than the association that really exists between the agent and the disease. Biases that require consideration are varied but are usually categorized as selection bias, information bias (e.g. error in measurement of exposure and diseases), and confounding (or confounding bias) (Rothman et al., 2008). Selection bias in an epidemiological study occurs when inclusion of participants from the eligible population or their follow-up in the study is influenced by their exposure or their outcome (usually disease occurrence). Under these conditions, the measure of association found in the study will not accurately reflect the association that would otherwise have been found in the eligible population (Hernán et al., 2004). Information bias results from inaccuracy in exposure or outcome measurement. Both can cause an association between hypothesized cause and effect to appear stronger or weaker than it really is. Confounding is a mixing of extraneous effects with the effects of interest (Rothman et al., 2008). An association between the purported causal factor and another factor that is associated with an increase or decrease in incidence of disease can lead to a spurious association or absence of a real association of the presumed causal factor with the disease. When either of these occurs, confounding is present.

In assessing study quality, the Working Group consistently considers the following aspects:

- **Study description:** Clarity in describing the study design and its implementation, and the completeness of reporting of all other key information about the study and its results.
- **Study population:** Whether the study population was appropriate for evaluating the association between the agent and cancer. Whether the study was designed and carried out to minimize selection bias. Cancer cases in the study population must have been identified in a way that was independent of the exposure of interest, and exposure assessed in a way that was not related to disease (outcome) status. In these respects, completeness of recruitment into the study from the population of interest and completeness of follow-up for the outcome are essential measures.
- **Outcome measurement:** The appropriateness of the cancer outcome measure (e.g. mortality vs incidence) for the agent and cancer type under consideration, outcome ascertainment methodology, and the extent to which outcome misclassification may have led to bias in the measure(s) of association.
- **Exposure measurement:** The adequacy of the methods used to assess exposure to the agent, and the likelihood (and direction) of bias in the measure(s) of association due to error in exposure measurement, including misclassification (as described in Part B, Section 1f).
- **Assessment of potential confounding:** To what extent the authors took into account in the study design and analysis other variables (including co-exposures, as described in Part B, Section 1d) that can influence the risk of disease and may have been related to the exposure of interest. Important sources of potential confounding by such variables should have been addressed either in the design of the study, such as by matching or restriction, or in the analysis, by statistical adjustment. In some instances, where direct information on confounders is unavailable, use of indirect methods to evaluate the potential impact of confounding on exposure–disease associations is appropriate (e.g. Axelson & Steenland, 1988; Richardson et al., 2014).

- **Other potential sources of bias:** Each epidemiological study is unique in its study population, its design, its data collection, and, consequently, its potential biases. All possible sources of bias are considered for their possible impact on the results. The possibility of reporting bias (i.e. selective reporting of some results and the suppression of others) should be explored.
- **Statistical methodology:** Adequacy of the statistical methods used and their ability to obtain unbiased estimates of exposure–outcome associations, confidence intervals, and test statistics for the significance of measures of association. Appropriateness of methods used to investigate confounding, including adjusting for matching when necessary and avoiding treatment of probable mediating variables as confounders. Detailed analyses of cancer risks in relation to summary measures of exposure such as cumulative exposure, or temporal variables such as age at first exposure or time since first exposure, are reviewed and summarized when available.

For the sake of economy and simplicity, in this Preamble the list of possible sources of error is referred to with the phrase "chance, bias, and confounding", but it should be recognized that this phrase encompasses a comprehensive set of concerns pertaining to study quality.

These sources of error do not constitute and should not be used as a formal checklist of indicators of study quality. The judgement of experienced experts is critical in determining how much weight to assign to different issues in considering how all of these potential sources of error should be integrated and how to rate the potential for error related to each of these considerations.

The informativeness of a study is its ability to show a true association, if there is one, between the agent and cancer, and the lack of an association, if no association exists. Key determinants of informativeness include: having a study population of sufficient size to obtain precise estimates of effect; sufficient elapsed time from exposure to measurement of outcome for an effect, if present, to be observable; presence of an adequate exposure contrast (intensity, frequency, and/or duration); biologically relevant definitions of exposure; and relevant and well-defined time windows for exposure and outcome.

(d) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to inconsistent results that are difficult to interpret or reconcile. Combined analyses of data from multiple studies may be conducted as a means to address this ambiguity. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis), and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland & O'Rourke, 2008).

The strengths of combined analyses are increased precision because of increased sample size and, in the case of pooled analyses, the opportunity to better control for potential confounders and to explore in more detail interactions and modifying effects that may explain heterogeneity among studies. A disadvantage of combined analyses is the possible lack of comparability of data from various studies, because of differences in population characteristics, subject recruitment, procedures of data collection, methods of measurement, and effects of unmeasured covariates that may differ among studies. These differences in study methods and quality can influence results of either meta-analyses or pooled analyses. If published meta-analyses are to be considered by the Working Group, their adequacy needs to be carefully evaluated, including the methods used to identify eligible studies

and the accuracy of data extracted from the individual studies.

The Working Group may conduct ad hoc meta-analyses during the course of a *Monographs* meeting, when there are sufficient studies of an exposure–outcome association to contribute to the Working Group's assessment of the association. The results of such unpublished original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies, or de novo analyses.

Irrespective of the source of data for the meta-analyses and pooled analyses, the following key considerations apply: the same criteria for data quality must be applied as for individual studies; sources of heterogeneity among studies must be carefully considered; and the possibility of publication bias should be explored.

(e) Considerations in assessing the body of epidemiological evidence

The ability of the body of epidemiological evidence to inform the Working Group about the carcinogenicity of the agent is related to both the quantity and the quality of the evidence. There is no formulaic answer to the question of how many studies of cancer in humans are needed from which to draw inferences about causality, although more than a single study in a single population will almost always be needed. The number will depend on the considerations relating to evidence described below.

After the quality of individual epidemiological studies of cancer has been assessed and the informativeness of the various studies on the association between the agent and cancer has been evaluated, a judgement is made about the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several aspects of the body of evidence (e.g. Hill, 1965; Rothman et al., 2008; Vandenbroucke et al., 2016).

A strong association (e.g. a large relative risk) is more likely to indicate causality than is a weak association, because it is more difficult for confounding to falsely create a strong association. However, it is recognized that estimates of effect of small magnitude do not imply lack of causality and may have impact on public health if the disease or exposure is common. Estimates of effect of small magnitude could also contribute useful information to the assessment of causality if level of risk is commensurate with level of exposure when compared with risk estimates from populations with higher exposure (e.g. as seen in residential radon studies compared with studies of radon from uranium mining).

Associations that are consistently observed in several studies of the same design, or in studies that use different epidemiological approaches, or under different circumstances of exposure are more likely to indicate a causal relationship than are isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (e.g. differences in study informativeness because of latency, exposure levels, or assessment methods). Results of studies that are judged to be of high quality and informativeness are given more weight than those of studies judged to be methodologically less sound or less informative.

Temporality of the association is an essential consideration: that is, the exposure must precede the outcome.

An observation that cancer risk increases with increasing exposure is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship, and there are several reasons why the shape of the exposure–response association may be non-monotonic (e.g. Stayner et al., 2003). The demonstration of a decline in risk after cessation of or reduction in exposure

in individuals or in whole populations also supports a causal interpretation of the findings.

Confidence in a causal interpretation of the evidence from studies of cancer in humans is enhanced if it is coherent with physiological and biological knowledge, including information about exposure to the target organ, latency and timing of the exposure, and characteristics of tumour subtypes.

The Working Group considers whether there are subpopulations with increased susceptibility to cancer from the agent. For example, molecular epidemiology studies that identify associations between genetic polymorphisms and inter-individual differences in cancer susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. Such studies may be particularly informative if polymorphisms are found to be modifiers of the exposure–response association, because evaluation of polymorphisms may increase the ability to detect an effect in susceptible subpopulations.

When, in the process of evaluating the studies of cancer in humans, the Working Group identifies several high-quality, informative epidemiological studies that clearly show either no positive association or an inverse association between an exposure and a specific type of cancer, a judgement may be made that, in the aggregate, they suggest evidence of lack of carcinogenicity for that cancer type. Such a judgement requires, first, that the studies strictly meet the standards of design and analysis described above. Specifically, the possibility that bias, confounding, or misclassification of exposure or outcome could explain the observed results should be considered and ruled out with reasonable confidence. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of relative effect of unity (or below unity) for any observed level of exposure, (b) when considered together, provide a combined estimate of relative risk that is at or below unity, and (c) have a narrow confidence interval. Moreover, neither any individual well-designed and well-conducted study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It must be noted that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the exposure levels reported and the timing and route of exposure studied, to the intervals between first exposure and disease onset observed in these studies, and to the general population(s) studied (i.e. there may be susceptible subpopulations or life stages). Experience from studies of cancer in humans indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; therefore, latency periods substantially shorter than about 30 years cannot provide evidence of lack of carcinogenicity. Furthermore, there may be critical windows of exposure, for example, as with diethylstilboestrol and clear cell adenocarcinoma of the cervix and vagina (IARC, 2012a).

3. Studies of cancer in experimental animals

Most human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species. For some agents, carcinogenicity in experimental animals was demonstrated before epidemiological studies identified their carcinogenicity in humans. Although this observation cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, such as strong evidence that a given agent causes cancer in

experimental animals through a species-specific mechanism that does not operate in humans (see Part B, Sections 4 and 6; Capen et al., 1999; IARC, 2003), these agents are considered to pose a potential carcinogenic hazard to humans. The inference of potential carcinogenic hazard to humans does not imply tumour site concordance across species (Baan et al., 2019).

(a) Types of studies considered

Relevant studies of cancer in experimental animals are identified by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below. Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (or possibly metabolites or derivatives of the agent) (see Part A, Section 7) after a thorough evaluation of the study features (see Part B, Section 3b). Those studies that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2018).

In addition to conventional long-term bioassays, alternative studies (e.g. in genetically engineered mouse models) may be considered in assessing carcinogenicity in experimental animals, also after a critical evaluation of the study features. For studies of certain exposures, such as viruses that typically only infect humans, use of such specialized experimental animal models may be particularly important; models include genetically engineered mice with targeted expression of viral genes to tissues from which human cancers arise, as well as humanized mice implanted with the human cells usually infected by the virus.

Other types of studies can provide supportive evidence. These include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies); studies in which the end-point was not cancer but a defined precancerous lesion; and studies of cancer in non-laboratory animals (e.g. companion animals) exposed to the agent.

(b) Study evaluation

Considerations of importance in the interpretation and evaluation of a particular study include: (i) whether the agent was clearly characterized, including the nature and extent of impurities and contaminants and the stability of the agent, and, in the case of mixtures, whether the sample characterization was adequately reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration and frequency of treatment, duration of observation, and route of exposure were appropriate; (iv) whether appropriate experimental animal species and strains were evaluated; (v) whether there were adequate numbers of animals per group; (vi) whether animals were allocated randomly to groups; (vii) whether the body weight, food and water consumption, and survival of treated animals were affected by any factors other than the test agent; (viii) whether the histopathology review was adequate; and (ix) whether the data were reported and analysed adequately.

(c) Outcomes and statistical analyses

An assessment of findings of carcinogenicity in experimental animals involves consideration of (i) study features such as route, doses, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age, and duration of follow-up; (ii) the spectrum of neoplastic response, from pre-neoplastic lesions and benign tumours to malignant neoplasms; (iii) the incidence, latency, severity, and multiplicity of neoplasms and pre-neoplastic

lesions; (iv) the consistency of the results for a specific target organ or organs across studies of similar design; and (v) the possible role of modifying factors (e.g. diet, infection, stress).

Key factors for statistical analysis include: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type or lesion, and (iii) duration of survival.

Benign tumours may be combined with malignant tumours in the assessment of tumour incidence when (a) they occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) they appear to represent a stage in the progression to malignancy (Huff et al., 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed.

Evidence of an increased incidence of neoplasms with increasing level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms. The form of the dose–response relationship can vary widely, including non-linearity, depending on the particular agent under study and the target organ. The dose–response relationship can also be affected by differences in survival among the treatment groups.

The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life and a survival-adjusted analysis would be warranted. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time that the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel–Haenszel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the poly-*k* test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other, more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

The concurrent control group is generally the most appropriate comparison group for statistical analysis; however, for uncommon tumours, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, sex, and strain, as well as other factors, such as basal diet and general laboratory environment, which may affect tumour response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003). It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls.

Meta-analyses and pooled analyses may be appropriate when the experimental protocols are sufficiently similar.

4. Mechanistic evidence

Mechanistic data may provide evidence of carcinogenicity and may also help in assessing the relevance and importance of findings of cancer in experimental animals and in humans (Guyton et al., 2009; Parkkinen et al., 2018) (see Part B, Section 6). Mechanistic studies have gained in prominence, increasing in their volume, diversity, and relevance to cancer hazard evaluation, whereas studies pertinent to other streams of evidence evaluated in the *Monographs* (i.e. studies of cancer in humans and lifetime cancer bioassays in rodents) may only be available for a fraction of agents to which humans are currently exposed (Guyton et al., 2009, 2018). Mechanistic studies and data are identified, screened, and evaluated for quality and importance to the evaluation by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below.

The Working Group's synthesis reflects the extent of available evidence, summarizing groups of included studies with an emphasis on characterizing consistencies or differences in results within and across experimental designs. Greater emphasis is given to informative mechanistic evidence from human-related studies than to that from other experimental test systems, and gaps are identified. Tabulation of data may facilitate this review. The specific topics addressed in the evidence synthesis are described below.

(a) Absorption, distribution, metabolism, and excretion

Studies of absorption, distribution, metabolism, and excretion in mammalian species are addressed in a summary fashion; exposure characterization is addressed in Part B, Section 1. The Working Group describes the metabolic fate of the agent in mammalian species, noting the metabolites that have been identified and their chemical reactivity. A metabolic schema may indicate the relevant metabolic pathways and products and whether supporting evidence is from studies in humans and/or studies in experimental animals. Evidence on other adverse effects that indirectly confirm absorption, distribution, and/or metabolism at tumour sites is briefly summarized when direct evidence is sparse.

(b) Evidence relevant to key characteristics of carcinogens

A review of Group 1 human carcinogens classified up to and including *IARC Monographs* Volume 100 revealed several issues relevant to improving the evaluation of mechanistic evidence for cancer hazard identification (Smith et al., 2016). First, it was noted that human carcinogens often share one or more characteristics that are related to the multiple mechanisms by which agents cause cancer. Second, different human carcinogens may exhibit a different spectrum of these key characteristics and operate through distinct mechanisms. Third, for many carcinogens evaluated before Volume 100, few data were available on some mechanisms of recognized importance in carcinogenesis, such as epigenetic alterations (Herceg et al., 2013). Fourth, there was no widely accepted method to search systematically for relevant mechanistic evidence, resulting in a lack of uniformity in the scope of mechanistic topics addressed across *IARC Monographs* evaluations.

To address these challenges, the key characteristics of human carcinogens were introduced to facilitate systematic consideration of mechanistic evidence in *IARC Monographs* evaluations (Smith et al., 2016; Guyton et al., 2018). The key characteristics described by Smith et al. (2016) (see Table 3), such as "is genotoxic", "is immunosuppressive", or "modulates receptor-mediated effects", are based on empirical observations of the chemical and biological properties associated with the human carcinogens identified by

Table 3 The key characteristics of carcinogens

	Ten key characteristics of carcinogens
1.	Is electrophilic or can be metabolically activated to an electrophile
2.	Is genotoxic
3.	Alters DNA repair or causes genomic instability
4.	Induces epigenetic alterations
5.	Induces oxidative stress
6.	Induces chronic inflammation
7.	Is immunosuppressive
8.	Modulates receptor-mediated effects
9.	Causes immortalization
10.	Alters cell proliferation, cell death, or nutrient supply

From Smith et al. (2016).

the *IARC Monographs* programme up to and including Volume 100. The list of key characteristics and associated end-points may evolve, based on the experience of their application and as new human carcinogens are identified. Key characteristics are distinct from the "hallmarks of cancer", which relate to the properties of cancer cells (Hanahan & Weinberg, 2000, 2011). Key characteristics are also distinct from hypothesized mechanistic pathways, which describe a sequence of biological events postulated to occur during carcinogenesis. As such, the evaluation approach based on key characteristics, outlined below, "avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence" (National Academies of Sciences, Engineering, and Medicine, 2017).

Studies in exposed humans and in human primary cells or tissues that incorporate end-points relevant to key characteristics of carcinogens are emphasized when available. For each key characteristic with adequate evidence for evaluation, studies are grouped according to whether they involve (a) humans or human primary cells or tissues or (b) experimental systems; further organization (as appropriate) is by end-point (e.g. DNA damage), duration, species, sex, strain, and target organ as well as strength of study design. Studies investigating susceptibility related to key characteristics of carcinogens (e.g. of genetic polymorphisms, or in genetically engineered animals) can be highlighted and may provide additional support for conclusions on the strength of evidence. Findings relevant to a specific tumour type may be noted.

(c) Other relevant evidence

Other informative evidence may be described when it is judged by the Working Group to be relevant to an evaluation of carcinogenicity and to be of sufficient importance to affect the overall evaluation. Quantitative structure–activity information, such as on specific chemical and/or biological features or activities (e.g. electrophilicity, molecular docking with receptors), may be informative. In addition, evidence that falls outside of the recognized key characteristics of carcinogens, reflecting emerging knowledge or important novel scientific developments on carcinogen mechanisms, may also be included. Available evidence relevant to criteria provided in authoritative publications (e.g. Capen et al., 1999; IARC, 2003) on thyroid, kidney, urinary bladder, or other tumours in experimental animals induced by mechanisms that do not operate in humans is also described.

(d) Study quality and importance to the evaluation

Based on formal considerations of the quality of the studies (e.g. design, methodology, and reporting of results), the Working Group may give greater weight to some included studies.

For observational and other studies in humans, the quality of study design, exposure assessment, and assay accuracy and precision are considered, in collaboration with the Working Group members reviewing exposure characterization and studies of cancer in humans, as are other important factors, including those described above for evaluation of epidemiological evidence (García-Closas et al., 2006, 2011; Vermeulen et al., 2018) (Part B, Sections 1 and 2).

In general, in experimental systems, studies of repeated doses and of chronic exposures are accorded greater importance than are studies of a single dose or time-point. Consideration is also given to factors such as the suitability of the dosing range, the extent of concurrent toxicity observed, and the completeness of reporting of the study (e.g. the source and purity of the agent, the analytical methods, and the results). Route of exposure is generally considered to be a less important factor in the evaluation of experimental studies, recognizing that the exposures and target tissues may vary across experimental models and in exposed human populations. Non-mammalian studies can be synthetically summarized when they are considered to be supportive of evidence in humans or higher organisms.

In vitro test systems can provide mechanistic insights, but important considerations include the limitations of the test system (e.g. in metabolic capabilities) as well as the suitability of a particular test article (i.e. because of physical and chemical characteristics) (Hopkins et al., 2004). For studies on some end-points, such as for traditional studies of mutations in bacteria and in mammalian cells, formal guidelines, including those from the Organisation for Economic Co-operation and Development, may be informative in conducting the quality review (OECD, 1997, 2016a, b). However, existing guidelines will not generally cover all relevant assays, even for genotoxicity. Possible considerations when evaluating the quality of in vitro studies encompass the methodology and design (e.g. the end-point and test method, the number of replicate samples, the suitability of the concentration range, the inclusion of positive and negative controls, and the assessment of cytotoxicity) as well as reporting (e.g. of the source and purity of the agent, and of the analytical methods and results). High-content and high-throughput in vitro data can serve as an additional or supportive source of mechanistic evidence (Chiu et al., 2018; Guyton et al., 2018), although large-scale screening programmes measuring a variety of end-points were designed to evaluate large chemical libraries in order to prioritize chemicals for additional toxicity testing rather than to identify the hazard of a specific chemical or chemical group.

The synthesis is focused on the evidence that is most informative for the overall evaluation. In this regard, it is of note that some human carcinogens exhibit a single or primary key characteristic, evidence of which has been influential in their cancer hazard classifications. For instance, ethylene oxide is genotoxic (IARC, 1994), 2,3,7,8-tetrachlorodibenzo-*para*-dioxin modulates receptor-mediated effects (IARC, 1997), and etoposide alters DNA repair (IARC, 2012a). Similarly, oncogenic viruses cause immortalization, and certain drugs are, by design, immunosuppressive (IARC, 2012a, b). Because non-carcinogens can also induce oxidative stress, this key characteristic should be interpreted with caution unless it is found in combination with other key characteristics (Guyton et al., 2018). Evidence for a group of key characteristics can strengthen mechanistic conclusions (e.g. "induces oxidative stress" together with "is electrophilic or can be metabolically activated to an

electrophile", "induces chronic inflammation", and "is immunosuppressive"); see, for example, 1-bromopropane (IARC, 2018).

5. Summary of data reported

(a) Exposure characterization

Exposure data are summarized to identify the agent and describe its production, use, and occurrence. Information on exposure prevalence and intensity in different settings, including geographical patterns and time trends, may be included. Exposure assessment methods used in key epidemiological studies reviewed by the Working Group are described and evaluated.

(b) Cancer in humans

Results of epidemiological studies pertinent to an evaluation of carcinogenicity in humans are summarized. The overall strengths and limitations of the epidemiological evidence base are highlighted to indicate how the evaluation was reached. The target organ(s) or tissue(s) in which a positive association between the agent and cancer was observed are identified. Exposure–response and other quantitative data may be summarized when available. When the available epidemiological studies pertain to a mixed exposure, process, occupation, or industry, the Working Group seeks to identify the specific agent considered to be most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data permit.

(c) Cancer in experimental animals

Results pertinent to an evaluation of carcinogenicity in experimental animals are summarized to indicate how the evaluation was reached. For each animal species, study design, and route of administration, there is a statement about whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or pre-neoplastic lesions was observed, and the tumour sites are indicated. Special conditions resulting in tumours, such as prenatal exposure or single-dose experiments, are mentioned. Negative findings, inverse relationships, dose–response patterns, and other quantitative data are also summarized.

(d) Mechanistic evidence

Results pertinent to an evaluation of the mechanistic evidence on carcinogenicity are summarized to indicate how the evaluation was reached. The summary encompasses the informative studies on absorption, distribution, metabolism, and excretion; on the key characteristics with adequate evidence for evaluation; and on any other aspects of sufficient importance to affect the overall evaluation, including on whether the agent belongs to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans, and on criteria with respect to tumours in experimental animals induced by mechanisms that do not operate in humans. For each topic addressed, the main supporting findings are highlighted from exposed humans, human cells or tissues, experimental animals, or in vitro systems. When mechanistic studies are available in exposed humans, the tumour type or target tissue studied may be specified. Gaps in the evidence are indicated (i.e. if no studies were available in exposed humans, in in vivo systems, etc.). Consistency or differences of effects across different experimental systems are emphasized.

6. Evaluation and rationale

Consensus evaluations of the strength of the evidence of cancer in humans, the evidence of cancer in experimental animals, and the mechanistic evidence are made using transparent criteria and defined descriptive terms. The Working Group then develops a consensus overall evaluation of the strength of the evidence of carcinogenicity for each agent under review.

An evaluation of the strength of the evidence is limited to the agents under review. When multiple agents being evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single and unified evaluation of the strength of the evidence.

The framework for these evaluations, described below, may not encompass all factors relevant to a particular evaluation of carcinogenicity. After considering all relevant scientific findings, the Working Group may exceptionally assign the agent to a different category than a strict application of the framework would indicate, while providing a clear rationale for the overall evaluation.

When there are substantial differences of scientific interpretation among the Working Group members, the overall evaluation will be based on the consensus of the Working Group. A summary of the alternative interpretations may be provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

The categories of the classification refer to the strength of the evidence that an exposure is carcinogenic and not to the risk of cancer from particular exposures. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used as descriptors of different strengths of evidence of carcinogenicity in humans; *probably carcinogenic* signifies a greater strength of evidence than *possibly carcinogenic*.

(a) Carcinogenicity in humans

Based on the principles outlined in Part B, Section 2, the evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** A causal association between exposure to the agent and human cancer has been established. That is, a positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.

***Limited evidence of carcinogenicity*:** A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence regarding carcinogenicity*:** The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and cancer, or no data on cancer in humans are available. Common findings that lead to a determination of inadequate evidence of carcinogenicity include: (a) there are no data available in humans; (b) there are data available in humans, but they are of poor quality or informativeness; and (c) there are studies of sufficient quality available in humans, but their results are inconsistent or otherwise inconclusive.

***Evidence suggesting lack of carcinogenicity*:** There are several high-quality studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and the studied cancers at any observed level of exposure. The results from these studies

alone or combined should have narrow confidence intervals with an upper limit below or close to the null value (e.g. a relative risk of unity). Bias and confounding were ruled out with reasonable confidence, and the studies were considered informative. A conclusion of *evidence suggesting lack of carcinogenicity* is limited to the cancer sites, populations and life stages, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

When there is *sufficient evidence*, a separate sentence identifies the target organ(s) or tissue(s) for which a causal interpretation has been established. When there is *limited evidence*, a separate sentence identifies the target organ(s) or tissue(s) for which a positive association between exposure to the agent and the cancer(s) was observed in humans. When there is *evidence suggesting lack of carcinogenicity*, a separate sentence identifies the target organ(s) or tissue(s) where evidence of lack of carcinogenicity was observed in humans. Identification of a specific target organ or tissue as having *sufficient evidence* or *limited evidence* or *evidence suggesting lack of carcinogenicity* does not preclude the possibility that the agent may cause cancer at other sites.

(b) Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity from studies in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** A causal relationship has been established between exposure to the agent and cancer in experimental animals based on an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories and/or under different protocols. An increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices (GLP), can also provide *sufficient evidence*.

Exceptionally, a single study in one species and sex may be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour, or age at onset, or when there are marked findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment and does not meet the criteria for *sufficient evidence*; (b) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; (c) the agent increases tumour multiplicity or decreases tumour latency but does not increase tumour incidence; (d) the evidence of carcinogenicity is restricted to initiation–promotion studies; (e) the evidence of carcinogenicity is restricted to observational studies in non-laboratory animals (e.g. companion animals); or (f) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.

***Inadequate evidence regarding carcinogenicity*:** The studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect because of major

qualitative or quantitative limitations, or no data are available on cancer in experimental animals.

***Evidence suggesting lack of carcinogenicity*:** Well-conducted studies (e.g. conducted under GLP) involving both sexes of at least two species are available showing that, within the limits of the tests used, the agent was not carcinogenic. The conclusion of *evidence suggesting lack of carcinogenicity* is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure covered by the available studies.

(c) Mechanistic evidence

Based on the principles outlined in Part B, Section 4, the mechanistic evidence is classified into one of the following categories:

***Strong mechanistic evidence*:** Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. Further support can be provided by studies that demonstrate experimentally that the suppression of key mechanistic processes leads to the suppression of tumour development. Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species. Quantitative structure–activity considerations, in vitro tests in non-human mammalian cells, and experiments in non-mammalian species may provide corroborating evidence but typically do not in themselves provide strong evidence. However, consistent findings across a number of different test systems in different species may provide strong evidence.

Of note, "strong" relates not to potency but to strength of evidence. The classification applies to three distinct topics:

(a) Strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans. The considerations can go beyond quantitative structure–activity relationships to incorporate similarities in biological activity relevant to common key characteristics across dissimilar chemicals (e.g. based on molecular docking, –omics data).

(b) Strong evidence that the agent exhibits key characteristics of carcinogens. In this case, three descriptors are possible:

1. The strong evidence is in exposed humans. Findings relevant to a specific tumour type may be informative in this determination.
2. The strong evidence is in human primary cells or tissues. Specifically, the strong findings are from biological specimens obtained from humans (e.g. ex vivo exposure), from human primary cells, and/or, in some cases, from other humanized systems (e.g. a human receptor or enzyme).
3. The strong evidence is in experimental systems. This may include one or a few studies in human primary cells and tissues.

(c) Strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Certain results in experimental animals (see Part B, Section 6b) would be discounted, according to relevant criteria and considerations in authoritative publications (e.g. Capen et al., 1999; IARC, 2003). Typically, this classification would not apply when there is strong mechanistic evidence that the agent exhibits key characteristics of carcinogens.

***Limited mechanistic evidence*:** The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in the studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.

***Inadequate mechanistic evidence*:** Common findings that lead to a determination of inadequate mechanistic evidence include: (a) few or no data are available; (b) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the studies; (c) the available results are negative.

(d) Overall evaluation

Finally, the bodies of evidence included within each stream of evidence are considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans. The three streams of evidence are integrated and the agent is classified into one of the following categories (see Table 4), indicating that the Working Group has established that:

The agent is carcinogenic to humans (Group 1)

This category applies whenever there is *sufficient evidence of carcinogenicity* in humans.

In addition, this category may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals.

The agent is probably carcinogenic to humans (Group 2A)

This category generally applies when the Working Group has made at least *two of the following* evaluations, *including at least one* that involves either exposed humans or human cells or tissues:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,
- *Strong evidence that the agent exhibits key characteristics of carcinogens.*

If there is *inadequate evidence regarding carcinogenicity* in humans, there should be *strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*. If there is *limited evidence of carcinogenicity in humans*, then the second individual evaluation may be from experimental systems (i.e. *sufficient evidence of carcinogenicity* in experimental animals or *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens).*

Additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2A.

Separately, this category generally applies if there is *strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A*.

The agent is possibly carcinogenic to humans (Group 2B)

This category generally applies when only one of the following evaluations has been made by the Working Group:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,

Table 4 Integration of streams of evidence in reaching overall classifications (the evidence in *bold italic* represents the basis of the overall evaluation)

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a]	**Evidence of cancer in experimental animals**	**Mechanistic evidence**	
Sufficient	Not necessary	Not necessary	**Carcinogenic to humans (Group 1)**
Limited or Inadequate	***Sufficient***	***Strong (b)(1) (exposed humans)***	
Limited	***Sufficient***	Strong (b)(2–3), Limited, or Inadequate	**Probably carcinogenic to humans (Group 2A)**
Inadequate	***Sufficient***	***Strong (b)(2) (human cells or tissues)***	
Limited	Less than Sufficient	***Strong (b)(1–3)***	
Limited or Inadequate	Not necessary	***Strong (a) (mechanistic class)***	
Limited	Less than Sufficient	Limited or Inadequate	**Possibly carcinogenic to humans (Group 2B)**
Inadequate	***Sufficient***	Strong (b)(3), Limited, or Inadequate	
Inadequate	Less than Sufficient	***Strong (b)(1–3)***	
Limited	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	
Inadequate	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	**Not classifiable as to its carcinogenicity to humans (Group 3)**
All other situations not listed above			

[a] Human cancer(s) with highest evaluation.

[b] The *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* must specifically be for the tumour sites supporting the classification of *sufficient evidence in experimental animals*.

• *Strong evidence that the agent exhibits key characteristics of carcinogens.*

Because this category can be based on evidence from studies in experimental animals alone, there is **no** requirement that the strong mechanistic evidence be in exposed humans or in human cells or tissues. This category may be based on *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens.*

As with Group 2A, additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2B.

The agent is not classifiable as to its carcinogenicity to humans (Group 3)

Agents that do not fall into any other group are generally placed in this category.

This includes the case when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites in experimental animals, the remaining tumour sites do not support an evaluation of *sufficient evidence in experimental animals*, and other categories are not supported by data from studies in humans and mechanistic studies.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent is of unknown carcinogenic potential and that there are significant gaps in research.

If the evidence suggests that the agent exhibits no carcinogenic activity, either through *evidence suggesting lack of carcinogenicity* in both humans and experimental animals, or through *evidence suggesting lack of carcinogenicity* in

experimental animals complemented by strong negative mechanistic evidence in assays relevant to human cancer, then the Working Group may add a sentence to the evaluation to characterize the agent as well-studied and without evidence of carcinogenic activity.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is summarized so that the basis for the evaluation offered is transparent. This section integrates the major findings from studies of cancer in humans, cancer in experimental animals, and mechanistic evidence. It includes concise statements of the principal line(s) of argument that emerged in the deliberations of the Working Group, the conclusions of the Working Group on the strength of the evidence for each stream of evidence, an indication of the body of evidence that was pivotal to these conclusions, and an explanation of the reasoning of the Working Group in making its evaluation.

References

Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. (2016). Mutational signatures associated with tobacco smoking in human cancer. *Science*. 354(6312):618–22. doi:10.1126/science.aag0299 PMID:27811275

Axelson O, Steenland K (1988). Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med*. 13(1):105–18. doi:10.1002/ajim.4700130107 PMID:3344750

Baan RA, Stewart BW, Straif K, editors (2019). Tumour site concordance and mechanisms of carcinogenesis (IARC Scientific Publication No. 165). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/578.

Bieler GS, Williams RL (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*. 49(3):793–801. doi:10.2307/2532200 PMID:8241374

Capen CC, Dybing E, Rice JM, Wilbourn JD, editors (1999). Species differences in thyroid, kidney and urinary bladder carcinogenesis (IARC Scientific Publication No. 147). Lyon, France: IARC Press. Available from: https://publications.iarc.fr/302 PMID:10627184

Chiu WA, Guyton KZ, Martin MT, Reif DM, Rusyn I (2018). Use of high-throughput in vitro toxicity screening data in cancer hazard evaluations by IARC Monograph Working Groups. *ALTEX*. 35(1):51–64. doi:10.14573/altex.1703231 PMID:28738424

Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. (2005). Transparency in IARC Monographs. *Lancet Oncol*. 6(10):747 doi:10.1016/S1470-2045(05)70380-6

Cogliano VJ, Baan RA, Straif K, Grosse Y, Secretan MB, El Ghissassi F, et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect*. 112(13):1269–74. doi:10.1289/ehp.6950 PMID:15345338

Dunson DB, Chen Z, Harry J (2003). A Bayesian approach for joint modeling of cluster size and subunit-specific outcomes. *Biometrics*. 59(3):521–30. doi:10.1111/1541-0420.00062 PMID:14601753

Fung KY, Krewski D, Smythe RT (1996). A comparison of tests for trend with historical controls in carcinogen bioassay. *Can J Stat*. 24(4):431–54. doi:10.2307/3315326

García-Closas M, Vermeulen R, Cox D, Lan Q, Caporaso N, Hunter D, et al. (2011). Population-based study designs in molecular epidemiology. In: Rothman N, Hainaut P, Schulte P, Smith M, Boffetta P, Perera FP, editors. Molecular epidemiology: principles and practices. Lyon, France: International Agency for Research on Cancer; pp. 241–59.

García-Closas M, Vermeulen R, Sherman ME, Moore LE, Smith MT, Rothman N (2006). Application of biomarkers in cancer epidemiology. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 3rd ed. New York (NY), USA: Oxford University Press; pp. 70–88. doi:10.1093/acprof:oso/9780195149616.003.0006

Gart JJ, Krewski D, Lee PN, Tarone RE, Wahrendorf J (1986). Statistical methods in cancer research, Volume III: The design and analysis of long-term animal experiments (IARC Scientific Publication No. 79). Lyon, France: International Agency for Research on Cancer.

Greenland S, O'Rourke K (2008). Meta-analysis. In: Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. 3rd ed. Philadelphia (PA), USA: Wolters Kluwer Health/Lippincott Williams & Wilkins; pp. 652–682.

Greim H, Gelbke H-P, Reuter U, Thielmann HW, Edler L (2003). Evaluation of historical control data in carcinogenicity studies. *Hum Exp Toxicol*. 22(10):541–9. doi:10.1191/0960327103ht394oa PMID:14655720

Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, et al. (2009). Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. *Mutat*

Res. 681(2–3):230–40. doi:10.1016/j.mrrev.2008.10.001 PMID:19010444

Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, et al. (2018). Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis*. 39(4):614–22. doi:10.1093/carcin/bgy031 PMID:29562322

Hanahan D, Weinberg RA (2000). The hallmarks of cancer. *Cell*. 100(1):57–70. doi:10.1016/S0092-8674(00)81683-9 PMID:10647931

Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. *Cell*. 144(5):646–74. doi:10.1016/j.cell.2011.02.013 PMID:21376230

Haseman JK, Huff J, Boorman GA (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol*. 12(2):126–35. doi:10.1177/019262338401200203 PMID:11478313

Herceg Z, Lambert MP, van Veldhoven K, Demetriou C, Vineis P, Smith MT, et al. (2013). Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation. *Carcinogenesis*. 34(9):1955–67. doi:10.1093/carcin/bgt212 PMID:23749751

Hernán MA, Hernández-Díaz S, Robins JM (2004). A structural approach to selection bias. *Epidemiology*. 15(5):615–25. doi:10.1097/01.ede.0000135174.63482.43 PMID:15308962

Hill AB (1965). The environment and disease: association or causation? *Proc R Soc Med*. 58:295–300. PMID:14283879

Hopkins AL, Groom CR, Alex A (2004). Ligand efficiency: a useful metric for lead selection. *Drug Discov Today*. 9(10):430–1. doi:10.1016/S1359-6446(04)03069-7 PMID:15109945

Huff JE, Eustis SL, Haseman JK (1989). Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metastasis Rev*. 8(1):1–22. doi:10.1007/BF00047055 PMID:2667783

IARC (1994). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*. 60:1–560. Available from: https://publications.iarc.fr/78 PMID:7869568

IARC (1997). Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. *IARC Monogr Eval Carcinog Risks Hum*. 69:1–631. Available from: https://publications.iarc.fr/87 PMID:9379504

IARC (2003). Predictive value of rodent forestomach and gastric neuroendocrine tumours in evaluating carcinogenic risks to humans (IARC Technical Publication No. 39). Lyon, France: IARC Press. Available from: https://publications.iarc.fr/362.

IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monogr Eval Carcinog Risks Hum*. 84:1–477. Available from: https://publications.iarc.fr/102 PMID:15645577

IARC (2012a). Pharmaceuticals. *IARC Monogr Eval Carcinog Risks Hum*. 100A:1–437. Available from: https://publications.iarc.fr/118 PMID:23189749

IARC (2012b). Biological agents. *IARC Monogr Eval Carcinog Risks Hum*. 100B:1–441. Available from: https://publications.iarc.fr/119 PMID:23189750

IARC (2014). Report of the IARC Advisory Group to Recommend on Quantitative Risk Characterization (IARC Internal Report 14/001). Available from: https://monographs.iarc.who.int/wp-content/uploads/2018/06/14-001.pdf.

IARC (2018). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*. 115:1–292. Available from: https://publications.iarc.fr/563.

National Academies of Sciences, Engineering, and Medicine (2017). Using 21st century science to improve risk-related evaluations. Washington (DC), USA: National Academies Press. doi:10.17226/24635 PMID:28267305

National Research Council (2012). Exposure science in the 21st century: a vision and a strategy. Washington (DC), USA: National Academies Press. doi:10.17226/13507 PMID:24901193

OECD (1997). Test no. 471: Bacterial reverse mutation test, OECD Guidelines for the Testing of Chemicals, Section 4. Paris, France: Organisation for Economic Co-operation and Development. doi:10.1787/9789264071247-en

OECD (2016a). Test no. 476: In vitro mammalian cell gene mutation tests using the *Hprt* and *xprt* genes, OECD Guidelines for the Testing of Chemicals, Section 4. Paris, France: Organisation for Economic Co-operation and Development. doi:10.1787/9789264264809-en

OECD (2016b). Test no. 490: In vitro mammalian cell gene mutation tests using the thymidine kinase gene, OECD Guidelines for the Testing of Chemicals, Section 4. Paris, France: Organisation for Economic Co-operation and Development. doi:10.1787/9789264264908-en

OECD (2018). Test no. 451: Carcinogenicity studies, OECD Guidelines for the Testing of Chemicals, Section 4: Health effects. Paris, France: Organisation for Economic Co-operation and Development. doi:10.1787/9789264071186-en

Parkkinen VP, Wallmann C, Wilde M, Clarke B, Illari P, Kelly MP, et al. (2018). Evaluating evidence of mechanisms in medicine. Principles and procedures. Switzerland: Springer Cham. doi:10.1007/978-3-319-94610-8

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, et al. (1980). Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: Long-term and short-term screening assays for carcinogens: a critical appraisal. *IARC Monogr Eval Carcinog Risk Chem Hum*. Suppl. 2. Lyon, France: International Agency for Research on Cancer; pp. 311–426. Available from: https://publications.iarc.fr/134 PMID:6935176

Portier CJ, Bailer AJ (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol*. 12(4):731–7. doi:10.1016/0272-0590(89)90004-3 PMID:2744275

Richardson DB, Laurier D, Schubauer-Berigan MK, Tchetgen Tchetgen E, Cole SR (2014). Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. *Am J Epidemiol*. 180(9):933–40. doi:10.1093/aje/kwu211 PMID:25245043

Rothman KJ, Greenland S, Poole C, Lash TL (2008). Causation and causal inference. In: Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. 3rd ed. Philadelphia (PA), USA: Wolters Kluwer Health/Lippincott Williams & Wilkins; pp. 5–31.

Sherman CD, Portier CJ, Kopp-Schneider A (1994). Multistage models of carcinogenesis: an approximation for the size and number distribution of late-stage clones. *Risk Anal*. 14(6):1039–48. doi:10.1111/j.1539-6924.1994.tb00074.x PMID:7846311

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*. 124(6):713–21. doi:10.1289/ehp.1509912 PMID:26600562

Stayner L, Steenland K, Dosemeci M, Hertz-Picciotto I (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scand J Work Environ Health*. 29(4):317–24. doi:10.5271/sjweh.737 PMID:12934726

Vandenbroucke JP, Broadbent A, Pearce N (2016). Causality and causal inference in epidemiology: the need for a pluralistic approach. *Int J Epidemiol*. 45(6):1776–86. doi:10.1093/ije/dyv341 PMID:26800751

Vermeulen R, Bell DA, Jones DP, Garcia-Closas M, Spira A, Wang TW, et al. (2018). Application of biomarkers in cancer epidemiology. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Schottenfeld and Fraumeni cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press; pp. 77–96.

Wild CP, Cogliano VJ (2011). A plea on behalf of expert evaluation and the experts involved. *Int J Epidemiol*. 40(1):253–61. doi:10.1093/ije/dyq038 PMID:20223796

GENERAL REMARKS

This one-hundred-and-thirty-second volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of occupational exposure as a firefighter.

Firefighting was previously classified by IARC as *possibly carcinogenic to humans* (*Group 2B*) (IARC, 2010a) on the basis of *limited* evidence of carcinogenicity in humans and *inadequate* evidence regarding carcinogenicity in experimental animals. Data in humans generally lacked exposure–response information, and findings among studies were inconsistent, although the evidence of excess risk appeared strongest for cancers of the testis and prostate, and non-Hodgkin lymphoma.

The Advisory Group to Recommend Priorities for the *IARC Monographs* that met in 2019 recommended that occupational exposure as a firefighter be evaluated with high priority (IARC, 2019a; Marques et al., 2019).

A summary of the findings of this volume appears in *The Lancet Oncology* (Demers et al., 2022).

Definition and scope of the agent

The Working Group carefully considered the scope of the agent under evaluation in this monograph. There is substantial heterogeneity in potential exposures in the firefighting occupation and in the nature of the occupation itself, which presented a challenge for defining the scope of "occupational exposure as a firefighter". Firefighting duties involve diverse types of fire, emergency, and disaster responses, as well as specialized training events. Firefighters are exposed to a complex mixture of combustion emissions and a wide range of other chemical and physical agents. Firefighters responding to catastrophic events (such as building collapse, release of radioactive material, or chemical spills) may be exposed to agents that are not typically generalizable to the majority of people in the occupation worldwide. Work conditions can also involve night shift work, extreme physical activity, heat exposure, dehydration, and stress. In addition, people employed in the firefighting occupation can work as career or volunteer firefighters; have full-time, part-time, or seasonal employment; or work in a municipal or rural setting. Moreover, firefighter trainers might only (or primarily) be exposed to active firefighting under training scenarios. Given this diversity, the Working Group decided to adopt a broad scope in their definition of the agent and considered all exposures and types of firefighting employment as part of the agent. Any activity required or exposure incurred as part of the duties of the occupation (including firefighter training) was considered as part of the agent definition. Exposure to specific agents that are common

during the course of duties for the majority of firefighters (e.g. fire smoke) was considered informative for the consideration of intensity of exposure, but employment in the occupation itself (either career or volunteer) was all that was required to meet the definition for inclusion in the review.

Gaps in the epidemiological literature on firefighting and cancer

Although firefighting occurs throughout the world, epidemiological studies of cancer among firefighters were available primarily from the USA, Canada, western and northern Europe, and Australia, with few studies identified in Asia. Consequently, studies of cancer among firefighters in other locations were not assessed in this evaluation. Studies of firefighters in low- and middle-income countries (including China and all countries of Africa and Latin America) were, in particular, unavailable. Nonetheless, the Working Group identified a large number of epidemiological studies with which to perform a systematic review and meta-analysis. The quality of the exposure assessments in these studies varied, with many studies assessing only having ever worked in the firefighting occupation and a small minority of studies assessing quantitative estimates of the number and types of fire response over time during firefighting. Studies with a detailed quantitative assessment of exposure to specific agents in the occupation were generally lacking. There were no studies of cancer in humans in which biological markers were measured as part of the exposure assessment.

Impact of climate change on occupational exposure as a firefighter

As much as 25–50% of the particulate matter with a diameter of ≤ 2.5 μm ($PM_{2.5}$) in ambient air across the USA is estimated to derive from wildland fires (Burke et al., 2021), and it is expected that there will be an increasing trend in the number and intensity of wildland fires associated with climate change (Ellis et al., 2022). Thus, wildland fires alone will engage more people in firefighting in the coming years, increasing the number of exposed firefighters and their subsequent cancer burden, as documented in the present monograph. Consequently, the evaluation of occupational exposure as a firefighter as *carcinogenic to humans* (*Group 1*) takes on added importance regarding the impact of these exposures. Very few studies of cancer in humans included wildland firefighters or measured exposure to rural or wildland fires; however, mechanistic studies in exposed firefighters found similar evidence of key characteristics of carcinogens in both wildland and municipal firefighters (see below). Accordingly, the Working Group concluded that its evaluation of occupational exposure as a firefighter should be presumed to apply to all firefighters, including men and women, and to all firefighting settings (e.g. municipal, wildland, vehicular) and employment arrangements (career, part-time, volunteer).

Relevance of previous *IARC Monographs* evaluations

The present evaluation of occupational exposure as a firefighter is supported by previous evaluations by the *IARC Monographs* programme of various combustion emissions and of many of the individual agents to which firefighters are exposed. Complex mixtures and combustion

emissions previously evaluated by the *IARC Monographs* programme as *carcinogenic to humans* (*Group 1*) include tobacco smoke (IARC, 2004, 2012b), indoor emissions from coal (IARC, 2012b), diesel exhaust (IARC, 2013), and particulate matter from air pollution (IARC, 2015b). Relevant complex occupational exposure circumstances include exposure as a chimney sweep (soot) and in aluminium production (polycyclic aromatic hydrocarbons, PAHs) (IARC, 2012c). Exposure to indoor emissions from biomass, primarily wood, is *probably carcinogenic to humans* (*Group 2A*) (IARC, 2010b). Some individual agents in combustion emissions that have been evaluated by IARC as human carcinogens (*Group 1*) and with documented exposures to firefighters include benzo[*a*]pyrene (IARC, 2010c), acrolein (IARC, 2021b), polychlorinated biphenyls (PCBs) and dioxin-like PCBs with specific toxicity equivalency factors (IARC, 2015a), asbestos (IARC, 2012a), dioxins (IARC, 1997, 2012c), benzene (IARC, 2012c, 2018), formaldehyde (IARC, 2006, 2012c), styrene (IARC, 2019b), and night shift work (IARC, 2020).

For these agents, mechanistic evidence is available for a variety of key characteristics of carcinogens; however, the levels of evidence and the terminology used to characterize the evidence according to the Preamble to the *IARC Monographs* (IARC, 2019c) have evolved over time. These details are described in Section 4.1, Evidence relevant to key characteristics of carcinogens. For firefighting, nearly all the available mechanistic data were in humans, and adequate exposure data were available; no cancer studies in experimental animals were available to the Working Group.

As documented in the present monograph, occupational exposure as a firefighter can result in exposures to PAHs from fire effluents and diesel exhaust. PAHs cause cancer of the urinary bladder (IARC, 2010c; 2021a), and there is *limited* evidence for exposure to diesel engine exhaust and cancer of the urinary bladder in humans (IARC, 2013). Supporting this observation is the finding of urinary mutagenicity in firefighters, which reflects exposure to a mixture of PAHs from smoky coal emissions and also by exposure to diesel exhaust (Wong et al., 2021). Although no reports have assessed the exposure of firefighters to aromatic amines, this chemical class contributes to the mutagenicity and carcinogenicity of combustion emissions (DeMarini & Linak, 2022), causes bladder cancer and urinary mutagenicity (IARC, 2010d), and is the product of the metabolism (by nitro-reduction) of nitroarenes (nitro-PAHs) in diesel exhaust (IARC, 2013); thus aromatic amines are another plausible causal agent that would support the observed association between firefighting and bladder cancer.

Despite the heterogeneity of the exposures, the exposure data show that firefighters working over a range of firefighting conditions are exposed to PAHs, including dermally. These data provide coherence across diverse settings and are consistent with the mechanistic role of PAHs in the mutagenicity and carcinogenicity of a wide variety of combustion emissions (DeMarini & Linak, 2022), making the evaluation generally applicable to firefighters.

Lung cancer findings

There was *inadequate* evidence that occupational exposure as a firefighter causes lung cancer. This finding was unexpected, and the Working Group concluded that negative confounding by smoking was a plausible explanation for the deficit in lung cancer seen among firefighters compared with the general population. Another factor may be that firefighters are potentially exposed to endotoxins, which are components of lipopolysaccharides derived from the outer membrane of Gram-negative bacteria (Lundin & Checkoway, 2009). Endotoxins modulate levels of circulating

inflammatory and immunological-response markers that are possibly associated with lung carcinogenesis (Lundin & Checkoway, 2009), and exposure to endotoxins in occupations with high exposure to organic dusts has been linked to decreased risk of lung cancer (Lenters et al., 2010). Although endotoxins are released during the indoor burning of wood (Semple et al., 2012), no studies have measured exposure of firefighters to endotoxins. However, indoor combustion of biomass fuel (primarily wood) has been classified as *probably carcinogenic to humans* (*Group 2A*), with *limited* evidence supporting a positive association with lung cancer in humans (IARC, 2010b). This finding, which has also been supported by a subsequent meta-analysis (Bruce et al., 2015), somewhat reduces the plausibility of endotoxin exposure as a major reason for the lack of excess lung cancer risk seen in firefighters compared with the general population.

Scope of systematic review

Standardized searches of the PubMed database (NCBI, 2022) were conducted for the agent and for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the key characteristics of carcinogens). For cancer in humans, searches were also conducted in the Web of Science (Clarivate, 2022) and Embase (Elsevier, 2022) databases. The literature tree for the agent, including the full set of search terms for the agent name and each outcome type, is available online.[1]

References

Bruce N, Dherani M, Liu R, Hosgood HD 3rd, Sapkota A, Smith KR, et al. (2015). Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. *Thorax*. 70(5):433–41. doi:10.1136/thoraxjnl-2014-206625 PMID:25758120

Burke M, Driscoll A, Heft-Neal S, Xue J, Burney J, Wara M (2021). The changing risk and burden of wildfire in the United States. *Proc Natl Acad Sci USA*. 118(2):e2011048118. doi:10.1073/pnas.2011048118 PMID:33431571

Clarivate (2022). Web of Science [online database]. Available from: https://www.webofscience.com/wos/woscc/basic-search.

DeMarini DM, Linak WP (2022). Mutagenicity and carcinogenicity of combustion emissions are impacted more by combustor technology than by fuel composition: A brief review. *Environ Mol Mutagen*. 63(3):135–50. doi:10.1002/em.22475 PMID:35253926

Demers PA, DeMarini DM, Fent KW, Glass DC, Hansen J, Adetona O, et al. (2022). Carcinogenicity of occupational exposure as a firefighter. *Lancet Oncol*. 23(8):985–6. doi:10.1016/S1470-2045(22)00390-4 PMID:35780778

Ellis TM, Bowman DMJS, Jain P, Flannigan MD, Williamson GJ (2022). Global increase in wildfire risk due to climate-driven declines in fuel moisture. *Glob Change Biol*. 28(4):1544–59. doi:10.1111/gcb.16006 PMID:34800319

Elsevier (2022). Embase [online database]. Elsevier. Available from: https://www.embase.com/.

IARC (1997). Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. *IARC Monogr Eval Carcinog Risks Hum*. 69:1–666. Available from: https://publications.iarc.fr/87 PMID:9379504

IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*. 83:1–1452. Available from: https://publications.iarc.fr/101 PMID:15285078

IARC (2006). Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxypropan-2-ol. *IARC Monogr Eval Carcinog Risks Hum*. 88:1–478. Available from: https://publications.iarc.fr/106 PMID:17366697

IARC (2010a). Painting, firefighting, and shiftwork. *IARC Monogr Eval Carcinog Risks Hum*. 98:1–804. Available from: https://publications.iarc.fr/116 PMID:21381544

[1] The literature tree for the present volume is available at: https://hawcproject.iarc.who.int/assessment/666/ (occupational exposure as a firefighter).

IARC (2010b). Household use of solid fuels and high-temperature frying. *IARC Monogr Eval Carcinog Risks Hum*. 95:1–430. Available from: https://publications.iarc.fr/113 PMID:20701241

IARC (2010c). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval Carcinog Risks Hum*. 92:1–853. Available from: https://publications.iarc.fr/110 PMID:21141735

IARC (2010d). Some aromatic amines, organic dyes, and related exposures. *IARC Monogr Eval Carcinog Risks Hum*. 99:1–692. Available from: https://publications.iarc.fr/117 PMID:21528837

IARC (2012a). Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum*. 100C:1–501. Available from: https://publications.iarc.fr/120 PMID:23189751

IARC (2012b). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*. 100E:1–575. Available from: https://publications.iarc.fr/122 PMID:23193840

IARC (2012c). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*. 100F:1–599. Available from: https://publications.iarc.fr/123 PMID:23189753

IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*. 105:1–703. Available from: https://publications.iarc.fr/129 PMID:26442290

IARC (2015a). Polychlorinated biphenyls and polybrominated biphenyls. *IARC Monogr Eval Carcinog Risks Hum*. 107:1–502. Available from: https://publications.iarc.fr/131 PMID:29905442

IARC (2015b). Outdoor air pollution. *IARC Monogr Eval Carcinog Risks Hum*. 109:1–448. Available from: https://publications.iarc.fr/538 PMID:29905447

IARC (2018). Benzene. *IARC Monogr Eval Carcinog Risks Hum*. 120:1–301. Available from: https://publications.iarc.fr/576 PMID:31769947

IARC (2019a). Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.fr/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf, accessed 25 September 2020.

IARC (2019b). Styrene, styrene-7,8-oxide, and quinoline. *IARC Monogr Eval Carcinog Risks Hum*. 121:1–345. Available from: https://publications.iarc.fr/582 PMID:31967769

IARC (2019c). Preamble to the *IARC Monographs* (amended January 2019). Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/, accessed 25 September 2020.

IARC (2020). Night shift work. *IARC Monogr Identif Carcinog Hazard Hum*. 124:1–371. Available from: https://publications.iarc.fr/593 PMID:33656825

IARC (2021a). Some aromatic amines and related compounds. *IARC Monogr Identif Carcinog Hazard Hum*. 127:1–267. Available from: https://publications.iarc.fr/599 PMID:35044736

IARC (2021b). Acrolein, crotonaldehyde, and arecoline. *IARC Monogr Identif Carcinog Hazard Hum*. 128:1–335. Available from: https://publications.iarc.fr/602 PMID:36924508

Lenters V, Basinas I, Beane-Freeman L, Boffetta P, Checkoway H, Coggon D, et al. (2010). Endotoxin exposure and lung cancer risk: a systematic review and meta-analysis of the published literature on agriculture and cotton textile workers. *Cancer Causes Control*. 21(4):523–55. doi:10.1007/s10552-009-9483-z PMID:20012774

Lundin JI, Checkoway H (2009). Endotoxin and cancer. *Environ Health Perspect*. 117(9):1344–50. doi:10.1289/ehp.0800439 PMID:19750096

Marques MM, Berrington de Gonzalez A, Beland FA, Browne P, Demers PA, Lachenmeier DW, et al.; *IARC Monographs* Priorities Group (2019). Advisory Group recommendations on priorities for the *IARC Monographs*. *Lancet Oncol*. 20(6):763–4. doi:10.1016/S1470-2045(19)30246-3 PMID:31005580

NCBI (2022). PubMed [online database]. Bethesda (MD), USA: National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/.

Semple S, Garden C, Coggins M, Galea KS, Whelan P, Cowie H, et al. (2012). Contribution of solid fuel, gas combustion, or tobacco smoke to indoor air pollutant concentrations in Irish and Scottish homes. *Indoor Air*. 22(3):212–23. doi:10.1111/j.1600-0668.2011.00755.x PMID:22007695

Wong JYY, Vermeulen R, Dai Y, Hu W, Martin WK, Warren SH, et al. (2021). Elevated urinary mutagenicity among those exposed to bituminous coal combustion emissions or diesel engine exhaust. *Environ Mol Mutagen*. 62(8):458–70. doi:10.1002/em.22455 PMID:34331495

1. EXPOSURE CHARACTERIZATION

1.1 Definition of the agent

The agent under evaluation is "occupational exposure as a firefighter". Firefighters' occupational exposures are complex and involve a highly heterogeneous mix of chemical, physical, biological, and psychosocial hazards resulting from fires, and from activities for training, controlling fires, and protecting life and property during emergencies (NFPA, 2021a; US BLS, 2021). The present monograph applies to any firefighter (career or volunteer) who has prepared for and participated in activities aimed at controlling fires (whether structure, vehicle, vegetation, or other types of fire), while acknowledging that firefighters are involved in numerous other occupational activities.

The occupation of firefighting can involve various roles and responsibilities, training requirements, and employer types. This variety may have an impact on the magnitude and character of occupational exposures. Firefighters respond to different types of fire and other emergency events (e.g. vehicle accidents, medical incidents, hazardous material releases, and building collapses). They also participate in non-emergency events, such as building inspections, training, and maintenance of the station or apparatus (engine) (Kales et al., 2007; Guia das Profissões, 2020; Pravaler, 2020; Fire and Rescue New South Wales, 2021a; United Kingdom National Careers Service, 2021; US BLS, 2021; Canadian Centre for Occupational Health and Safety, 2022). Specific types of firefighter may be characterized by the types of fire for which they are trained and that they are likely to encounter (e.g. structure, industrial, aircraft, marine, and wildland). Firefighters may also be defined by their employer (e.g. municipal, federal, military, tribal, or private), their employment status (e.g. full-time, part-time, volunteer, on-call, or seasonal), or their primary duties (e.g. investigator, instructor, engineer/pump operator, and hazardous materials specialist) (Hwang et al., 2019a, b; United Kingdom Home Office, 2020; US BLS, 2021; Miami Dade College, 2022). Note that fire investigators, hazardous materials specialists, or others who have not fought fires at any point in their tenure are not included in the definition of the agent (i.e. occupational exposure as a firefighter) in the present monograph. [The Working Group noted that, although terminology varies throughout the world, these general categories or types of firefighter exist in many regions. However, specialization in a particular area of firefighting may be less likely in low- and middle-income countries.]

Firefighters' tasks vary with their job assignments, rank or seniority, and location. For example, municipal firefighters in large cities may respond to more structure fires than do firefighters in rural areas, whereas firefighters

near major roads or highways may respond to more vehicle fires than structure fires (Kales et al., 2007; US Fire Administration, 2018; NFPA, 2020b, 2021b). Wildland firefighting requires a different skillset to that required for municipal firefighting and has its own subspecialities (USDA Forest Service, 2021a; Forest Fire Management Victoria, 2022). Responsibilities change as firefighters advance or are promoted within the fire service. For example, a fire chief or commissioner is involved in management activities and is less likely to be directly engaged in fire suppression or rescue operations (Fleming & Zhu, 2009) (see Section 1.2 for more details about the occupation of firefighting). [The Working Group noted that there is a paucity of data with respect to promotional systems and advancement among firefighters in low- and middle-income countries.]

Firefighters can be exposed to a very wide range of airborne chemical exposures. The most common exposures are to combustion products from fires and exhaust from diesel or petrol engines. The chemical composition and airborne concentrations of combustion products depend on the materials being burned, the duration of the fire, and the ventilation conditions (Stec, 2017). Combustion products may include (but are not limited to) fine and ultrafine particulates; oxides of carbon, nitrogen, and sulfur; hydrocarbons, aromatic hydrocarbons, and polycyclic aromatic hydrocarbons (PAHs) with or without functional groups such as amine, thiol, alcohol, or carbonyl groups; halogenated compounds including acid gases; and metals and metal oxides (Austin et al., 2001a; Baxter et al., 2010; Blomqvist et al., 2014; Fent et al., 2018; Keir et al., 2020) (see Sections 1.3.1 and 1.4 for more information on the composition of fire smoke). Firefighters may also be exposed to silica (Reinhardt & Broyles, 2019) and building materials affected by structure fires, such as asbestos and synthetic fibres (Bendix, 1979; Bolstad-Johnson et al., 2000; Lioy et al., 2002; Stec et al., 2019). Chemical flame retardants added to furnishings and other products may be released into the environment unaltered (Hewitt et al., 2017; Fent et al., 2020a). Firefighters may also be exposed to chemicals they use during firefighting, such as per- and polyfluoroalkyl substances (PFAS) contained in some aqueous film-forming foams (AFFF) (Khalil et al., 2020; Leary et al., 2020) (see Section 1.5.1 for more information on exposures other than fire smoke). Depending on the properties of compounds released, use of personal protective equipment (PPE), contamination of skin, and decontamination measures, firefighters can potentially inhale, ingest, and/or dermally absorb a variety of chemicals during or after fire responses (Fent et al., 2017, 2020b; Stec et al., 2018; Burgess et al., 2020) (see Sections 1.4.5 and 1.6 for more information on routes of exposure and control methods).

Wildfires predominantly involve the combustion of timber, brush, and other vegetation but can also produce many of the same combustion products as structure fires (e.g. aromatic hydrocarbons, aldehydes, and particulates) (Adetona et al., 2016; Cherry et al., 2021a). As wildfires encroach on urban areas (known as the wildland–urban interface, or WUI), firefighters – both wildland and municipal – have increasingly been simultaneously fighting structure and vegetation fires (Radeloff et al., 2018) (see Section 1.4.2 for more information about exposures during wildfires).

Firefighters who rarely respond to emergency fires or other chemical incidents (e.g. airport firefighters) may still have exposures from live-fire training, use of chemicals (e.g. AFFF), or from contamination of previously used protective equipment or workplace surfaces (Fent et al., 2017, 2019a; Engelsman et al., 2019; Leary et al., 2020). Most fire departments have diesel-fuelled vehicles and equipment, so firefighters can also be exposed to diesel engine exhaust (Bott et al., 2017) (see Section 1.5.1(d)). There are also non-chemical carcinogenic hazards to which many

firefighters may be exposed. These include night shift work, infectious agents, and ultraviolet (UV) radiation from working outdoors (Mahale et al., 2016; Jang et al., 2020) (see Sections 1.5.2(a), 1.5.2(b), and 1.5.1(f)).

The PPE worn by firefighters around the world shares many similarities. The turnout gear of municipal firefighters typically includes self-contained breathing apparatus (SCBA), helmet, hood, gloves, and insulating clothing consisting of multiple layers of protective fabric (NFPA, 2018; CEN, 2020), although there can be notable differences in the design of each of these components according to geographical location. Wildland firefighters, in comparison, wear much lighter protective clothing and may not wear any respiratory protection (Carballo-Leyenda et al., 2018; Navarro et al., 2019a) (see Section 1.6 for more details on PPE).

Firefighters may have second jobs in occupations within or outside the fire service discipline (Beaton & Murphy, 1993; Murphy et al., 1999; Baikovitz et al., 2019; Pedersen et al., 2019, 2020). For example, it is not uncommon for a firefighter to be assigned to a municipal fire department as a full-time municipal firefighter/paramedic and also work part-time as a fire instructor or in another industry, such as construction or landscaping. Second jobs are possible because firefighters often work extended shifts, sometimes in excess of 24 hours, but with several rest days between shifts (Billings & Focht, 2016). [Career firefighters may also serve as volunteer firefighters in their community. Second jobs outside of the fire service discipline are not included as part of the agent under evaluation (i.e. occupational exposure as a firefighter). The proportion of firefighters with second jobs probably varies throughout the world.]

The present monograph will consider studies spanning firefighting activities from 1915 to the present. The occupation of firefighting has changed over this period, and advances in PPE and other control technologies may have reduced firefighters' exposures; however, the introduction of synthetic materials (e.g. foams, plastics, and glues in engineered wood products) has resulted in fire smoke that contains additional and more abundant hazardous chemicals and fires that propagate more rapidly (Kerber, 2012; Pedersen et al., 2019) (see Section 1.2 for more information on how the fire service has changed over time). Chemicals (e.g. PFAS) added to materials and equipment used by firefighters may also add to their potentially harmful exposures. The present evaluation was focused primarily on exposures (e.g. combustion products including particulates and metals, PAHs, volatile organic compounds (VOCs), semi-volatile organic compounds (sVOCs), PFAS, flame retardants, diesel exhaust, heat, UV and other radiation, and shift work) that commonly apply across the firefighting occupation and could potentially have an impact on carcinogenesis (see Table 1.1 for potential firefighter exposures classified by IARC). Highly specific exposures that would be rare for the rest of the firefighting discipline (e.g. ionizing radiation from nuclear accidents) or other known hazards that are unlikely to be directly associated with carcinogenesis (e.g. noise and psychosocial factors) are only briefly reviewed here.

1.2 Qualitative information about firefighting

1.2.1 Types of firefighter and firefighting activity

A firefighter is an individual who has been educated and trained in the prevention and suppression of fires that threaten life, property, and the environment. The fire service can be made up of different firefighter occupational subgroups and specializations, such as municipal firefighters, volunteer firefighters, fire trainers, wildland firefighters, WUI firefighters, fire cause investigators, and industrial, airport, or military firefighters. In some countries, firefighters may be

Table 1.1 Potential exposures in firefighting that have been evaluated by IARC

Exposure	Overall evaluation (IARC Group)[a]	Volume	Year	Evaluation for cancer in humans	
				Cancer sites with *sufficient* evidence in humans	Cancer sites with *limited* evidence in humans
Acetaldehyde	2B	71	1999		
Acrolein	2A	128	2021		
Acrylonitrile	2B	71	1999		
Arsenic and inorganic arsenic compounds	1	100C	2012	Lung, urinary bladder, skin	Liver, bile duct, prostate, kidney
Asbestos (all forms)	1	100C	2012	Larynx, lung, mesothelium, ovary	Pharynx, stomach, colon, rectum
Benz[*a*]anthracene	2B	92	2010		
Benzene	1	120	2018	AML, other acute non-lymphocytic leukaemia	Lung, childhood AML, chronic myeloid leukaemia, chronic lymphocytic leukaemia, NHL (all combined), multiple myeloma
Benzo[*b*]fluoranthene	2B	92	2010		
Benzo[*j*]fluoranthene	2B	92	2010		
Benzo[*k*]fluoranthene	2B	92	2010		
Benzofuran (coumarone)	2B	63	1995		
Benzo[*a*]pyrene	1	100F	2012		
Bromochloroacetic acid	2B	101	2013		
1-Bromopropane	2B	115	2018		
1-Bromo-3-chloropropane	2B	125	2020		
1,3-Butadiene	1	100F	2012	Leukaemia (all combined), lymphoma (all combined), multiple myeloma or haematolymphatic organs	
Cadmium and cadmium compounds	1	100C	2012	Lung	Prostate, kidney
Carbon black (total)	2B	93	2010		
Carbon nanotubes, multiwalled MWCNT-7	2B	111	2017		
2-Chloronitrobenzene	2B	123	2020		
4-Chloronitrobenzene	2B	123	2020		
Chromium(VI) compounds	1	100C	2012	Lung	Nasal cavity and paranasal sinus
Chrysene	2B	92	2010		
Cobalt(II) oxide	2B	131	2023		
Crotonaldehyde	2B	128	2021		
Dibenz[*a*,*h*]anthracene	2A	92	2010		

Table 1.1 (continued)

Exposure	Overall evaluation (IARC Group)[a]	Volume	Year	Evaluation for cancer in humans	
				Cancer sites with *sufficient* evidence in humans	Cancer sites with *limited* evidence in humans
Dibenzo[*a*,*i*]pyrene	2A	92	2010		
Dibromoacetic acid	2B	101	2013		
1,3-Dichloro-2-propanol	2B	101	2013		
Dichloroacetic acid	2B	106	2014		
Dichloromethane (methylene chloride)	2A	110	2017		Bile duct, NHL (all combined)
2,4-Dichloro-1-nitrobenzene	2B	123	2020		
1,4-Dichloro-2-nitrobenzene	2B	123	2020		
1,2-Dichloropropane	1	110	2017	Biliary tract (cholangiocarcinoma)	
Diethanolamine	2B	101	2013		
N,*N*-Dimethylformamide	2A	115	2018		Testis
Engine exhaust, diesel	1	105	2014	Lung	Urinary bladder
Engine exhaust, gasoline	2B	105	2014		
Ethyl acrylate	2B	122	2019		
Ethylbenzene	2B	77	2000		
Ethylene oxide	1	100F	2012		Breast, chronic lymphocytic leukaemia, NHL (all combined), multiple myeloma
Formaldehyde	1	100F	2012	Nasopharynx, AML, other acute non-lymphocytic leukaemia, chronic myeloid leukaemia	Nasal cavity and paranasal sinus
Furan	2B	63	1995		
Hepatitis B virus	1	59	1994	Liver	Bile duct, NHL (all combined)
Hepatitis C virus	1	59	1994	Liver, NHL (all combined)	Bile duct
HIV type 1	1			Anus, uterine cervix, endothelium (Kaposi sarcoma), eye, Hodgkin lymphoma, NHL (all combined)	Liver, skin (malignant non-melanoma), vulva, vagina, penis
Hydrazine	2A	115	2018		Lung
Indeno-1,2,3-[*cd*]pyrene	2B	92	2010		
Isoprene	2B	71	1999		
Lead compounds, inorganic	2A	87	2006		Stomach
Molybdenum trioxide	2B	118	2018		
3-Monochloro-1,2-propanediol	2B	101	2013		
Naphthalene	2B	82	2002		

Table 1.1 (continued)

Exposure	Overall evaluation (IARC Group)[a]	Volume	Year	Evaluation for cancer in humans	
				Cancer sites with *sufficient* evidence in humans	Cancer sites with *limited* evidence in humans
Nickel compounds	1	100C	2012	Lung, nasal cavity, paranasal sinuses	
Night shift work	2A	124	2020		Breast, prostate, colon, rectum
2-Nitroanisole (*ortho*-nitroanisole)	2A	127	2021		
Perfluorooctanoic acid (PFOA)	2B	110	2017		Testis, kidney
Polybrominated biphenyls	2A	107	2016		
Polychlorophenols	2B	71	1999		
2,3,4,7,8-Pentachlorodibenzofuran	1	100F	2012	All cancers combined	
3,4,5,3′,4′-Pentachlorobiphenyl (PCB-126)	1	100F	2012		
Pentachlorophenol	1	117	2019	NHL	
2,4,6-Trichlorophenol	2B	117			
Polychlorinated biphenyls	1	107	2016	Malignant melanoma	
Pyridine	2B	119	2019		
Radioactivity (γ activity)	1	100D	2012	All sites combined	
Radionuclides (α-particle-emitting)	1	100D	2012	All sites combined	
Radionuclides (β-particle-emitting)	1	100D	2012	All sites combined	
Silica (crystalline: quartz or cristobalite)	1	100C	2012	Lung	
Styrene	2A	121	2019		Leukaemia (all combined), lymphoma (all combined), multiple myeloma
Styrene-7,8-oxide	2A	121	2019		
Sulfuric acid[b]	1	100F	2012	Larynx	
Tetrabromobisphenol A	2A	115	2018		
2,3,7,8-Tetrachloro dibenzo-*para*-dioxin (2,3,7,8-TCDD)	1	100F	2012	All cancer sites combined	Lung, soft tissue, NHL
Tetrachloroethylene (perchloroethylene)	2A	106	2014		Urinary bladder
1,1,1-Trichloroethane	2A	130	2022		Multiple myeloma
Toluene diisocyanates	2B	71	1999		
Trichloroethylene	1	106	2014	Kidney	Liver, bile duct, NHL (all combined)
Trichloromethane (chloroform)	2B	73	1999		

Table 1.1 (continued)

Exposure	Overall evaluation (IARC Group)[a]	Volume	Year	Evaluation for cancer in humans	
				Cancer sites with *sufficient* evidence in humans	Cancer sites with *limited* evidence in humans
Trivalent antimony	2A	131	2023		Lung
Ultraviolet radiation	1	100D	2012	Cutaneous malignant melanoma, squamous cell carcinoma of the skin, basal cell carcinoma of the skin	
Vinyl chloride	1	100F	2012	Angiosarcoma of the liver, hepatocellular carcinoma	
Vinylidene chloride	2B	119	2019		

AML, acute myeloid leukaemia; HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma.

[a] Group 1, *carcinogenic to humans*; Group 2A, *probably carcinogenic to humans;* Group 2B, *possibly carcinogenic to humans*.

[b] Strong inorganic acid mists.

trained to serve in many of these subgroups (i.e. wildland, municipal, investigation, etc.), whereas in other countries, a fire department (also known as a fire brigade) may have a workforce with firefighters working solely in one subgroup. [The Working Group noted that the tasks carried out by firefighters have changed over time, which may influence exposures. In particular, medical emergency call responses have been an increasing responsibility for firefighters in some countries.]

(a) Employment status of firefighters

The International Association of Fire and Rescue Services reported that there are more than 15 million firefighters (including 1.49 million career firefighters) in 57 countries, including most high-income countries and some low- and middle-income countries, such as China (CTIF, 2021; see Table S1.2, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). In the USA, two thirds of firefighters are volunteers or part-time paid per call (which includes paid on-call or paid per call) (Fahy et al., 2021). In England, about one third of firefighters are retained (i.e. paid on-call) (United Kingdom Home Office, 2021a). Higher proportions of all firefighters were reported to be volunteers in the Netherlands (80%), Canada (83%), and Australia (89%) (Haynes & Stein, 2018; Australian Government Productivity Commission, 2022; CBS, 2022). Career and volunteer firefighters perform the same basic jobs and tasks, but career firefighters usually work more hours and may have more advanced training than do volunteers (Hwang et al., 2019a; Fahy et al., 2021; NFPA, 2022). Volunteer firefighters are likely to attend fewer fires on average than do career firefighters (Monash University, 2014), but this is not always the case (Fig. 1.1).

[The Working Group noted that payment structures and employment status vary by country and that some fire departments may contain both volunteer and career firefighters.] Volunteer firefighters may not have the same resources as career firefighters. For example, in some geographical locations in the USA, volunteer firefighters are less likely than career firefighters to be equipped with turnout gear, helmets, and even SCBA that are compliant with the recommendations of the National Fire Protection Association (NFPA). Volunteers also tend to be firefighters in smaller departments, in more rural communities, and may lack the resources or finances to properly maintain or decontaminate their equipment or safety gear (Hwang et al., 2019a; NFPA, 2022). [The Working Group noted that it is not well understood how these organizational factors impact volunteer firefighters' exposures.]

(b) Minority and under-represented groups

Traditionally, the firefighter workforce has been a male-dominated profession. Women are under-represented in firefighting (see Table S1.2, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Among career firefighters, the proportion of women in the workforce reported ranged from 2% (Germany) and 4% (USA, Canada) up to 8% (New Zealand) (Statistics Canada, 2018; Fire and Emergency New Zealand, 2021; German Network of Female Firefighters, 2022). In an Australian cohort study covering employment from pre-1970 to 1995 and later, 4% of the full-time career firefighters and 8% of part-time career firefighters were women (Monash University, 2014). Among volunteer firefighters, 10% were women in the USA and Germany (Fahy et al., 2021; German Network of Female Firefighters, 2022). In Australia, this was 19% (Monash University, 2014). Among all firefighters in Portugal, 13% were reported to be women (Lam, 2009).

Minority groups (e.g. racial and/or ethnic groups that make up a small proportion of the regional or national population being studied) are also often under-represented in firefighting.

Fig. 1.1 Distribution of the number of incidents attended by individual firefighters (career full-time and part-time and volunteer)

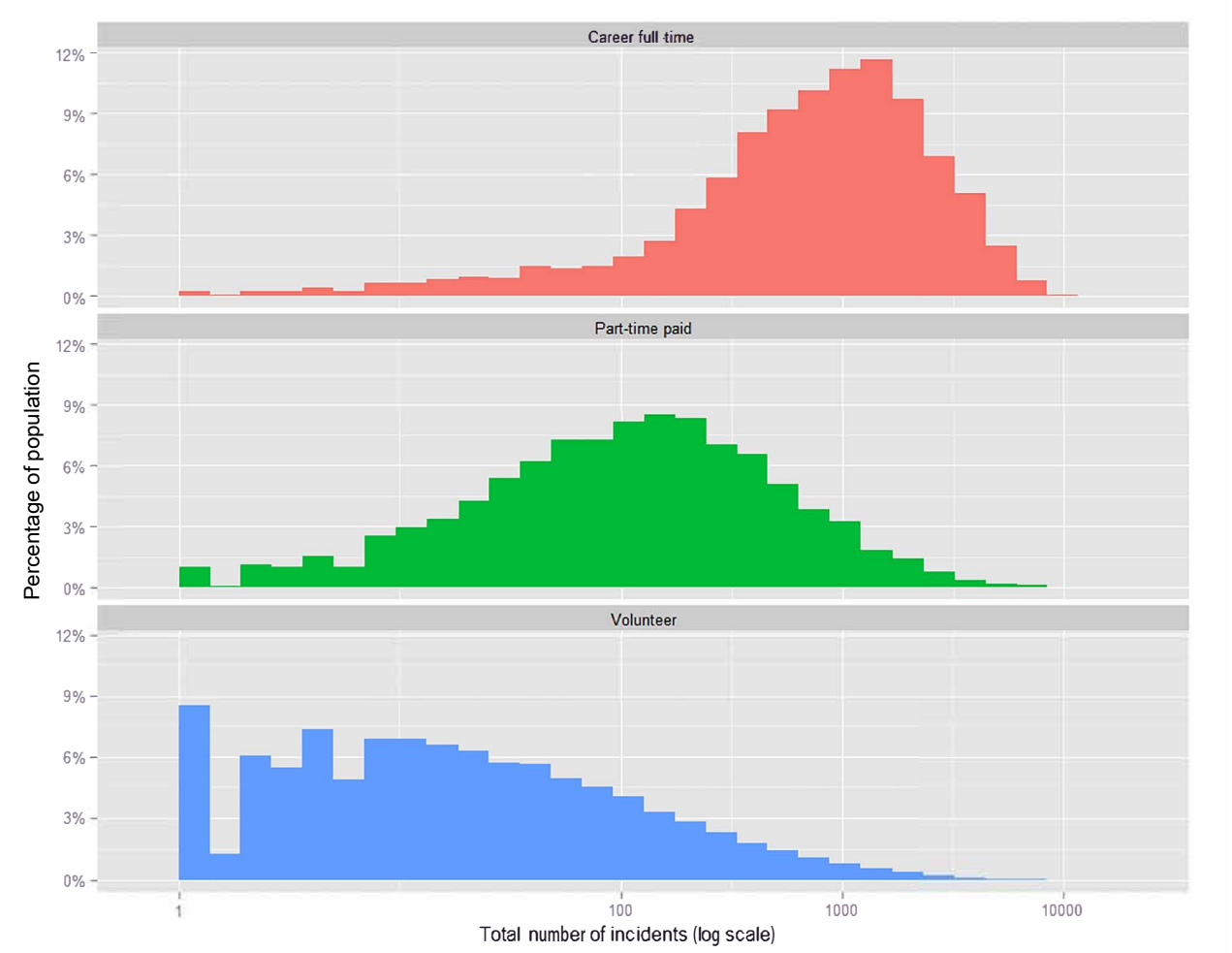


Fig. 1.1 shows that most career full-time firefighters attended more incidents than did part-time firefighters, and the volunteer firefighters attended fewer incidents than did part-time firefighters. For career full-time, volunteer, and part-time firefighters, respectively, 47%, 53%, and 78% of incidents attended were fires.
From Monash University (2014), with permission.

In the USA, the Bureau of Labor Statistics documented that in 2015 more than 1.2 million people were employed as firefighters and other first responders; the majority were White, non-Hispanic men, and aged between 25 and 54 years (Schafer et al., 2015). In England in 2020, 93% of firefighters were men and only 4% were members of an ethnic minority group (United Kingdom Home Office, 2021b). [The Working Group has identified a lack of information on firefighter exposures by race, ethnicity, and sex.]

(c) Municipal firefighters

Municipal (also referred to in the literature as "structural" or "urban") firefighters are an occupational subgroup of firefighters who engage in activities of fire suppression, rescue, and property conservation in buildings and

enclosed structures that are involved in a fire or emergency situation. These firefighters may work for urban, suburban, or rural fire departments or agencies, and may have complex and variable work histories and exposures because of their changing occupational roles and fire responses (Fahy et al., 2021).

Potential assignments for firefighters at a structure fire incident include attack, search and rescue, outside ventilation, overhaul, backup or rapid intervention, engineer or pump operation, rehabilitation, and incident command (US Fire Administration, 2008; Fent et al., 2017) (Fig. 1.2, Fig. 1.3). Attack involves advancing a hose line and suppressing all active fire. Search and rescue may involve forcible entry into the structure and then a search for any victims. Outside ventilation typically involves creating openings at the windows and roof for horizontal and vertical ventilation of smoke and gases. Backup teams often set up a second hose line and are available for additional suppression or support as needed. Rapid intervention teams typically set up just outside the structure and are available for emergency rescue or support services as needed. Overhaul is performed after the fire has been suppressed and involves the active search for and suppression of any residual flames or smouldering items that could reignite the fire. Rehabilitation is a component of incident response in which firefighters are typically checked after an interior fire response and hydrated to prevent more serious conditions such as heat exhaustion or heat stroke. The engineer (also known as a vehicle/pump operator or chauffeur) is responsible for operating the pump and ensuring that hose lines are charged, and the incident commander directs the response activities (US Fire Administration, 2008; Horn et al., 2018; Engel, 2020).

Other job assignments are possible depending on the size and height of the structure and spread of the fire, the capabilities and resources of the responding fire companies, and incident management at the scene. A structure fire response may be very different in low- and middle-income countries where resources and technology are limited. For example, interior fire attack and search and rescue are mainly possible where firefighters have the appropriate PPE, such as coat, trousers, gloves, boots, helmet, and SCBA. [The Working Group noted that little research on job assignments and fire structures in low- and middle-income countries, including detailed information on safety gear and PPE, was available in the literature.] In addition to responding to structure fires, firefighters can respond to other emergencies, e.g. vehicle and waste container (dumpster) fires, building collapse, and medical emergencies (Kinsey & Ahrens, 2016), and have other specialities within their department, including emergency medical technician, paramedic, urban search and rescue, and hazardous materials ("hazmat") specialist (Miami Dade College, 2022).

(d) Life at the fire station

Municipal firefighters are typically assigned to a fire hall or station that mimics a residential home and includes a kitchen, living room, shower facilities, and sleeping quarters (Kitt, 2009; Markham et al., 2016). Typically, firefighters will start their shift conducting daily equipment checks, preparing their PPE and equipment, and liaising with the outgoing shift. During their shift, firefighters may perform station duties (cleaning, maintenance, cooking), engage in physical activity, participate in training activities, and have free time, depending on the number of emergency events received during their shift. Firefighters often work extended shifts (Section 1.5.2), so some departments allow firefighters to sleep during shifts (Firefighter Connection, 2022).

(e) Wildland firefighters

Wildland firefighters are tasked with combatting and preventing wildfires in wildlands and at the WUI (Theobald et al., 2007; Mell et al., 2010).

Fig. 1.2 Municipal firefighters during exterior attack of a structure fire

Fighting structure fires involves suppressing active fires and advancing a hose line.
From © Scott Stilborn/Ottawa Fire Services.

Fig. 1.3 Firefighter performing overhaul

Overhaul involves the suppression of any remaining flames or smouldering items after the main fire has been suppressed.
From Professor Anna A. Stec, Centre for Fire and Hazards Sciences, University of Central Lancashire, UK.

They may be career or volunteer firefighters and are often seasonal workers. Deployments of thousands of wildland firefighting personnel to wildfires have been reported within a single country across a fire season (e.g. 7373 firefighters during the 2019–2020 Australian bushfires) (Parliament of Australia, 2020) or on single days (e.g. in the USA) (NIFC, 2022a). [Data on the number of wildland firefighters are not systematically documented in most countries. In the USA, estimates of the number of wildland firefighters employed by federal agencies are around the tens of thousands (Butler et al., 2017; Broyles et al., 2019).]

Factors that may have an impact on exposure, including fire behaviour, release of fire effluents, and firefighting technique, may vary across wildfires, since wildfires occur in wildlands with varying vegetation types (e.g. peat forest, conifer forest, grassland) and sometimes in the WUI, with structures and vehicles that also contain synthetic materials (HomChaudhuri et al., 2010; Caton et al., 2017; Cruz et al., 2018; Kganyago & Shikwambana, 2020). In addition to wildfire suppression, wildland firefighters carry out fire prevention by performing prescribed burns, which are controlled fires that are intentionally set to achieve resource management objectives, including fuel reduction and ecological purposes (Navarro et al., 2019a). [It is likely that the cumulative occupational smoke exposure of wildland

firefighters has been increasing since the annual acreage of wildfire burns (NIFC, 2022a), number of workdays spent at wildfires per year (Navarro et al., 2019a), and/or the total area of land managed by prescribed burns (NIFC, 2022a) have probably increased, as trends in the USA indicate. Similar trends have also been observed in other countries (see Section 1.2.2).]

Job assignments during wildland fire responses differ substantially from structure fire responses (Semmens et al., 2016; Belval et al., 2017). However, municipal firefighters in areas where wildfires are common (e.g. western USA and parts of rural Australia) may be trained and involved in wildfire response activities, and 86% of the 26 000 local (municipal) fire departments in the USA in 2010 were estimated to have wildland firefighting duties (Butler et al., 2017). Wildland firefighters working at wildfires and prescribed burns are typically assigned to hand crews or engine crews (Department of Interior, 2022). Hand crews are responsible for clearing brush and other burnable vegetation along the expected pathway of the fire to construct a fire line or linear fire barrier. Hand crews often use gasoline-powered chainsaws, shovels, and other hand tools to construct the fire line; this is strenuous, time-consuming work and may involve hiking long distances (Reinhardt & Ottmar, 2004; Williamson et al., 2016). After a fireline has been secured, mop-up can proceed; this involves the extinction of any burning or smouldering vegetation, usually by covering the material with soil. Mop-up may also involve the removal of partially burned vegetation, including the felling of standing dead trees (USDA Forest Service, 2021b). Wildland firefighters may also use hand drip torches fuelled by a mixture of gasoline and diesel for backfiring (burning out unburned fuels between an active wildfire and a defensible perimeter) during wildfire suppression or for lighting vegetation during prescribed burns or backburns (Reinhardt & Ottmar, 2004; Adetona et al., 2019; McCormick & May, 2021).

Engine crews work with diesel-powered fire engines that carry water or foam and are used to suppress active fires where access is possible (USDA Forest Service, 2021c). There are other speciality disciplines in wildland firefighting, such as smoke jumpers and helitack crews, who parachute, rappel, or land near the wildfires to provide more targeted interventions (USDA Forest Service, 2021d). [Numerous other tasks beyond those discussed here may also be carried out to control the spread of wildfires or manage prescribed burns.]

Wildland firefighters usually carry their equipment with them in backpacks and wear light protective clothing, such as long-sleeved fire-resistant shirts, trousers, and gloves, mountaineering boots, and hard hats. Respiratory protection is not commonly used (see Fig. 1.4). However, the type of protective gear worn and the way in which wildfires are managed may differ between countries.

Studies have shown that wildland firefighters are exposed to high physiological workloads, extended work hours, and dangerous environmental weather extremes (Carballo-Leyenda et al., 2017; Vincent et al., 2017; Hemmatjo et al., 2018). During a wildfire, these fire crews must provide around-the-clock fire suppression to protect life and property, which may last days, weeks, or months. For example, there is a standard 14-day wildfire assignment for federally employed wildland firefighters in the USA, but this may be extended up to 30 days (with a 2-day break in the middle of the period) under certain circumstances (NWCG, 2004). These extended response times in remote locations not only increase exposure duration, but also make it difficult to clean protective clothing and skin (Cherry et al., 2019). Wildland firefighters are temporarily housed at base camps in the proximity of wildfires during fire suppression deployments (McNamara et al., 2012). They may experience additional exposures at these base camps because of the transport of wildfire smoke

Fig. 1.4 Wildland firefighter during a controlled forest fire in northern Portugal

It is common for wildland firefighters not to wear self-contained breathing apparatus, despite proximity to fire effluents.
From Marta Oliveira (4FirHealth Research Team).

plume over the camps, vehicle and power generator exhausts, and road dust (McNamara et al., 2012).

(f) Fire instructors

Fire instructors play a critical role in the development and training of firefighters (Reeder & Joos, 2019). When the firefighter recruit begins training, their first experience with live or simulated fire is led by an instructor. In many countries, a fire instructor is required to possess certification as a fire service instructor and/or subject matter expertise in subject areas of fire science demanded by fire departments and organizations. Fire service instructors teach in both classroom and laboratory settings (training grounds) from prepared lesson plans and under the direct supervision of or in collaboration with another senior fire service instructor (IFSTA, 2022). Fire instructors can be involved in multiple fire-training exercises on a given day.

Live-fire training may involve different types of fuel. Live-fire training environments in which an unconfined open flame or device propagates fire to the building or structure are designed to simulate the operational fire environment, but

the specific chemical exposures to instructors may be quite different from those of real-world fires (Kirk & Logan, 2015a). For example, using plywood and chipboard as the fuel in training fires produces more pollutants than do pure pine or spruce, whereas the exposures measured during propane-burning training fires are lowest (Laitinen et al., 2010). A different study found that training exercises burning a certain type of oriented strand board (as well as pallet and straw) produced higher concentrations of certain chemicals (some of those already classified by IARC as *carcinogenic to humans*, Group 1) than did training exercises burning pallet and straw alone (Fent et al., 2019a).

Fire instructors may also experience cumulative exposure to air contaminants that far exceeds that of firefighters in operational fire environments (Kirk & Logan, 2015a; Fent et al., 2019a). Additionally, the behaviours and role of fire instructors in the training environment are different from those at an active fire scene. The non-emergency situation may not elicit the same work rate and physiological response, therefore increasing the length of exposure to chemicals (Kirk & Logan, 2015a). [The Working Group noted that evaluating the difference between air contaminant concentrations in the training environment and those in the microenvironment inside the instructor's firefighting ensemble, from which the majority of dermal uptake would occur, has received little research attention.]

(g) Fire cause investigators

A smaller subgroup of the firefighter workforce comprises fire cause investigators, who have responsibility for investigating and analysing incidents involving fires and explosions (NFPA, 2021c). They conduct root cause analysis of fire incidents and render an expert opinion as to the origin, cause, responsibility for, or prevention of fire incidents. Fire cause investigators are educated and trained in several topics, including fire science, fire chemistry, thermodynamics, thermometry, fire dynamics, explosion dynamics, computer fire modelling, and fire investigation and analysis (IAAI, 2018).

Fire cause investigators may work in either the public or private sector. Typically, those in the public sector are employed by municipalities, such as fire or police departments, or by state or federal agencies. Those working in the private sector may be employed by insurance companies, lawyers, or private firms. Many fire investigators come up through the firefighter ranks, starting out as municipal firefighters, and gaining experience in various aspects of fire behaviour before specializing in fire cause investigations. Some may begin in law enforcement and gain experience or training in arson investigations but do not necessarily have any direct firefighting experience (Belfiglio, 2022). Only fire cause investigators who have worked as or are working as firefighters are considered in the present monograph.

Although fire cause investigators usually report to the fire scene to conduct their analysis immediately after either the fire suppression and overhaul phases of a fire incident response, their attendance and investigation can be delayed hours or days post-fire suppression (Horn et al., 2022). A fire investigation can take from a few days up to a few months (Firefighter Insider, 2022). Fire cause investigators will use scientific methods to systematically review the fire scene, determine the circumstances as to the cause of the fire, and issue a determination, such as natural, deliberate, accidental incendiary, or undetermined cause (Daeid, 2005). Depending on the jurisdiction and standard operating procedures for the fire department, a fire investigator may use different approaches to conduct the investigation. Fire cause investigators generally attend more fire scenes than do most firefighters; however, they typically wear less PPE than firefighters, despite potentially harmful exposures at the investigation scene well after the fire is extinguished. [The Working Group noted that little research on

exposure of fire cause investigators in high-income countries or in low- and middle-income countries (including the use of safety gear and PPE) was available in the literature.]

(h) Other subspecialities in the fire service

Firefighters can be employed in other work settings, including airports, military environments, and industrial complexes. Aviation rescue and firefighting is a type of firefighting that involves the emergency response, mitigation, evacuation, and rescue of passengers, crew, and property from aircraft involved in aviation accidents and fire incidents (Braithwaite, 2001; Smith et al., 2018). Although variations across countries can occur, airports with scheduled passenger flights are required to have firefighters and firefighting apparatus at the airport ready to respond at any time to an aircraft fire incident (Blocker, 2020). Airports may have regulatory oversight by an arm of their individual national governments or voluntarily under standards of the International Civil Aviation Organization (National Academies of Sciences, Engineering, and Medicine, 2011). Military firefighters are first responders in emergencies and may be required to perform fire suppression activities, rescue operations during a fire or other emergencies, or respond to hazardous spills in the military environment or war theatre (Moore et al., 2022). Industrial firefighters are specially trained firefighters who serve at manufacturing facilities, petrochemical plants, and refineries, among other industrial settings (Shelley et al., 2007; Ghasemi et al., 2021). They encounter unique challenges not commonly encountered by municipal firefighters, such as site-specific hazards, access areas, equipment, business priorities, and personnel, that will impact their fire suppression approach and tools at the industrial fire.

Firefighters at airports use AFFFs to extinguish class B fires, which are fires that arise from petroleum products or flammable liquids or gases, such as oil, gasoline, jet fuel, and other fuels (Rotander et al., 2015b; Milley et al., 2018; Environmental Litigation Group PC, 2020) (see Fig. 1.5). Until 2021, airports in the USA were required to use AFFF that contains fluorinated surfactants (Andrews et al., 2021; Shepardson, 2021). Additional information on PFAS use is included in Section 1.5.1(b). All United States (US) military branches were required to use fluorinated firefighting foams at bases located in the USA. Fluorinated AFFFs have also been used in other countries, such as Germany, Sweden, and the United Kingdom (UK) (Hu et al., 2016; Allcorn et al., 2018; Nordic Council of Ministers, 2019). Local municipalities also use and store AFFF. In the USA, almost 75% of AFFF is used by the military, and the remaining 25% is used by organizations such as refineries, fuel tank farms, municipal airports, and other industries (Andrews et al., 2021; Environmental Litigation Group PC, 2020). See Section 1.7 for regulations on use of firefighting foams.

1.2.2 Changes in frequency and intensity of fires

[Global trends in structure fires are difficult to ascertain because fire statistics are not available in all countries. These statistics do not include training fires or chemical incidents, which may also contribute to firefighters' exposures.] In the USA, there were 4.2 fires per 1000 population in 2020, which is about the same rate as in 2010, but more than 60% lower than the rate in 1980. Of those fires, approximately 35% were structure fires, 15% were vehicle fires, and 50% were outdoor or vegetation fires (Ahrens & Evarts, 2021). In England, firefighters responded to more than 151 000 fires in the year ending March 2021, which is a 34% decrease compared with 10 years previously. More than 40% of those fires occurred in a building, vehicle, or outdoor structure, or involved a fatality or casualty (Government of the United Kingdom, 2021). In Australia, there was a trend towards increased

Fig. 1.5 Firefighters using fire suppression foam on a class B fire at an airport

From Rich/Adobe Stock.

frequency of bushfires between 2011 and 2016 (Bushfire and Natural Hazards CRC, 2019). In Asia, Tishi & Islam (2018) reported that of all the fires in Bangladesh in the years 2010–2013, the fire incidence in Dhaka Metropolitan Area corresponded to the mean of [16.5%], and the highest frequency (36%) occurred in residential areas. The highest density of fire incidents occurred in areas of commercial and mixed use (38% and 26%, respectively). For other regions, e.g. Latin America and Africa, no information was available.

[Wildfire statistics are presented both on area burned and number of fires, and these may appear contradictory.] In southern Europe (Portugal, Spain, France, Italy, and Greece), the annual area burnt in forest fires has decreased from around 600 000 hectares in the 1980s to less than 400 000 hectares in the 2010s (San-Miguel-Ayanz et al., 2022). From the 1950s to the 2000s, the average annual area burnt in forest fires in Finland has decreased from 5760 hectares to 643 hectares (Suokas, 2015). According to one analysis, the global area burned by wildfires appears to have declined overall over past decades; however, the probability and severity of wildland fire is increasing in some regions of Europe (Doerr & Santín, 2016; Fernandez-Anez et al., 2021; San-Miguel-Ayanz et al., 2022).

Other analyses also suggest that the frequency of wildfires is increasing in some parts of the world. In the UK, peat, grass, and

wildfires are becoming increasingly common, reflecting the changing weather patterns that are making the UK hotter and drier (Belcher et al., 2021). According to the European Forest Fire Information System, there is wide variation in the number of wildfires and the area burned each year (San-Miguel-Ayanz et al., 2022). Spatial and temporal trends in the incidence and severity of wildfires in Canada is tracked by the Canadian National Fire Database (Government of Canada, 2021); more than 8000 fires per year burn an average of more than 2.1 million hectares. Recent research suggests that climate change is responsible for noteworthy increases (i.e. 1.5- to 6-fold) in the frequency of extreme burning conditions and, by extension, the incidence and severity of wildfires in Canada (Coogan et al., 2020).

During the last decade, the USA has experienced exceptionally large fires, California being one of the most affected regions (Keeley & Syphard, 2021; State of California, 2021). During the 2017 wildfire season, a total of 71 499 wildfires was reported in the USA (National Interagency Coordination Center, 2017). These wildfires consumed 10 026 086 acres [4 057 413 hectares] of land (153% of the 10-year average) nationally and a total of 12 306 structures were destroyed, meaning that the 2017 wildfire season was the worst on record in terms of total structures lost. In Australia, the length and severity of the wildfire season are also increasing across much of the country, as measured by annual indices of the Forest Fire Danger Index (AFAC, 2021). Regarding Latin America, some studies suggest that there has been an increase in the frequency and length of wildfires over the last decade (González et al., 2018; Urrutia-Jalabert et al., 2018; Barni et al., 2021).

WUI fires are similarly becoming more common (Mell et al., 2010; Stein et al., 2013; Ribeiro et al., 2020). In the USA, significantly destructive WUI fires occurred in Florida in 1998, and in California in 2003, 2007, and, most recently, 2017. WUI fires have also had an impact in Europe, particularly in Portugal, France, Spain, and Greece. This has resulted in large losses of property and numerous human casualties (Ferreira-Leite et al., 2013; Darques, 2015; Tedim et al., 2015; Cardoso Castro Rego et al., 2018; Oliveira et al., 2020a).

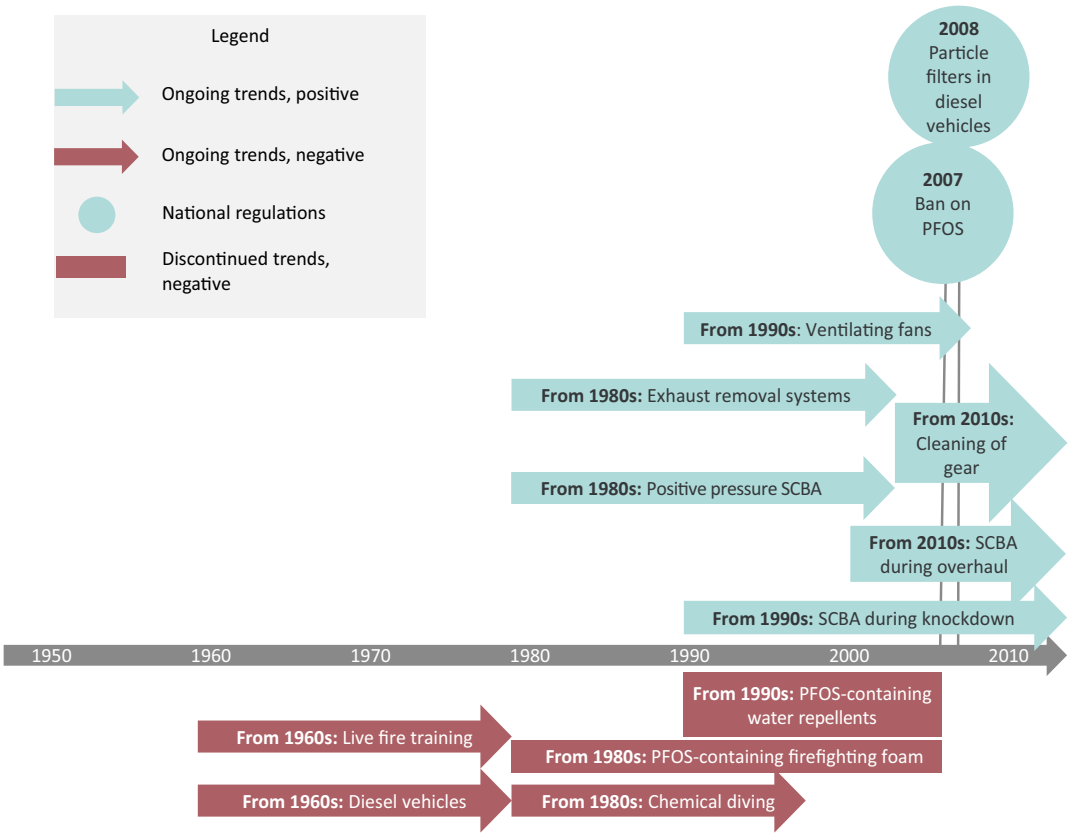
1.2.3 Temporal changes in personal protective equipment

The types of respiratory and dermal protection worn by municipal firefighters have changed over time. A major advancement in respiratory protection occurred around the 1960s when compressed-air demand-type SCBA was adapted for use by municipal firefighters, although it took another decade or longer for these respirators to gain widespread acceptance and use among fire departments (Spelce et al., 2018; Pedersen et al., 2019; London Fire Brigade, 2022). Many firefighters now wear SCBA during overhaul, but this was not common practice before the 2000s (Jakobsen et al., 2020) (see Fig. 1.6 for work-related trends observed in fire departments in Norway). [The Working Group noted that variability in this practice probably exists in fire departments throughout the world.]

Personal protective clothing has also changed from long rubber trench coats and three-quarter length rubber boots to the first iterations of modern turnout gear consisting of full-length trousers and jacket made of multiple layers of protective textiles capable of meeting heat-resistance and other performance specifications in the early 1970s (with broad adoption and standardization occurring over the next 10–20 years) (British Standards Institution, 2006, 2019b, 2020; Hasenmeier, 2008; NFPA, 2018). [Before the late 1970s, it is possible that asbestos was used in firefighter PPE; there are reports of asbestos in helmet covers (Lumley, 1971), respirators, and protective clothing.]

Fire departments began adding protective hoods to the turnout gear ensemble in the 1990s

Fig. 1.6 Changes in work conditions for firefighters from the 1950s until 2010 in Norway



PFOS, perfluorooctane sulfonate; SCBA, self-contained breathing apparatus.
Timeline of changes in policies, standards, or practices that have probably had an impact on carcinogenic exposures for firefighters in Norway. Many of these changes have also been undertaken for firefighters in other countries over similar periods. Chemical diving is part of the clean-up under water after chemical spills or accidents and firefighters/hazardous materials specialists wear special protective equipment.

(Prezant et al., 2001). In the late 2010s, PFAS were identified as constituents in the manufacture of firefighting turnout gear in the USA (Peaslee et al., 2020).

Greater awareness of contamination of turnout gear resulting from firefighting activities developed in the 2010s. New policies and procedures on turnout-gear cleaning after firefighting activities soon followed. According to a survey of fire departments in Norway, since the 1990s every department (n = 16) has responded that turnout gear should be washed after it has been used in a contaminated environment (Jakobsen et al., 2020). [However, variability in this practice probably exists in fire companies throughout the world. In addition, some firefighters perform on-scene gross decontamination of their gear, some launder their gear, and some do both after use in a contaminated environment. Having a second set of turnout gear and onsite extraction washers is also helpful for allowing this practice, which is not common in under-resourced fire departments.] See Section 1.6 for more information on PPE cleaning practices.

1.2.4 Other temporal changes that could affect firefighters' exposures

Building materials and the items within buildings have also changed over time (Stec & Hull, 2008; Stec et al., 2019; Jones et al., 2021; Peck et al., 2021). Once built and furnished with natural materials, like wood, clay, cotton, wool, and minerals (including asbestos), residential and commercial structures today commonly include laminated or engineered wood products (e.g. containing glues and resins), polymeric cladding, and numerous other synthetic materials, such as plastics and foams. These synthetic materials, along with open floor plans, can cause the fires to propagate, consume oxygen, and produce toxic gases at much faster rates than in the past (Stec & Hull, 2011; Kerber, 2012; McKenna et al., 2019; Stec et al., 2019). Some of these synthetic materials also contain chemical additives to provide certain desirable properties, such as plasticizers (e.g. phthalates), stain-resistant coatings (e.g. PFAS), and flame retardants (e.g. organophosphorus compounds). These substances may present their own unique exposure hazards. Foam insulation used within or outside the building envelope can also contribute to fire spread (e.g. the Grenfell Tower in London, UK) (Grenfell Tower Inquiry, 2019; McKenna et al., 2019; Jones et al., 2021; Peck et al., 2021). [Although asbestos is no longer used as an insulating material, and lead is no longer used in paint (having been banned for more than four decades in most countries), these compounds are likely to be present in many older homes and buildings and could still be released during structure fires.]

Diesel engines were largely introduced in the 1960s, hence diesel exhaust exposure has been prevalent in the fire service since that time. However, fire departments began installing diesel-exhaust capture systems in the 1980s to control these exposures in the apparatus bays (see Fig. 1.7). [The Working Group noted that the implementation of diesel-exhaust capture systems in fire stations has taken time and varies between and within geographical locations. Fire stations in low- and middle-income countries are unlikely to have these systems, and even some stations in high-income countries (especially in under-resourced departments) may not have them. The efficacy of these systems is highly dependent on proper use and maintenance (Chung et al., 2020).] More recently (in the mid-2000s), diesel-engine emission controls (e.g. diesel particulate filters) became available in the marketplace (IARC, 2013; Jakobsen et al., 2020). Battery electric vehicles (BEV) are now available, including BEV or hybrid-electric fire trucks, which may also reduce diesel exhaust exposure for fire personnel. Additional controls that have been implemented include general exhaust ventilation, diesel fuel additives, separations between the vehicle bay and living quarters, and various administrative policies, such as idling restrictions. See Section 1.5.1(d) for more information on diesel exhaust.

BEVs and hybrid-electric vehicles are growing in popularity and, like combustion engine vehicles, occasionally catch fire. Battery storage facilities can also catch fire (Gilbert, 2021). The lithium-ion batteries in these vehicles and storage facilities may produce very hot fires that require tremendous amounts of water and time to fully extinguish (Wang et al., 2012). [These types of fire may become more common as the population transitions to BEVs and back-up battery power.] See Section 1.5.1(h) for more information on lithium-ion battery fires and other emerging concerns in the fire service.

1.2.5 Health and health behaviours

Health behaviours can have an important impact on health status and cancer risk (Klein et al., 2014). Risky health behaviours, such as smoking, drinking alcohol, and sedentary behaviour, have been documented in firefighters. Studies have investigated obesity and overall

Fig. 1.7 Fire station in Chicago, USA, with diesel-exhaust capture system attached to a fire truck

The diesel exhaust extractor can be seen in yellow.
From Beatrice Prève/Adobe Stock.

health in firefighters. In a survey of 677 male firefighters from the midwestern USA, the prevalence of obesity (body mass index, BMI ≥ 30) was 32.6% and 38.5% for career and volunteer firefighters, respectively, compared with the age-standardized prevalence in US adults (33.8%) at the time of the survey (Poston et al., 2011). Munir et al. (2012) surveyed 735 male firefighters from the UK and discovered that 53% were overweight and 13% were obese; these were higher percentages than in the general population in England. In contrast, a survey of female career (n = 2398) and volunteer (n = 781) firefighters in the USA and Canada found an age-standardized prevalence of obesity in both career (17.2%) and volunteer (32.8%) firefighters that was lower than in women in the general population (41.1%) (Jahnke et al., 2022). A pilot study using actigraphy to objectively measure occupational and non-occupational physical activity among paid career firefighters found varying levels of physical activity during a typical work week, and these levels varied according to firefighter weight status categories (Kling et al., 2020). The study found that healthy-weight firefighters spent more time engaged in light and moderate physical activity than did overweight and obese firefighters, whereas overweight and obese firefighters spent more time engaged in vigorous physical activity than did their healthy-weight counterparts.

Firefighters have also been reported to experience workplace stress, have poor sleep quality, and have high levels of comorbidities. A survey of 1244 US firefighters (> 94% volunteers) revealed important statistics regarding health determinants and conditions (NVFC, 2010). For example, 54% of respondents said they experienced some or a lot of stress, 26% reported having trouble falling asleep, 28% reported having trouble staying asleep, 37% reported having high blood pressure, and 34% reported having high blood cholesterol.

Studies have also evaluated tobacco use and alcohol consumption among firefighters. A study of tobacco use among 677 male firefighters in the central USA found that career and volunteer firefighters had current cigarette smoking rates (13.6% and 17.4%, respectively) that were below national unadjusted averages between 2008 and 2010 (23.4% for adult men). However, rates for use of smokeless tobacco (18.4% and 16.8%, respectively) were above national unadjusted averages (7.0% for adult men) (Haddock et al., 2011). In the NVFC (2010) survey of mostly volunteer US firefighters, only 10% of respondents were current smokers, but 12% were current users of smokeless tobacco. Phan et al. (2022) examined trends in current smoking and smokeless tobacco use among US firefighters and law enforcement personnel and compared smoking and smokeless tobacco use prevalence in firefighters and law enforcement personnel to that in US adults in non-first-responder occupations. During the study observation period (1992–2019), the authors noted that smoking prevalence declined overall and was highest for individuals in other occupations, and that use of smokeless tobacco was higher among firefighters and law enforcement personnel (Phan et al., 2022). Among 1712 female career firefighters surveyed in 2015, the unadjusted rate for smoking was 5.1%, and the unadjusted rate for smokeless tobacco use was 1.2%; the age standardized smoking rates were lower than that of US adult women, which at the time of the study was estimated at 13.5% (Jamal et al., 2018; Jitnarin et al., 2019).

Firefighters, like individuals with other occupations, may engage in risky or binge drinking. Haddock et al. (2017) surveyed 1913 female firefighters in the USA and found that nearly 40% reported binge drinking in the past 30 days, well above rates reported nationally among women at the time (12–15%). Binge drinking for men was defined as five or more drinks on an occasion in this survey, and 56% of career firefighters and 45% of volunteer firefighters reported binge drinking one or more times in the past 30 days (Haddock et al., 2012), about twice the national average for adult men at the time (Kanny et al., 2013).

Some of the unhealthy behaviours reported among firefighters may be related to occupational stressors and/or peer pressure. Jitnarin et al. (2017) surveyed 1474 career male firefighters in the USA and found that nearly 16% of current users of smokeless tobacco initiated use after joining the fire service, which is substantially higher than expected compared with rates in the general population (i.e. 0.8% late initiation for adult males). Haddock et al. (2017) conducted a survey of 1913 US female firefighters and reported that those who screened positive for problem drinking (16.5% of those who drank alcohol) were 2.5 times as likely as the general population to have been diagnosed with depression or have post-traumatic stress disorder symptoms, and were 40% more likely to have experienced an occupational injury in the past year. Some of these adverse health behaviours (e.g. smoking, binge drinking, and caloric intake from alcohol – i.e. higher amounts of carbohydrates and lower amounts of fibre and vitamins) have been associated with night shift work in other worker populations (Bøggild & Knutsson, 1999; Lowden et al., 2010; Bae et al., 2017; Richter et al., 2021). See Section 1.5.2(a) for more details on shift work.

[The Working Group noted that the information on modifiable risk factors was limited,

with nearly all available information stemming from a small number of cross-sectional surveys published since 2011. The representativeness of these studies was low given that the study populations were few (mainly USA) and sample sizes were relatively small. Moreover, longitudinal information was not available (with the exception of tobacco use in the USA, where data from a series of cross-sectional studies were available), although temporal trends probably varied given changes in firefighter behaviours and fire department policies over time.]

1.3 Detection and quantification

1.3.1 Composition of fire smoke

Combustion products are dependent on the chemical composition of the fuel that is burnt and ventilation conditions (temperature and oxygen availability) (Stec, 2017). Combustible materials vary across different types of fire, such as residential, industrial, vehicle, agricultural, and wildland fires, and any fire that is a combination of these (i.e. WUI). The fuel composition ranges from mostly lignocellulosic vegetative biomass in wildland and agricultural fires to various mixes of solid natural materials, solid synthetic materials including plastics, and liquid petrochemical fuels (Yang et al., 2007; Hess-Kosa, 2016). Common fire effluents in different types of fire are presented in Table 1.3.

Vegetation contains mostly carbon, oxygen, and hydrogen, and various types of vegetative biomass including wood have been measured and/or estimated to contain 36.2–58.4%, 31.4–49.5%, and 4.4–10.2% of these elements, respectively, by dry or dry ash-free weight (Parikh et al., 2007; Vassilev et al., 2010). Vegetative biomass also contains minor amounts of other elements, including 0.1–3.4% nitrogen and 0.01–0.60% sulfur. [Since vegetative biomass is mostly composed of carbon, hydrogen, and oxygen, the emissions from wildland fires are dominated by carbon monoxide (CO), hydrocarbons, and oxygenated carbon compounds (Yi & Bao, 2016; Liu et al., 2017; Hu et al., 2018). A major difference between wildland fires and other types of fire, including structure, vehicle, and WUI fires, is the presence and number of synthetic materials. Little is known about the chemical composition of consumer products used, for example, in buildings or cars. A non-targeted analysis by Phillips et al. (2018) measured numerous compounds in consumer products, of which 88% were not listed in a database of chemicals known to be used or present in consumer products.]

Fires traverse different stages and commonly evolve from non-flaming oxidative pyrolysis, to early well-ventilated flaming, through to fully developed under-ventilated flaming (Purser & Maynard, 2015; Stec, 2017). Oxidative pyrolysis generates low concentrations of partially oxidized organic species (e.g. carbonyl compounds and organic acids). [These may be significant in the case of fuels with a higher moisture content (for example, in peat fires).] Similarly, well-ventilated fires are generally small, and with an increase in temperature and decrease in oxygen concentration can turn into ventilation-controlled (under-ventilated) fires that exhibit much higher concentrations of the released fire effluents (Stec et al., 2007). It has been demonstrated that the yield of combustion products such as CO, hydrogen cyanide (HCN), and other smoke components increases by a factor of between 10 and 50 as the fire changes from well-ventilated to under-ventilated (Stec et al., 2007; Stec, 2017). The impact of ventilation conditions on the yields of major gases emitted by fires is presented in Table 1.4.

Combustion of most aliphatic materials (consisting only of carbon and hydrogen), such as polyethylene and polypropylene, follows the trend whereby CO concentration increases from a low value in well-ventilated conditions, to a much higher value in under-ventilated flaming.

Table 1.3 Common fire effluents produced by different types of fire

Fire effluent(s)	Type of fire			
	Structure[a]	Wildland[b]	Waste[c]	Vehicle[d]
Acrolein	✓	✓		✓
Ammonia	✓	✓	✓	✓
Asbestos	✓			
Carbon monoxide	✓	✓	✓	✓
Formaldehyde	✓	✓	✓	✓
Hydrogen bromide	✓		✓	
Hydrogen chloride	✓		✓	✓
Hydrogen cyanide	✓	✓	✓	✓
Hydrogen fluoride	✓		✓	
Isocyanates	✓			✓
Metals	✓	✓	✓	✓
Nitrogen oxides	✓	✓	✓	✓
Particulate matter	✓	✓	✓	✓
Per-fluorinated chemicals	✓			✓
Polybrominated and polychlorinated dibenzo-*para*-dioxins and furans (PBCD/Fs and PCCD/Fs)	✓		✓	✓
Polychlorinated biphenyls (PCBs)	✓		✓	
Polybrominated diphenyl ethers (PBDEs)	✓		✓	
Polycyclic aromatic hydrocarbons (PAHs)	✓	✓	✓	✓
Semi- and volatile organic compounds (sVOCs and VOCs)	✓	✓	✓	✓
Sulfur dioxide	✓	✓	✓	✓
Synthetic vitreous fibres	✓			

[a] Brandt-Rauf et al. (1988); Persson & Simonson (1998); Lioy et al. (2002); Landrigan et al. (2004); Stec & Hull (2008); Organtini et al. (2015); Fent et al. (2018, 2020a); Stec et al. (2018); Alharbi et al. (2021).
[b] Urbanski et al. (2008); Hu et al. (2018).
[c] Nammari et al. (2004); Lönnermark & Blomqvist (2006); National Air Quality Modelling & Assessment Unit (2009); Pivnenko et al. (2017); Cai et al. (2020); Hadden & Switzer (2020).
[d] Lönnermark & Blomqvist (2006); NIOSH (2010); Fent & Evans (2011); Caban-Martinez et al. (2018).

Partially oxidized organic compounds such as carbonyl compounds, organic acids, and PAHs are also present in the smoke from combustion of such materials. Higher yields of aromatic compounds are released in smoke from the combustion of polystyrene, which is an aromatic hydrocarbon polymer (Purser & Maynard, 2015).

A wider range of products are formed when materials containing oxygen or other elements are combusted (Purser & Maynard, 2015). More-oxidized combustion products, such as nitrogen oxides and ammonia, are released in higher concentrations than HCN when nitrogen-containing polymeric materials, e.g. polyurethane and polyisocyanurate foams, are combusted under well-ventilated fire conditions (Stec & Hull, 2008). Much higher concentrations of CO and HCN are observed for under-ventilated conditions of these materials (following the patterns for products that only contain hydrocarbons) (Stec & Hull, 2011). Also, gaseous mono-isocyanates were observed in studies of under-ventilated, fully developed enclosure fires of materials including polyurethane foam (Blomqvist et al., 2010, 2014; Stec & Hull, 2011; McKenna et al., 2019, Peck et al., 2021).

Materials containing chlorine (e.g. polyvinyl chloride, PVC) release CO and hydrogen chloride

Table 1.4 The main fire gases and their dependence on ventilation conditions

Yield largely independent of fire conditions	Yield decreases as ventilation decreases	Yield increases as ventilation decreases
Hydrogen fluoride (HF)	Carbon dioxide (CO_2)	Carbon monoxide (CO)
Hydrogen chloride (HCl)	Nitrogen dioxide (NO_2)	Hydrogen cyanide (HCN)
Hydrogen bromide (HBr)	Sulfur dioxide (SO_2)	Acrolein (C_3H_4O)
		Formaldehyde (CH_2O)

(HCl). The fire gas pattern is very different from that for all other polymers, since the yields of CO and HCl are independent of the fire scenario (Molyneux et al., 2014), and relatively low carbon dioxide (CO_2) yields and high yields of CO, particulates, and organics, and significant residues are observed in well-ventilated combustion conditions (Stec & Hull, 2008; Molyneux et al., 2014). Most of the chlorine contained in the material is released as HCl, but a small proportion of it is released as other chlorine-containing gas or vapour species, such as chloro-aliphatic and chloro-aromatic hydrocarbons. Formation of carcinogenic polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans (PCDD/Fs) in residential fires commonly occurs when halogenated materials that are widely used in building construction (e.g. in pipes, siding, flooring, and wire insulation) are combusted (Ruokojärvi et al., 2000; Katami et al., 2002; Lavric et al., 2004; Zhang et al., 2015). In addition, the presence of specific metals increases the yields of polychlorinated dibenzo-*para*-dioxins and dibenzofurans (PCDD/Fs). This occurs with construction wood that is impregnated with legacy preservatives (e.g. chromated copper arsenate and pentachlorophenol) and newer preservatives (e.g. alkaline copper quaternary and copper azole) (Wang et al., 2002; Tame et al., 2009; Rabajczyk et al., 2020). The production of polychlorinated biphenyls (PCBs) has been banned since 1979 in the USA and since 1981 in the UK, and an international agreement in 1986 banned most uses; however, combustion of PCBs in existing electrical equipment and electric fires might result in emission of PCDD/Fs (Buser, 1985; Hutzinger et al., 1985).

Another fire-derived combustion product is sulfur dioxide (e.g. from phenolic foam) (Stec & Hull, 2011). Aliphatic and aromatic hydrocarbons (e.g. benzene and 1,3-butadiene), oxygenated organic compounds (e.g. formaldehyde, acetaldehyde, and acrolein), PAHs, and soot particles are found in almost all fires, and their concentrations are increased when combustion is ventilation-limited (Austin et al., 2001b; IARC, 2010; Purser et al., 2010; Hewitt et al., 2017; Bralewska & Rakowska, 2020).

Concentrations of released combustion products may change when the fuel contains fire retardants. Fire retardants that act in the gas phase and interfere with flame reactions (i.e. flame retardants) are frequently applied to insulation foams, electrical equipment, and upholstered furniture (Blomqvist et al., 2004a, b; Stec & Hull, 2011; McKenna et al., 2019). When burning PVC, a similar gas-phase inhibitory effect is observed. In terms of fire emissions, gas-phase halogenated flame retardants (e.g. organophosphate flame retardants, OPFRs) will release hydrogen bromide (HBr) or HCl, and considerable quantities of CO, HCN, smoke, and other products of incomplete combustion (e.g. acrolein and formaldehyde), as well as larger cyclic molecules such as PAHs and soot particulates (Molyneux et al., 2014; McKenna et al., 2019). Brominated flame retardants have been banned in the USA since 2004 and in the

European Union since 2003 (e.g. polybrominated diphenyl ethers, PBDEs), and those currently on the market (e.g. tetrabromobisphenol A, TBBPA; and other brominated phenols) are known to enhance concentrations of mixed polybrominated dibenzo-*para*-dioxins and furans (PBDD/Fs) (Weber & Kuch, 2003; Ortuño et al., 2014; Organtini et al., 2015; Zhang et al., 2016).

Additionally, emission of fine and polydisperse particles that are mostly smaller than $PM_{2.5}$ and generally in the nanometre to submicron range has been reported for wildfires, laboratory combustion testing of wood, and laboratory building and automobile compartment tests simulating overhaul conditions of firefighting (Lachocki et al., 1988; Jankovic et al., 1993; Leonard et al., 2000, 2007; Shemwell & Levendis, 2000; Fine et al., 2001; Valavanidis et al., 2008; Baxter et al., 2010; IARC, 2010; Carrico et al., 2016; Kleinman et al., 2020). Smoke, soot, and particulate emissions vary greatly according to fuel composition and fire conditions (Shemwell & Levendis, 2000; Valavanidis et al., 2008; Blomqvist et al., 2010). However, it is recognized that more and larger-sized particles tend to be generated by fires with less ventilation or oxygen (Shemwell & Levendis, 2000; Blomqvist et al., 2010; Carrico et al., 2016). This effect is enhanced in the presence of halogens, which tend to increase the distribution and concentrations of particulate matter and other volatiles (Blomqvist et al., 2010).

Various metals (e.g. cadmium, cobalt, chromium, copper, nickel, lead, antimony, thallium, and zinc) and persistent free radicals are also found in the particulate soot and ash residues resulting from wildland, structure, or vehicle fires (Smith et al., 1982; O'Keefe et al., 1985; Jankovic et al., 1993; Leonard et al., 2000, 2007; Dellinger et al., 2007; Valavanidis et al., 2008; Organtini et al., 2015). Carbon- and oxygen-centred radicals in the particles and ash residue persist for up to 6 months, with electron paramagnetic resonance signals in the samples remaining the same across the period. Persistence has also been attributed to trapping within and adsorption to the polymeric carbonaceous matrix (Valavanidis et al., 2008).

Various types and quantities of gaseous species are also often found to be attached to particulates. This includes, for example, acid gases (HCl, HBr), isocyanates, and various metals (Blomqvist et al., 2010, 2014; Stec et al., 2013).

Vehicle fires, in addition to having an increased yield of released metals, can release acid gases (HCl and HF), carbonyl fluoride (COF_2), and phosphoryl fluoride (POF_3); however, the fire composition may change depending on the type of battery in the vehicle (Lönnermark & Blomqvist, 2006; Larsson et al., 2017; Sturk et al., 2019).

[Although emissions from diesel engine exhaust are not fire smoke components, gases such as nitrogen oxides (NO_x) and particulate matter are released by a combustion process in equipment (the fire engine) that is essential to firefighting operations; these gases are hazards both in firefighting environments and at fire stations, if not captured through local exhaust ventilation (e.g. an exhaust capture system).]

1.3.2 Air sampling and analytical methods for fire effluents

The choice of sampling and analytical method used to characterize airborne contaminants at a fire incident depends on the contaminant(s) of interest, the physical nature of the airborne samples (i.e. vapour and/or aerosol), the estimated concentrations of contaminants, and any potential interactions with or interferences from other contaminants (Ronnee & O'Connor, 2020). The choice of sampling and analytical method is also strongly influenced by the activities of firefighters at the scene, e.g. whether they are engaged in attack or overhaul activity; the extinguishing agents used; the method of extinguishing agent application; and physical placement, which will

have an effect on both the concentration and state of airborne contaminants, as well as the practicality of sampling device placement (Materna et al., 1992; Fent et al., 2018; Alharbi et al., 2021; Banks et al., 2021a).

[While tremendous advances in analytical chemistry have been observed over the past 30 years, little progress has been made in the detailed analysis of combustion chemicals. The major limiting factors to such progress are access to real (accidental) fires, and the complexity involved in sampling and measuring fire effluents, leading to significant difficulties in assessing firefighters' chemical exposures while attending a fire incident.]

Analysis of fire smoke at a particular incident involves prior identification of which of these (pre-defined) chemicals are considered to be the most significant or major components of the smoke (e.g. based on knowledge of fuel sources, specific fire conditions, etc.). The choice of specific gases or chemicals to monitor is based on the availability of methods that reliably collect and analyse air-contaminant samples in the fire environment (Caban-Martinez et al., 2018; Fent et al., 2018; Sjöström et al., 2019b). The most common methods are listed in Table 1.5.

Ambient or personal-monitoring air samples can be collected either actively or passively. In active sampling, a pumping device actively draws air into a container or through a medium such as a filter, solid adsorbent, denuder, solution, or reagent, and determination of the total volume of air sampled is required (NIOSH, 1994a; Bolstad-Johnson et al., 2000; Fent et al., 2019b). In passive sampling, molecular diffusion and gravity are exploited to collect analytes onto a medium or adsorbent, and no pump is required (Mayer et al., 2022).

Samples can also be classified as integrated, continuous, or grab samples. For integrated samples, the analyte is collected over time (e.g. 15 minutes, 8 hours, full shift, or task) and the average concentration is calculated over the whole measurement period. This does not allow for observations of peaks or troughs in the exposure over time. Continuous samples are collected using a direct reading instrument (i.e. real-time monitor) that provides exposure measurements at set time intervals (e.g. 10 seconds, 1 minute), indicating changes in exposure over the measurement period, such as peaks (Jankovic et al., 1991; Fabian et al., 2014; Evans & Fent, 2015). Grab samples are collected in a bag or container (e.g. evacuated canister) at a specific point in time (Treitman et al., 1980; Reinhardt et al., 2000; Booze et al., 2004; Dills & Beaudreau, 2008). They are a representative sample of the environment from which they are drawn, usually over short periods (e.g. less than 5 minutes), although samples can be collected over longer periods (i.e. hours).

Air samples can be collected over different time periods – a few seconds (e.g. peak measurements), several minutes (e.g. 15–30 minutes, task-based sampling), or longer (e.g. several hours, work-shift sampling). A series of samples or continuous measurements can also be collected and then integrated (i.e. integrated sampling) to calculate a time-weighted average (Bolstad-Johnson et al., 2000; Slaughter et al., 2004; Fabian et al., 2010; Adetona et al., 2013a; Wu et al., 2021).

The choice of analytical method will vary according to the sampling method and sample type (Ronnee & O'Connor, 2020). Selectivity of the analytical method (i.e. avoiding matrix effects and/or interference from other fire species), limit of detection (LOD) and limit of quantification (LOQ), and levels of sensitivity and accuracy between different methodologies also need to be carefully considered when selecting from the large number of analytical methodologies currently available for characterizing fire effluents (NIOSH 1992a, b; Bolstad-Johnson et al., 2000; Fabian et al., 2010; Fent et al., 2020a) These methods are summarized in Table 1.5, which highlights types of fire effluent identified and

Table 1.5 Air sampling and analytical methods available for characterizing firefighters' exposure to fire effluents

Fire effluent(s)	Sampling method(s)	Analytical method(s) (LOD and LOQ[a])	Selected reference(s)
Aldehydes	• Impregnated sieves • Gas collection tubes • Sorbent tubes • XAD-2 tube/ORBO23 sorbent tube impregnated with 2-(hydroxymethyl) piperidine • DNPH sorbent tubes, C-18 silica gel Sep-Paks • UMEX 100 passive sampling badges • XAD-2 sorbent tubes (2-hydroxymethyl piperidine) • Direct gas (multigas) detector	• GC desorption (chromotropic acid) • Infrared spectroscopy • NIOSH Method 2016 formaldehyde (LOD, 0.07 µg/sample), NIOSH Method 2539 aldehydes (LOD, 2 µg aldehyde/sample), NIOSH Method 2541 formaldehyde (LOD, 1 µg/sample) • EPA TO-11 (acrolein LOD, 0.017 ppm, formaldehyde LOD, 0.033 ppm); (acrolein LOD, 3 ppb, 2 hours, formaldehyde LOD, 6 ppb, 2 hours), • OSHA 52 formaldehyde (LOD, 482 ng/sample) and acrolein (LOD, 291 ng/sample) • EPA IP-6 A (active sampling) C (passive sampling) formaldehyde and other aldehydes (LOD, 0.03 µg/sample)	Treitman et al. (1980); Lowry et al. (1985); NIOSH (1992a, b; 1994a; 2010); Materna et al. (1992); Bolstad-Johnson et al. (2000); Reinhardt et al. (2000); Booze et al. (2004); Reinhardt & Ottmar (2004); Slaughter et al. (2004); Reisen et al. (2006); Dills & Beaudreau (2008); Reisen & Brown (2009); Fabian et al. (2010); Reisen et al. (2011); Fent & Evans (2011); Fent et al. (2019b)
Ammonia	• Direct gas detector	• Infrared spectroscopy: FTIR	Fabian et al. (2010); Caban-Martinez et al. (2018); Alharbi et al. (2021)
Asbestos	• Mixed cellulose ester filters	• NIOSH Method 7400 (LOD, 7 fibres/mm^2 filter area)	Bolstad-Johnson et al. (2000)
Carbon monoxide	• Gas sampling (Tedlar) collection bags • Gas collection tubes • Diffusion tubes • Direct gas detector	• Infrared spectroscopy: NDIR, FTIR analysers	Gold et al. (1978); Treitman et al. (1980); Lowry et al. (1985); NIOSH (1992a, b; 1994a); Reinhardt et al. (2000); Booze et al. (2004); Reinhardt & Ottmar (2004); Slaughter et al. (2004); Naeher et al. (2006); Reisen et al. (2006, 2011); Dills & Beaudreau (2008); Reisen & Brown (2009); Fabian et al. (2010); Adetona et al. (2013a); Alharbi et al. (2021); Wu et al. (2021)
Carbon dioxide	• Gas sampling (Tedlar) collection bags • Direct gas detector	• Direct analyser (LOD, 7.6 ppm, 2 hours)	Gold et al. (1978); Treitman et al. (1980); Reinhardt et al. (2000); Reinhardt & Ottmar (2004); Dills & Beaudreau (2008); Caban-Martinez et al. (2018)
Flame retardants	• Glass fibre filter with XAD-2 sorbent tubes	• UPLC-APPI, • EPA 23A PBDEs and NPBFRs (LOD depends on the substance, sampling conditions and analytical procedures)	Fent et al. (2020a)

Table 1.5 (continued)

Fire effluent(s)	Sampling method(s)	Analytical method(s) (LOD and LOQ[a])	Selected reference(s)
Hydrogen cyanide	• Gas collection tubes • Disposable syringes • Gas sampling (Tedlar) collection bag • Soda lime sorbent tubes • Multiple colorimetric detectors • Direct gas (multigas) detector	• Colorimetric method (pyridine) • Infrared spectroscopy: UV-VIS spectrophotometric method, FTIR • NIOSH Method 6010 (LOD, 1 µg/sample), NIOSH Method 7904 (LOD, 2.5 µg)	Gold et al. (1978); Treitman et al. (1980); Lowry et al. (1985); Caban-Martinez et al. (2018); Bolstad-Johnson et al. (2000); Dills & Beaudreau (2008); Fabian et al. (2010); Fent et al. (2018, 2019b); Alharbi et al. (2021)
Hydrogen sulfide	• Direct gas (multigas) detector		Fabian et al. (2010); Alharbi et al. (2021)
Inorganic acids (HCl)	• Multiple colorimetric detectors • ORBO53 tube • Direct gas (multigas) detector	• Mercuric thiocyanate method • Zall colorimetric method • NIOSH 7903 (LOD, 0.6–2 µg/sample)	Gold et al. (1978); Treitman et al. (1980); NIOSH (1994a); Bolstad-Johnson et al. (2000); Dills & Beaudreau (2008); Fent et al. (2018, 2019b); Alharbi et al. (2021)
Isocyanates	• Denuder attached to polypropylene cassette impregnated with a dibutyl-*n*-amine filter (glass fibre, impregnated); or • Impinger; or impinger + filter	• ISO 17734-(2013) • NIOSH Method 5525 (0.2 nmol NCO per species/sample (0.2 nmol NCO equals 0.017 µg HDI/sample)	NIOSH (2010); Fent & Evans (2011); Fent et al. (2019b)
Metals	• PVC and cellulose ester filters • Teflon filter • Hyder tube (mercury) • XAD-2 sorbent tube between PUF disks	• NIOSH Method 7300 ICP-AES (Cd LOD, 0.3 ng/mL; Cr LOD, 0.8 ng/mL; Pb LOD, 2.5 ng/mL) • Airborne mercury: NIOSH Method 6009 (LOD, 0.03 µg/sample) • ICP-MS (LOD, 0.027 µg/g for Sb to 51.62 µg/g for K)	Bolstad-Johnson et al. (2000); Fabian et al. (2010); Wu et al. (2021)
Nitrogen oxides	• Molecular sieve coated with triethanolamine sorbent tubes • Diffusion tubes • Direct gas (multigas) detector	• Saltzmann method • Infrared spectroscopy: FTIR analyser • NIOSH Method 6014 (1 µg NO_2/sample)	Gold et al. (1978); Treitman et al. (1980); NIOSH (1994a); Dills & Beaudreau (2008); Fabian et al. (2010); Caban-Martinez et al. (2018)

Table 1.5 (continued)

Fire effluent(s)	Sampling method(s)	Analytical method(s) (LOD and LOQ[a])	Selected reference(s)
Particulate matter	• Glass fibres, PTFE or PVC filters • Aluminium cyclone • Cyclone with PVC or Teflon filters • Filter-cassette with a nylon cyclone • Cyclone with PTFE filters • Cascade Impactor with PVC filters • Cascade Impactor with aluminium foil substrates and glass fibre filter • HEPA and/or quartz fibre filters • Electrical low-pressure impactor	• NIOSH Method 0500 (LOD, 0.03 mg/sample), • NIOSH Method 0600 (LOD, 0.03 mg/sample) • Gravimetric measurements (LOD, 10–100 µg) • Condensation particle counter • Environmental β attenuation monitor • Personal aerosol monitor • Particle size spectrometer • Particle counter • Aerosol sensor • Diffusion charger • Photoelectric aerosol sensor	Gold et al. (1978); Treitman et al. (1980); NIOSH (1992a, 1994a, 2010, 2013a); Materna et al. (1992); Reinhardt et al. (2000); Booze et al. (2004); Reinhardt & Ottmar (2004); Slaughter et al. (2004); Naeher et al. (2006); Reisen et al. (2006, 2011); Reisen & Brown (2009); Baxter et al. (2010); Fabian et al. (2010); Fent et al. (2018, 2019b); Adetona et al. (2013a); Evans & Fent (2015); Navarro et al. (2019b); Sjöström et al. (2019b); Nelson et al. (2021); Wu et al. (2021)
Polycyclic aromatic hydrocarbons (PAHs)	• Evacuated canister • Teflon or quartz filter • PUF cartridge • PTFE filter and sorbent tube (XAD-2 resin/ORBO43 sorbent tube) • Teflon filter with XAD-2 sorbent tube • Aluminium cyclone and XAD-2 sorbent tube • XAD-2 sorbent tubes with glass fibre filter • XAD-2 sorbent tube with quartz fibre filters and XAD-4 sorbent tube • XAD-7 sorbent tube	• NIOSH Method 5023 various organic-soluble compounds (LOD, 0.05 mg/sample), NIOSH Method 5506 LOD depends on the substance (e.g. naphthalene LOD, 0.20–0.80 µg/sample), NIOSH Method 5515 (LOD, 0.3–0.5 µg/sample), NIOSH Method 5528 (LOD 0.08–0.2 µg/sample, • EPA 1625 (LOD depends on the substance) • GC-MS (LOD, 1.71–7.14 ng/m^3; LOQ, 1.0–5.3 ng/m^3) • HRGC-MS • GC-TQMS	Materna et al. (1992); NIOSH (1992b, 1994a, 2013a); Bolstad-Johnson et al. (2000); Dills & Beaudreau (2008); Fabian et al. (2010); Keir et al. (2017); Navarro et al. (2017); Fent et al. (2018, 2019b); Navarro et al. (2019b); Sjöström et al. (2019b); Banks et al. (2021a)
Polychlorinated, polybrominated dibenzo-*para*-dioxins and furans (PCDD/Fs and PBDD/Fs)	• Fire debris • Glass fibre filter with XAD-2 sorbent tubes	• APGC-MS/MS: Ontario Ministry of Environment E3418 (LOD, 0.15–1.4 pg/g for tetra- through octa- halogenated dioxins and furans) • EPA 23A	Organtini et al. (2015)

Table 1.5 (continued)

Fire effluent(s)	Sampling method(s)	Analytical method(s) (LOD and LOQ[a])	Selected reference(s)
Semi-volatile and volatile organic compounds (sVOCs and VOCs)	• Tedlar bag • Evacuated canister • Cylindrical PUF • Pressurized vacuum canisters • Evacuated glass bottles • Charcoal sorbent tubes • Carbotrap 317 tubes • Catecholamine-treated charcoal tube • Thermal desorption tubes (qualitative, Carbopack Y/Carbopack B/Carboxen), charcoal tubes • Adsorbent Carbopack X 60/80 tubes • Sorbent tubes (Carbograph 1TD/ Carboxen 1000) • Direct gas (multigas) detector	• Thermal desorption GC-MS • GC-MS, GC-FID • NIOSH Method 1003 (LOD depends on the substance), NIOSH 1500 (LOD depends on the substance), NIOSH Method 1501 (LOD depends on the substance), NIOSH Method 2549 volatile organic compounds (LOD, 100 ng/tube) • EPA TO-15 (LOD depends on the substance) • GC-MS (benzene LOD, 0.1 µg; styrene LOD, 1.2 µg; VOCs and sVOCs LOD, 1–5 ppm)	Treitman et al. (1980); Lowry et al. (1985); NIOSH (1992b, 1994a, 2010, 2013a); Materna et al. (1992); Bolstad-Johnson et al. (2000); Reinhardt et al. (2000); Booze et al. (2004); Reinhardt & Ottmar (2004); Reisen et al. (2006, 2011); Dills & Beaudreau (2008); Reisen & Brown (2009); Fabian et al. (2010); Fent & Evans (2011); Caban-Martinez et al. (2018); Fent et al. (2018, 2019b); Sjöström et al. (2019b); Alharbi et al. (2021)
Silica	• Cyclone with PVC filters	• NIOSH Method 7500 (LOD, 0.005 mg SiO_2/ sample)	Materna et al. (1992); NIOSH (1992a, b)
Sulfur dioxide	• Diffusion tubes, • Filter with mixed-cellulose ester with sodium carbonate • Direct gas (multigas) detector	• NIOSH Method 6004 (LOD, 3 µg SO_2/ sample) • Infrared spectroscopy: FTIR	NIOSH (1992a, b, 1994a); Dills & Beaudreau (2008); Fabian et al. (2010); Caban-Martinez et al. (2018); Alharbi et al. (2021)

AES, atomic emission spectrometry; APGC-MS/MS, atmospheric pressure gas chromatography-tandem mass spectrometry; Cd, cadmium; Cr, chromium; DNPH, 2,4-dinitrophenylhydrazine; EPA, US Environmental Protection Agency; FID, flame ionization detector; FTIR, Fourier transform infrared spectroscopy; GC-FID, gas chromatography-flame ionization detector; GC-MS, gas chromatography-mass spectrometry; GC-TQMS, gas chromatography-triple quadrupole mass spectrometry; HEPA, high-efficiency particulate air filter; HRGC-MS, high-resolution gas chromatography-mass spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectroscopy; ICP-MS, inductively coupled plasma-mass spectrometry; ISO, International Organization for Standardization; K, potassium; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NCO, isocyanate; NDIR, non-dispersive infra-red spectroscopy; NIOSH, National Institute for Occupational Safety and Health; NO_2, nitrogen dioxide; NPBFR, non-PBDE brominated flame retardant; OSHA, Occupational Safety and Health Administration; Pb, lead; PBDE, polybrominated diphenyl ether; ppb, parts per billion; ppm, parts per million; PTFE, polytetrafluoroethylene; PUF, polyurethane foam; PVC, polyvinyl chloride; Sb, antimony; SiO_2, silicon dioxide; SO_2, sulfur dioxide; sVOC, semi-volatile organic compound; UPLC-APPI, ultra-performance liquid chromatography-atmospheric pressure photoionization; UV-VIS, ultraviolet visible spectroscopy; VOC, volatile organic compound.

[a] Only included when available.

measured, sampling methods, analytical techniques, and LOD/LOQ, when available.

In the 1980s, sampling and analytical methodologies were refined for several different gases, such as CO, HCN, and aldehydes, using colorimetric or charcoal sorbent tubes followed by infrared spectroscopy, and gas chromatography (gas chromatography-mass spectrometry, GC-MS, and/or gas chromatography-flame ionization detection, GC-FID) (Gold et al., 1978; Treitman et al., 1980; Lowry et al., 1985; Reisen et al., 2006; Navarro et al., 2017, 2019b). Methods for the collection and analysis of particulate matter have been developed continuously, with the implementation of different sampling media (e.g. different types of filter), particle collection devices (e.g. cyclones or cascade impactors) for investigating particle size distribution, and more reliable and robust analytical methodologies (NIOSH, 1992a, 1994a, 2013a, 2019; Fent & Evans, 2011; Evans & Fent, 2015; Fent et al., 2019b). Research in the 1990s was dominated by the characterization of firefighters' exposures in forest or wildland fire settings and subsequently by increasing interest in the characterization and effects of diesel exhaust emissions (at fire stations) and the effectiveness of SCBA (Jankovic et al., 1991; NIOSH, 1994a, 1998b; Than et al., 1995). A wealth of research has also been published on simulated residential fires (NIOSH, 1992a, b, 1994a; Materna et al., 1992). Sampling and analytical methodologies included the use of sampling bags, charcoal tubes for the monitoring of VOCs and PAHs (analysis by chromatography, e.g. GC-MS or GC-FID), silica gel tubes for acid gases (high-pressure ion chromatography, HPIC), soda lime tubes for HCN (spectroscopy), or polymer tubes for aldehydes (GC-FID), or high-performance liquid chromatography (HPLC) coupled with UV or diode-array detection (HPLC-UV-DAD). Analysis of particulate matter was also enhanced using cyclones or cascade impactors for investigating particle size distribution. During this time, long-term diffusion tubes (colorimetric tubes) were used together with continuous direct reading sensors or multigas analysers (for CO, CO_2, and methane, CH_4) (NIOSH, 1992a, b, 1994a; Materna et al., 1992; Naeher et al., 2006).

The implementation of more sophisticated analytical methods, principally spectroscopic and chromatographic methodologies (e.g. gas-phase Fourier transform infrared spectroscopy, FTIR; gas chromatography-nitrogen–phosphorus detection, GC-NPD; high-resolution gas chromatography-high-resolution mass spectrometry, HRGC-HRMS, atmospheric pressure gas chromatography-tandem mass spectrometry, APGC-MS/MS; and high-performance liquid chromatography with ultraviolet or fluorescence detection, HPLC-UV, HPLC-FL) allowed the quantification of standard pollutants with higher sensitivity (lower LODs/LOQs) and accuracy, thus extending analytical capacity to detect and quantify the presence of pollutants that could not previously be determined (e.g. PCBs, PBDEs, OPFRs, PCDD/Fs, etc.) (Organtini et al., 2015; Fent et al., 2020a). More recently, on-site, and real-time determination of the concentrations of airborne gaseous and particulate pollutants present in fire smoke has been achieved using portable, low-cost screening devices and sensors (e.g. multigas sensors and particle counting devices) with increasing selectivity and accuracy (Caban-Martinez et al., 2018; Alharbi et al., 2021; Nelson et al., 2021).

The use of sensor-based devices has been reported for a wide variety of air pollutants that can be detected at concentrations ranging from parts per million (ppm) to parts per billion (ppb). They include optical particle counters for measuring the size distribution of particles and electrochemical sensors used for quantitative determination of gases and vapours (CO, HCl, HCN, NO_2, SO_2, etc.) (Baxter et al., 2010; Reisen et al., 2011; Caban-Martinez et al., 2018; Alharbi et al., 2021; Nelson et al., 2021).

[The use of these sensor devices has been an important breakthrough in the monitoring of firefighters' occupational exposure to health-relevant pollutants during firefighting. Moreover, on-site and real-time portable sensors can be used in firefighters' health surveillance programmes. However, these devices have several limitations that need to be considered, including cross sensitivity and interference from environmental factors (e.g. temperature, humidity, wind, and rain).]

1.3.3 Dermal sampling and analytical methods

Skin exposure to fire effluents can occur via contaminated PPE (Stull et al., 1996; Kirk & Logan, 2015b; Fent et al., 2017). This may happen during donning, doffing, or other handling of contaminated PPE, or if contaminants are transferred from PPE or other equipment to surfaces (e.g. fire apparatus) that subsequently come into contact with the firefighter's skin. In addition, dermal exposure is possible via permeation or penetration of contaminants through or around the protective barriers of the turnout gear (see Section 1.6 for more information). In the available literature, dermal exposure samples were mostly collected using wipes or simulant patches from the face, hand, neck, forehead, wrist, or scrotum of firefighters and analysed mostly for PAHs using GC-MS standard analytical methods (NIOSH, 2013a; Baxter et al., 2014; Keir et al., 2017; Stec et al., 2018). Recently, tape stripping has been used and validated for collecting organic chemicals (PAHs) from firefighters' skin (Strandberg et al., 2018; Sjöström et al., 2019a, b). Sampling of the air under turnout gear has also been conducted as a way of measuring dermal exposure potential, as well as the attenuation provided by protective clothing, for PAHs or VOCs (Kirk & Logan, 2015b; Wingfors et al., 2018; Mayer et al., 2022). Table 1.6 provides further detail on the current body of research characterizing the measurement of contaminants on firefighters' skin.

1.3.4 Sampling and analytical methods for contaminants in fire stations

The analytical methods for the measurement of fire effluents described in Section 1.3.2 are applicable to the measurement of exposures in fire stations. No direct measurement of diesel engine exhaust as such (i.e. from fire vehicles or apparatus) was available, therefore measurement relies on the measurement of individual exhaust components (e.g. elemental carbon, CO, nitrogen oxides, sulfur dioxide, aldehydes, PAHs, and soot). Chemical species (e.g. sVOCs and VOCs, PAHs, flame retardants, and perfluorinated chemicals) detected and the corresponding sampling and analytical methods are reported in Table 1.7 (Froines et al., 1987; Than et al., 1995; NIOSH, 1994b, 1998b, 2001; Oliveira et al., 2017a; Sparer et al., 2017; Shen et al., 2018; Stec et al., 2018; Banks et al., 2020; Hall et al., 2020).

Early methods to measure the particulate fraction of diesel engine exhaust relied on gravimetric approaches; however, these methods were not specific to diesel particulate (Birch, 2002). Later methods focused on the carbonaceous fraction (i.e. elemental and organic carbon). Whereas many potential sources of organic carbon exist (e.g. tobacco smoke and cooking), there are few sources of elemental carbon, making this the better surrogate for exposure to diesel engine exhaust (Birch, 2002; NIOSH, 2016a). For more detailed information on firefighters' exposure to diesel exhaust, see Section 1.5.1(d).

1.3.5 Other sampling and analytical methods

(a) Protective clothing

Different types of firefighter PPE and its use are described in Section 1.6. Few studies (summarized in Table 1.8) have characterized the extent of contamination of firefighter PPE.

Table 1.6 Most common dermal sampling and analytical methods

Fire effluents	Fire location or activity	Sampling method	Analytical method	Reference
Polycyclic aromatic hydrocarbons (PAHs)	• Controlled building fire • Simulated/controlled residential room (structure) fires • Fire suppression activities • Smoke diving and fire extinguishing training events • Fire training events • Firefighters' work environment	• Sunflower oil wiped with cellulose ester towels • Skin simulant patches • Wipes (isopropyl alcohol, polyester) • Wipe samples saturated with corn oil • Glass fibre filter wetted with acetone • Semipermeable low-density polyethylene membranes and three tape-stripping • Tape stripping (three consecutive tapes)	• GC-MS: EPA TO-13A • GC-FID: NIOSH 5515 • HPLC (fluorescence/UV detection): NIOSH 5506 • HRGC-MS • GC-MS/MS • GC-TQMS • GPC: EPA 3640A	Laitinen et al. (2010); Kirk et al. (2011); NIOSH (2013a); Fent et al. (2014, 2017); Baxter et al. (2014); Keir et al. (2017); Stec et al. (2018); Strandberg et al. (2018); Wingfors et al. (2018); Sjöström et al. (2019a, b); Beitel et al. (2020); Keir et al. (2020); Banks et al. (2021a)
Methoxyphenols	• Burn houses (training)	• Wipes (isopropanol)	• GC-MS MDL	Fernando et al. (2016)

EPA, US Environmental Protection Agency; GC-FID, gas chromatography-flame ionization detector; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; GC-TQMS, gas chromatography-triple quadrupole mass spectrometry; GPC, gel permeation chromatography; HPLC, high-performance liquid chromatography; HRGC-MS, high-resolution gas chromatography-mass spectrometry; MDL, method detection limit; NIOSH, National Institute for Occupational Safety and Health; UV, ultraviolet.

Table 1.7 Sampling and analytical methods for fire effluents identified at fire stations

Fire effluents	Sampler or sampling method	Analytical method	Reference
Flame retardants	• Vacuum cleaner • PUF with glass fibre filter	• GC-MS: EPA TO-13A • GC-HRMS • HRGC-MS • GC-MS/MS • GC-HRMS-EI • HPLC-MS/MS • GC-TQMS	Brown et al. (2014); Park et al. (2015); Shen et al. (2015, 2018); Bott et al. (2017); Gill et al. (2020b); Young et al. (2021)
Nitrogen oxides	• Triethanolamine treated molecular sieve sorbent tube	• Visible absorption spectrophotometry: NIOSH 6014	NIOSH (1994b, 1998b, 2001)
Particulate matter	• Teflon glass fibre filters • Quartz fibre filters • Single stage impactor with PTFE disks	• Gravimetry • Thermal optical analysis (FID): NIOSH 5040 • Model 227B laser particle counter • $PM_{2.5}$, personal modular impactor • SidePak aerosol monitor AM510	Froines et al. (1987); NIOSH (1994b, 2001); Baxter et al. (2014); Bott et al. (2017); Oliveira et al. (2017a, b); Sparer et al. (2017)
Per-fluorinated compounds	• Vacuum cleaner	• HPLC-ESI-MS/MS • GC-MS-EI	Hall et al. (2020)
Polycyclic aromatic hydrocarbons (PAHs)	• Teflon filter followed by XAD-2 sorbent tube, • Vacuum cleaner • Glass tubes with Tenax between two PUF • PTFE disks • XAD-2 sorbent tubes • Wipe sampling with isopropyl alcohol • PUF with glass-fibre filter	• GC-MS • GC-FID: NIOSH 5515 • GC-MS-EI • LC-PAD-FLD • Ecochem PAS 2000CE	Baxter et al. (2014); Shen et al. (2015); Oliveira et al. (2017a, b); Sparer et al. (2017); Stec et al. (2018); Banks et al. (2020)
Semi-volatile and volatile organic compounds (sVOCs and VOCs)	• Thermal desorption tubes (Carbopack Y, Carbopack B, and Carboxen 1003) • Charcoal tubes	• GC-FID: NIOSH 1501 • Thermal desorption GC-MS: NIOSH 2549	NIOSH (1998b, 2001)
Sulfur dioxide	• Grab samples	• Sensidyne colorimetric detector tubes	NIOSH (2001)
Elemental/organic carbon	• Quartz fibre filters	• Thermal-optical analysis; flame ionization detector (FID): NIOSH 5040	NIOSH (2016a)
Respirable combustible dust	• Cyclone with silver membrane filter (with/without impactor)	• Gravimetry	Grenier et al. (2001)

EPA, US Environmental Protection Agency; GC-FID, gas chromatography-flame ionization detector; GC-HRMS, gas chromatography-high-resolution mass spectrometry; GC-HRMS-EI, gas chromatography-high-resolution mass spectrometry-electron ionization; GC-MS, gas chromatography-mass spectrometry; GC-MS-EI, gas chromatography-mass spectrometry-electron ionization; GC-MS/MS, gas chromatography-tandem mass spectrometry; GC-TQMS, gas chromatography-triple quadrupole mass spectrometry; HPLC-ESI-MS/MS, high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; HRGC-MS, high-resolution gas chromatography-mass spectrometry; LC-PAD-FLD, liquid chromatography-photodiode array-fluorescence detector; NIOSH, National Institute for Occupational Safety and Health; $PM_{2.5}$, fine particulate matter of 2.5 µm or less in diameter; PTFE, polytetrafluoroethylene; PUF, polyurethane foam.

Table 1.8 Sampling and analytical methods for contaminants in firefighters' PPE

Fire effluents analysed	Surfaces analysed	Sampling method	Analytical method	Reference
Acid gases	• SCBA mask • Respirator cartridges • Clothing	• Silica gel tube • Glass sorbent tubes packed with silica gel	• HPIC: NIOSH Method 7903	Jankovic et al. (1991); Kirk et al. (2011); Kirk & Logan (2015b)
Aldehydes	• SCBA mask • Clothing • Respirator cartridges	• Treated porous polymer tube • Formaldehyde filter • Glass sorbent tubes • DNPH sorbent tube with silica gel	• HPLC (UV): EPA TO-11 and TO-11A	Jankovic et al. (1991); De Vos et al. (2006); Anthony et al. (2007); Kirk et al. (2011); NIOSH (2013b); Kirk & Logan (2015b)
Carbon monoxide	• SCBA mask	• Direct gas monitor	• FTIR spectrometer	Jankovic et al. (1991); Austin et al. (1997)
Fibres		• Cellulose ester filter	• Phase-contrast microscopy	Jankovic et al. (1991)
Flame retardants	• Clothing	• Swab samples • Cotton wipes (hexane and cotton gauze pads) • XAD-2 sorbent tubes • Wipe sampling (isopropanol)	• GC-HRMS • GC-MS: EPA 8270D • UPLC-APPI • GC-TQMS • HPLC-MS/MS	Stull et al. (1996); Kelly et al. (2002); Park et al. (2015); Alexander & Baxter (2016); Easter et al. (2016); Mayer et al. (2019); Fent et al. (2020a); Banks et al. (2021b, c); Young et al. (2021)
Hydrogen cyanide	• SCBA mask • Clothing	• Soda lime tube • Glass sorbent tubes with soda lime	• Spectrophotometry (visible absorption): NIOSH 6010	Jankovic et al. (1991); Kirk et al. (2011); Kirk & Logan (2015b)
Metals	• Clothing	• PUF and quartz filters	• AAS: EPA 245.1 • ICP-AES: OSHA ID-125G, NIOSH Method 730, NIOSH 7303 • ICP-MS: US EPA 305B	Stull et al. (1996); Fabian et al. (2014); Keir et al. (2020)
Nitrogen oxides	• SCBA mask	• Silica gel tube	• HPIC	Jankovic et al. (1991)
Particulate matter	• Half face-piece masks • Respirator cartridges • Half-mask respirators	• Cascade impactor • Cyclones • Filter in a cassette and a carbonyl compound sorption tube • PVC filters and cellulose backup • P100 pancake-shaped filters • Battery-operated scanning mobility spectrometer • Real-time monitoring	• Gravimetric NIOSH Method 0500/0600	Jankovic et al. (1991); De Vos et al. (2006); Anthony et al. (2007); Dietrich et al. (2015)

Table 1.8 (continued)

Fire effluents analysed	Surfaces analysed	Sampling method	Analytical method	Reference
Per-fluorinated chemicals	• Turnout gear and fabric swatches		• HPLC-MS/MS	Peaslee et al. (2020)
Phthalates	• Clothing		• GC-MS: EPA 8270 • Headspace GC-MS	Alexander & Baxter (2016); Easter et al. (2016); Shinde & Ormond (2020)
Polychlorinated and polybrominated dibenzo-*para*-dioxins and furans (PCDD/Fs and PBCD/Fs)	• Clothing	• Swab samples • Glass fibre paper saturated with acetone • Cellulose wipes • Cotton twill wipes (hexane) and cotton gauze pads	• HRGC-HRMS: EPA 1613B and 8290A, Ontario Ministry of Environment Method E3418 • GC × GC-TOFMS	Kelly et al. (2002); Hsu et al. (2011); Organtini et al. (2014); Fent et al. (2020a)
Polycyclic aromatic hydrocarbons (PAHs)	• SCBA mask • Respirator cartridges • Clothing • Turnout gear fabrics	• Cloth samples • Wipe samples (heptane) • Wipe samples (isopropyl alcohol) • PTFE filter • PUF glass tubes with glass fibre filter • XAD-7 sorbent tubes • Glass sorbent tubes with PUF and glass fibre filter • XAD-2 sorbent tubes • XAD-2 sorbent tube between PUF disks • PUF and quartz filters	• GC-MS: EPA TO-13A, NIOSH Method 5528 • GC-FID • HPLC (fluorescence/UV): NIOSH Method 5506 • Headspace GC-MS • GC-TQMS	Jankovic et al. (1991); Anthony et al. (2007); Kirk et al. (2011); Fabian et al. (2014); Kirk & Logan (2015b); Easter et al. (2016); Abrard et al. (2019); Fent et al. (2017); Wingfors et al. (2018); Stec et al. (2018); Mayer et al. (2019); Shinde & Ormond (2020); Banks et al. (2021b, c); Corbally et al. (2021); Alexander & Baxter (2016); Mayer et al. (2020); Keir et al. (2020)
Semi-volatile and volatile organic compounds (sVOCs and VOCs)	• SCBA mask • Clothing • Turnout gear fabrics	• Evacuated canisters • Charcoal tubes • Tenax/Carboxen 569 tubes • Wipe samples (isopropanol, benzalkonium chloride)	• GC-MS: EPA TO1/TO2, TO-15, 8270 • Thermal desorption GC-MS: EPA TO-17 • Headspace GC-MS • GC-FID	Jankovic et al. (1991); Stull et al. (1996); Anthony et al. (2007); Kirk et al. (2011); NIOSH (2013b); Fent et al. (2015, 2017); Kirk & Logan (2015b); Shinde & Ormond (2020); Corbally et al. (2021); Mayer et al. (2020)

AAS, atomic absorption spectroscopy; DNPH, 2,4-dinitrophenylhydrazine; EPA, US Environmental Protection Agency; FTIR, Fourier transform infrared spectroscopy; GC-FID, gas chromatography-flame ionization detector; GC-HRMS, gas chromatography-high-resolution mass spectrometry; GC-MS, gas chromatography-mass spectrometry; GC-TOFMS, gas chromatography-time-of-flight mass spectrometry; GC-TQMS, gas chromatography-triple quadrupole mass spectrometer; HPIC, high-pressure ion chromatography; HPLC, high-performance liquid chromatography; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; HRGC-HRMS, high-resolution gas chromatography-high-resolution mass spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectroscopy; ICP-MS inductively coupled plasma-mass spectrometry; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PPE, personal protective equipment; PTFE, polytetrafluoroethylene; PUF, polyurethane foam; PVC, polyvinyl chloride; SCBA, self-contained breathing apparatus; UPLC-APPI, ultra-performance liquid chromatography-atmospheric pressure photoionization; UV, ultraviolet.

Fig. 1.8 Wipe sampling of contaminants from a firefighter's helmet

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Sample collection in these studies, for both new and used ("soiled" or contaminated) PPE, mostly involved exposures to simulated structure fires. The locations from which samples were collected included: (i) the outer layer of turnout gear (Hsu et al., 2011; Kirk et al., 2011; Stec et al., 2018); (ii) the inner liner of turnout gear (Alexander & Baxter, 2016; Easter et al., 2016; Kesler et al., 2021); (iii) clothing or surfaces under turnout gear (Keir et al., 2020; Mayer et al., 2020); and (iv) air space around turnout gear to measure off-gassing of contaminants (Kirk & Logan, 2015b; Fent et al., 2017; Banks et al., 2021b).

A variety of contaminants were measured in these samples (e.g. PAHs, VOCs, HCN, aldehydes, acid gases, OPFRs, PCDD/Fs, PBDD/Fs, metals), and these are summarized in Table 1.8, together with the specific sampling media and analytical techniques used.

[Although PPE usage histories are usually not reported, some findings suggested that contamination of firefighter protective clothing increases with longer periods of use (Stec et al., 2018). Variations in reported results may arise not only from the sampling and analytical methods used, but also from different firefighting activities, exposure to various chemicals, and PPE age and decontamination or storage practices (Stec et al., 2018; Fent et al., 2020a; Banks et al., 2021b) (Fig. 1.8).]

Table 1.9 Other sampling and analytical methods

Fire effluents	Exposure scenario	Sampling method	Analytical method	Reference
Perfluorinated chemicals	Off-duty and on-duty firefighters	Wrist: silicone-based wristbands	LC-MS/MS	Levasseur et al. (2022)
Polychlorinated biphenyls (PCBs); phthalates, brominated flame retardants, organophosphate esters, polycyclic aromatic hydrocarbons (PAHs); semi-volatile organic compounds (sVOCs)	Off-duty and on-duty firefighters	Wrist: silicone-based wristbands	GC hybrid quadrupole-Orbitrap GC-MS/MS system	
Polycyclic aromatic hydrocarbons (PAHs)	Firefighters work environment During 24-hour shift Fire training events	Wrist: silicone-based wristbands	GC-MS	Baum et al. (2020); Caban-Martinez et al. (2020); Bakali et al. (2021)

GC-MS, gas chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

(b) Wristbands

Recently, silicone wristbands (or dog tags) have been proposed and validated for collecting fire effluents while the firefighter is at work (Strandberg et al., 2018; Sjöström et al., 2019a, b; Baum et al., 2020; Caban Martinez et al., 2020; Levasseur et al., 2022). Silicone wristbands are a type of passive sampler that collect unbound VOCs and sVOCs in air, sediment, or water by diffusion into lipophilic polymers (Dixon et al., 2019). These studies are summarized in Table 1.9.

[Little information is available on the limitations of these sampling techniques, for example, information on collection efficiency or diffusion rates for various types of chemical and how the samples relate to standardized exposure monitoring methods.]

1.3.6 Biomonitoring methods

(a) Fire smoke components

Numerous studies have employed biomonitoring to assess firefighters' exposures to chemicals of concern. Biomonitoring, which has become a critical tool in occupational exposure assessment, involves measurement of the presence and levels of chemicals (or their metabolites) in human tissues (including hair and nails), bodily fluids (e.g. blood, sputum, saliva, breast milk), excreta (e.g. urine, faeces), or exhaled breath (Angerer et al., 2006, 2007; Manno et al., 2010; Scheepers et al., 2011; Arnold et al., 2013; Decker et al., 2013; Bader et al., 2021). Samples can be collected before and/or after suppression of various types of fires including, for example, intentionally set training fires, municipal structure fires, industrial fires, and wildfires. Subsequent sample analyses can examine the effect of fire suppression on the levels of selected chemicals, and/or their metabolites, in the aforementioned biological matrices (e.g. Kales et al., 1994; Dunn et al., 2009; Miranda et al., 2012; Fent et al., 2014; Waldman et al., 2016; Jackson & Logue, 2017; Keir et al., 2017, 2020; Andersen et al., 2018b; Santos et al., 2019; Grashow et al., 2020; Allonneau et al., 2021; Mayer et al., 2021).

Biomonitoring data reflect exposures from all sources (e.g. firefighting, indoor and outdoor air, drinking-water, and consumer products), and exposures via all routes of entry into the body (e.g. inhalation, oral ingestion, and dermal absorption) (Angerer et al., 2006, 2007; Laitinen et al., 2012; Arnold et al., 2013). Assessing the levels of chemicals or chemical metabolites in biomonitoring samples does not necessarily permit

identification of the source(s) and/or route(s) of exposure. Moreover, the presence of a substance in a biological matrix does not necessarily mean it is causing harm, nor does the absence of a substance indicate that an individual was not exposed (Angerer et al., 2006, 2007; Arnold et al., 2013; Government of Canada, 2022).

As noted in Section 1.3.1, as well as Sections 1.4.1 through 1.4.4, firefighters are exposed to complex mixtures that can include an array of chemicals, including gases (e.g. CO and NO_2), VOCs, particulate matter, sVOCs, and fibres. Exposures to these chemicals can occur during the various phases of fire suppression (e.g. attack, knockdown, overhaul) and in the firefighters' workplace, such as the fire station (see Sections 1.1, 1.2, and 1.3.4(b)). Although firefighter PPE restricts contact with combustion-derived chemicals, exposures can occur via gear penetration, contact with exposed areas of the face, neck, and wrist, and/or contact with contaminated gear (NIOSH, 2013a; Fent et al., 2014, 2015, 2017; Andersen et al., 2018b; Wallace et al., 2019a; Beitel et al., 2020; Keir et al., 2020; Peaslee et al., 2020) (see Section 1.6).

Biomonitoring to assess firefighter exposures to gases, VOCs, and sVOCs generally involves measurement of analytes in the blood (e.g. serum), urine, or exhaled breath (e.g. Fernando et al., 2016; Wallace et al., 2017, 2019a; Andersen et al., 2018b; Wingfors et al., 2018; Cherry et al., 2019; Grashow et al., 2020). The biomonitoring strategy employed (i.e. strategy for sample collection, handling, and analysis), and the instrumentation employed to detect and quantify the chemicals or chemical metabolites, depends on the properties of the analyte, the analytical approach (e.g. targeted or non-targeted), and the parameters of absorption, distribution, metabolism, and excretion of the analyte (see Section 1.4.5). Table 1.10 provides a brief overview of analytical techniques that have been employed for biomonitoring of firefighters' exposures to selected chemicals.

Assessment of exposures to combustion-derived gases (e.g. CO, NO_2) generally involves direct analysis of exhaled breath or blood (e.g. Stewart et al., 1976; Kales et al., 1994; Dunn et al., 2009; Miranda et al., 2012; Table 1.10).

Assessment of exposures to VOCs (e.g. benzene) generally involves extraction of analytes from exhaled breath or urine using a solid adsorbent; thermally desorbed analytes are generally detected and quantified using gas chromatography or high-performance liquid chromatography coupled with tandem mass spectrometry (GC-MS/MS or HPLC-MS/MS) (e.g. Bader et al., 2014; Wallace et al., 2017, 2019a, b; Rosting & Olsen, 2020; Kim et al., 2021; Table 1.10). Biomonitoring of sVOCs generally involves examination of analytes in the serum or urine (Table 1.10); urine (e.g. spot sample, morning sample, 24-hour void) is sometimes preferred since collection is not invasive. In most cases, extraction and concentration of samples (e.g. via solid-phase or solvent extraction) is followed by detection and quantification using GC-MS/MS or HPLC-MS/MS (e.g. Moen & Øvrebø, 1997; Naeher et al., 2013; Oliveira et al., 2016; Keir et al., 2017; Gill et al., 2019, 2020a; Jayatilaka et al., 2019). It is also possible to assess exposures to some sVOCs using analyses of saliva or exhaled breath (e.g. Wallace et al., 2017, 2019a, b; Santos et al., 2019). Although targeted analyses are predominant, non-targeted approaches are becoming increasingly popular (Wallace et al., 2017, 2019b).

To determine whether firefighter biomonitoring data indicate exposure levels that differ from those of other individuals or populations, the levels of chemicals and/or their metabolites can be compared with those of control groups (e.g. fire service office workers), published population reference values, or the general population (e.g. Edelman et al., 2003; Dobraca et al., 2015; Keir et al., 2017; Grashow et al., 2020; Khalil et al., 2020; CDC, 2022; HBM4EU, 2022). Additionally, levels of chemicals or chemical metabolites

Table 1.10 Biomonitoring methods used to assess firefighter exposures to selected chemicals

Chemical component or agent	Biomarker and sample processing	Instrumentation (LOD and/or LOQ)	Comments and other relevant information	Reference
Benzene	Urinary *trans*,*trans*-muconic acid, acidification, and solvent extraction	HPLC with UV detection (LOQ, 0.02 mg/L)	Modified procedure of Angerer et al. (1997)	Bader et al. (2014)
Benzene	Urinary SPMA, acidification, and solvent extraction	HPLC with MS detection (LOD, 0.3 µg/L)	Modified procedure of Müller et al. (1997)	Bader et al. (2014)
Benzene	Unmetabolized urinary benzene	GC-MS headspace analysis (LOD, 10 ng/L)	Modified procedure of Angerer et al. (1994)	Bader et al. (2014)
Benzene and toluene	Urinary SPMA and *S*-benzylmercapturic acid, direct analysis	UPLC-MS, selected reaction monitoring (LOQ, 0.2 ng/mL)		Rosting & Olsen (2020)
Carbon monoxide	Blood carboxyhaemoglobin as carbon monoxide in exhaled breath after holding breath for set period of time	Exhaled breath monitor, electrochemical detection (LOD not reported)	Carboxyhaemoglobin level based on research conducted by Jarvis et al. (1986)	Stewart et al. (1976); Dunn et al. (2009)
Carbon monoxide	Carboxyhaemoglobin in diluted whole blood	Carbon monoxide-oximetry or manual spectrophotometry (LOD not reported)	Based on method described by Rodkey et al. (1979)	Kales et al. (1994)
Respiratory toxicants, carbon monoxide	TcDTPA, carboxyhaemoglobin and methaemoglobin in blood	Scintillation detection of ^{99m}Tc in the thigh, carboxyhaemoglobin and methaemoglobin by carbon monoxide-oximetry (LODs not reported)	^{99m}Tc-based method measures transfer of inhaled TcDTPA to blood and tissues	Minty et al. (1985)
Cyanide	Thiocyanate in blood serum	Spectrophotometric analysis of thiocyanate (LOD not reported)	Based on thiocyanate analysis method described by Bowler (1944)	Levine & Radford (1978)
Formaldehyde	Derivatized urinary thiazolidine-4-carboxylic acid, solvent extraction	GC-MS with SIM (details and LOD not reported)	Based on method of Shin et al. (2007) (MDL, 1 µg/L)	Kim et al. (2021)
Nitrogen dioxide	Exhaled breath nitric oxide (eNO) using portable hand-held NO analyser	NIOX MINO® electrochemical NO analyser, (details and LOD not reported)	Instrument designed and manufactured by Aerocine, Solna, Sweden	Miranda et al. (2012)
para-Chloroaniline	Urinary *para*-chloroaniline, alkaline hydrolysis and solvent extraction	HPLC with ECD (LOD, 2 µg/L)	Modified procedure of Lewalter et al. (1994)	Bader et al. (2014)
PAHs	PAHs in saliva, solvent extraction	Programmed temperature vaporizer GC-MS, synchronous SIM/scan mode (LOD ≤ 0.057 µg/L)	Measurement of 16 PAHs	Santos et al. (2019)
PAHs	Exhaled breath PAHs collected using dual-bed thermal desorption tubes	GC-MS following thermal desorption, SIM (LOD not reported)	Synchronous SIM/scan mode used for analyses of targeted analytes. PAH results not reported	Wallace et al. (2017, 2019a)

Table 1.10 (continued)

Chemical component or agent	Biomarker and sample processing	Instrumentation (LOD and/or LOQ)	Comments and other relevant information	Reference
PAHs	Urinary 1-OHP, enzymatic deconjugation and solvent extraction	LC-MS/MS, negative ion mode with multiple reaction monitoring (LOD, 10 ng/L)	Inter-laboratory comparison of two analytical methods	Gill et al. (2019)
PAHs	Urinary 1-OHP, enzymatic deconjugation, SPE, and derivatization	GC-HRMS with APCI (LOD, 0.64 ng/L)	Inter-laboratory comparison of two analytical methods	Gill et al. (2019)
PAHs	Urinary 1-OHP, acidification, enzymatic deconjugation, and SPE	HPLC with fluorescence detection (LOD not reported)	Based on method of Jongeneelen et al. (1987)	Moen & Øvrebø (1997)
PAHs	Urinary 1-OHP glucuronide, acidification and solvent extraction	MSI-CE-MS/MS, negative ion mode with multiple reaction monitoring (LOD, ≈7 ng/L)	Good agreement with 1-OHP determined using GC-MS	Gill et al. (2020a)
PAHs	Urinary hydroxylated PAHs, enzymatic deconjugation, solvent extraction and derivatization	GC-MS/MS with multiple reaction monitoring (LOD, 0.0007–0.04 µg/L)	Analyses of 19 hydroxylated PAH metabolites; method of Gaudreau et al. (2016)	Keir et al. (2017)
PAHs	Urinary hydroxylated PAHs, enzymatic deconjugation and solvent extraction	HPLC with fluorescence detection (LOD, 0.8 ng/L to 0.195 µg/L)	Analyses of six hydroxylated PAH metabolites	Oliveira et al. (2016)
PAHs	Urinary PAHs, enzymatic deconjugation and solvent extraction	PAH-CALUX assay, luminescence detection (LOD not reported)	Results expressed as B[*a*]P equivalents	Beitel et al. (2020)
Phenolic compounds	Urinary concentrations of seven phenolic compounds, deconjugated and concentrated by SPE	LC-MS/MS with SIM (LOD, 0.2–2.3 µg/L)	FOX (Firefighters Occupational Exposures) study	Waldman et al. (2016)
Non-targeted sVOCs	Blood serum sVOCs, concentrated via SPE	LC-MS/MS, non-targeted general suspect screen	WFBC (Women Firefighters Biomonitoring Collaborative) study. General suspect screen to identify chemicals of interest; tentatively identified chemicals subjected to confirmation	Grashow et al. (2020)
Non-targeted VOCs and sVOCs	Exhaled breath VOCs and sVOCs collected using dual-bed thermal desorption tubes	GC-MS following automated thermal desorption, SIM (LOD not reported)	Scan chromatograms used for analyses of non-target analytes	Wallace et al. (2017, 2019b)
Targeted VOCs	VOCs or VOC metabolites in urine, headspace analysis of parent compounds, SPE of selected metabolites	GC-MS or LC-MS/MS, depending on compound or metabolite (details and LOD not reported)	Based on NIOSH Method 8321 (NIOSH, 2016c) or NHANES 2011–2012 Laboratory Method (CDC, 2012)	Kim et al. (2021)

Table 1.10 (continued)

Chemical component or agent	Biomarker and sample processing	Instrumentation (LOD and/or LOQ)	Comments and other relevant information	Reference
Targeted VOCs	Exhaled breath VOCs collected using dual-bed thermal desorption tubes	GC-MS after automated thermal desorption, SIM for VOCs of interest (LOD not reported)	Synchronous SIM/scan mode used for analyses of targeted analytes, measurement of 8 targeted VOCs	Wallace et al. (2017, 2019a)
Wood smoke	Urinary levoglucosan, solvent extraction and derivatization	GC-MS/MS with multiple reaction monitoring (LOD, 10 ng/mL)		Naeher et al. (2013)
Wood smoke	22 methoxyphenols in acid-hydrolysed urine, SPE concentration	GC-MS with SIM (LODs, ≈ 0.004 µg/mL)	Based on methods of Dills et al. (2001) and Dills et al. (2006)	Neitzel et al. (2009)

APCI, atmospheric-pressure chemical ionization; B[*a*]P, benzo[*a*]pyrene; CE, capillary electrophoresis; CO, carbon monoxide; ECD, electron capture detection; GC-HRMS, gas chromatography-high-resolution mass spectrometry; GC-MS, gas chromatography-mass spectrometry; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LOD, limit of detection; LOQ, limit of quantification; MDL, method detection limit; MSI-CE-MS/MS, multi-segment injection-capillary electrophoresis-tandem mass spectrometry; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; NO, nitric oxide; 1-OHP, 1-hydroxypyrene; PAH, polycyclic aromatic hydrocarbon; SIM, selected ion monitoring; SPE, solid-phase extraction; SPMA, *S*-phenyl mercapturic acid; TcDTPA, ^{99m}Tc diethylene triamine penta-acetate; sVOC, semi-volatile organic compound; UPLC-MS, ultra-performance liquid chromatography-mass spectrometry; UV, ultraviolet; VOC, volatile organic compound.

can be toxicologically evaluated via comparisons with reference values such as biological exposure indices (BEIs), binding biological limit values (BBLVs), or biological limit values (BLVs) (Morgan, 1997; Viegas et al., 2020) (see Section 1.7(b)).

(b) Other chemical and physical agents

Published biomonitoring methods for chemical and physical agents excluding fire smoke components are listed in Table S1.11 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). This list is illustrative and not comprehensive. Biomonitoring for exposures to diesel exhaust typically use urinary PAH metabolites, which are described in Section 1.4.5(d).

Biomonitoring for asbestos exposure is generally not conducted in firefighters, although bronchial lavage fluid analysis for macrophage asbestos fibres has been reported in a firefighter responder to the World Trade Center (WTC) disaster in New York City, USA, in 2001 (Rom et al., 2002).

PBDEs and PCBs can be measured in serum using gas chromatography-high-resolution mass spectrometry (GC-HRMS) (Park et al., 2015) and are generally expressed in units of ng/g of lipid, given their high lipid solubility. Although less commonly studied, PCBs can also be measured in urine (Haga et al., 2018). PCDD/Fs and PBDD/Fs (as well as PBDEs) have been measured by gas chromatography-isotope dilution-high-resolution mass spectrometry (GC-HRMS) (Mayer et al., 2021). PBDEs can also be measured in sweat but are more difficult to detect than in urine (Genuis et al., 2017). Non-PBDE flame retardants, such as 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) metabolized to 2,3,4,5-tetrabromobenzoic acid (TBBA), have been measured using HPLC-MS/MS in the urine of firefighters (Jayatilaka et al., 2017, 2019). These, together with chlorinated alkyl and non-chlorinated aryl OPFRs were introduced after PBDEs were phased out. In addition, dialkylphosphate metabolites of organophosphate pesticides have also been measured in firefighters' urine using the same method (Jayatilaka et al., 2017, 2019).

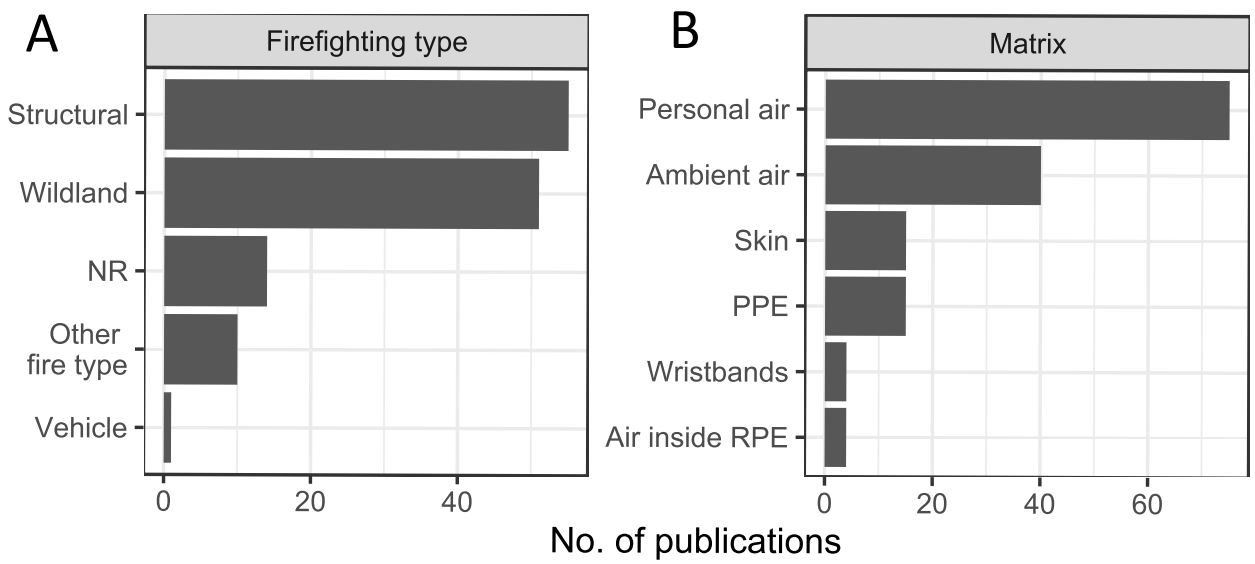
PFAS have been measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Trowbridge et al., 2020). In another study using quadrupole time-of-flight tandem mass spectrometry (QTOF-MS/MS), both targeted and untargeted PFAS were measured; the LODs and LOQs for PFOS were 0.02 and 0.06 ng/mL, respectively, and for PFHxS were 0.07 and 0.35 ng/mL respectively (Rotander et al., 2015a). Targeted serum PFAS levels have been measured in 50 µL of sample using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) with an LOD of 0.05–0.04 ng/mL (Mottaleb et al., 2020).

Inductively coupled plasma-mass spectrometry (ICP-MS) has been used to measure serum total mercury, manganese, cadmium, and lead in firefighters, resulting in LODs of 0.02–0.54 ng/mL (Dobraca et al., 2015). Metals have also been measured using atomic absorption spectrophotometry (AAS) for lead, cadmium, and antimony, and the atomic absorption spectrophotometry-hydride vapour generator method (AAS-HG) for serum arsenic and mercury (Al-Malki, 2009). LODs using AAS varied according to instrument, but typical values were 1–100 ng/mL. Metals can also be measured in urine by the same methods (Wolfe et al., 2004).

1.4 Exposure to fire effluents, according to type of fire and level of exposure

Published data on exposures during firefighting activities identified by the Working Group derived primarily from studies performed in the USA (58%), Canada (9%), and Australia (9%). Limited data were also available for the

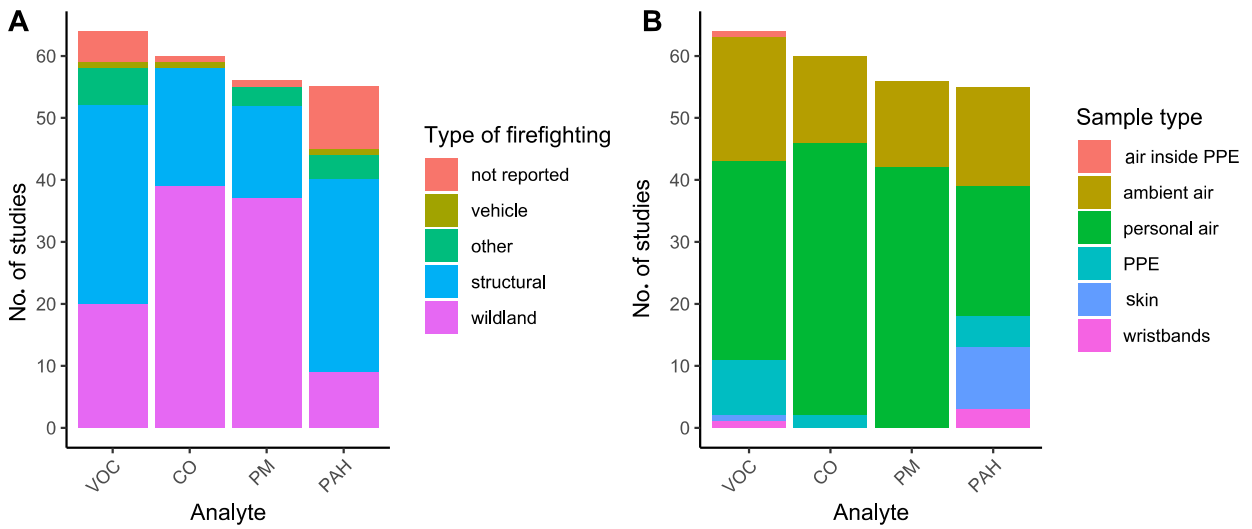
Fig. 1.9 Number of publications that report measurements of fire smoke components in firefighting context by (A) type of firefighting; and (B) sample matrix



NR, type of firefighting not specified; PPE, personal protective equipment; RPE, respiratory protective equipment. [The Working Group compiled information from all studies identified on PubMed until May 2022 that provided measurement data on firefighters' exposure.] Created by the Working Group.

UK and some other countries in Europe (e.g. Denmark, Finland, France, the Netherlands, Poland, Portugal, Spain, and Sweden) and Asia (e.g. China, Kuwait, and Saudi Arabia), but not for Central and South America. One study was available from the Caribbean region and none from Africa (Table S1.12, Table S1.13, Table S1.14, and Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Most of the available information characterized the presence of different fire effluents, including particulates, VOCs, sVOCs, CO, and PAHs in the breathable air (ambient or personal) during structure and forest fires (Fig. 1.9(a)). The available information demonstrated a high degree of variability in the chemical composition of fire smoke and in the levels of exposure in different firefighting scenarios and sample types (Fig. 1.9 and Fig. 1.10). Information retrieved from the literature suggested the presence of higher concentrations of total and respirable particulate matter, VOCs and sVOCs (including benzene, toluene, ethylbenzene, and xylene, a group known as "BTEX"), and CO in structure fires than in wildfires, prescribed burns, and other types of fire (e.g. vehicles, warehouses, diesel oil, and experimental fires). Studies report considerable variability in the concentrations of PAHs in different types of fire, with the lowest levels being found during wildfires and prescribed burns (Fig. 1.11(a)). [There are several environmental factors, as well as fuel and fire conditions, firefighters' tasks on scene, and duration of exposure/shift that affect exposure during different firefighting activities.] [The data in Fig. 1.11, Fig. 1.12, Fig. 1.13, and Fig. 1.14 shown in this section are from studies that reported

Fig. 1.10 Number of publications that reported measurements of VOCs, sVOCs, CO, particulate matter, and PAHs in the firefighting context by (A) type of firefighting; and (B) type of sample



CO, carbon monoxide; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; PPE, personal protective equipment; sVOC, semi-volatile organic compound; VOC, volatile organic compound. [The Working Group compiled information from all studies identified on PubMed until May 2022 that provided measurement data on firefighters' exposure.]
Created by the Working Group.

mean or median values (range values were not included). The figures do not differentiate by time period of the sample; for detailed information, consider Tables S1.12–S1.15 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).]

Approaches using biomonitoring to characterize firefighters' exposure to fire effluents are described in Section 1.4.5.

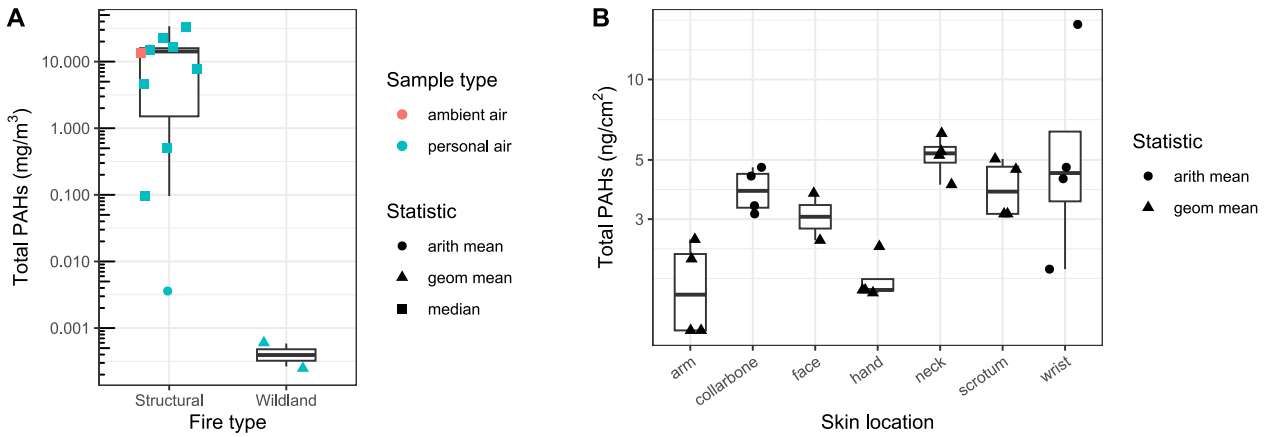
1.4.1 Structure fires

Table 1.16 presents the available studies that assessed concentrations of particulates, VOCs, sVOCs, CO, and PAHs in structure fires by sample type; detailed information is presented in Table S1.12 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

(a) Particulate matter

Measurement of environmental contamination with particulates, expressed as concentration of total particulate matter, ranged from 0.137 mg/m^3 during training fires (Sjöström et al., 2019b) to 560 mg/m^3 at the knockdown of training and/or urban fires involving the burning of wood, paper, kerosene, PVC plastic, stuffed furniture, tenement, and rubbish, among other materials (Jankovic et al., 1991). The maximum reported single measurement was 15 000 mg/m^3 (Burgess & Crutchfield, 1995). Ambient concentrations of respirable particulate matter varied from < 0.10 mg/m^3 in burned houses (with different fire origins) furnished with typical household materials during fire training exercises (NIOSH, 1998a) to 484 mg/m^3 (maximum

Fig. 1.11 Concentrations of total PAHs (A) in breathable air (ambient and personal) during different types of firefighting; and (B) on different skin locations of firefighters after municipal firefighting



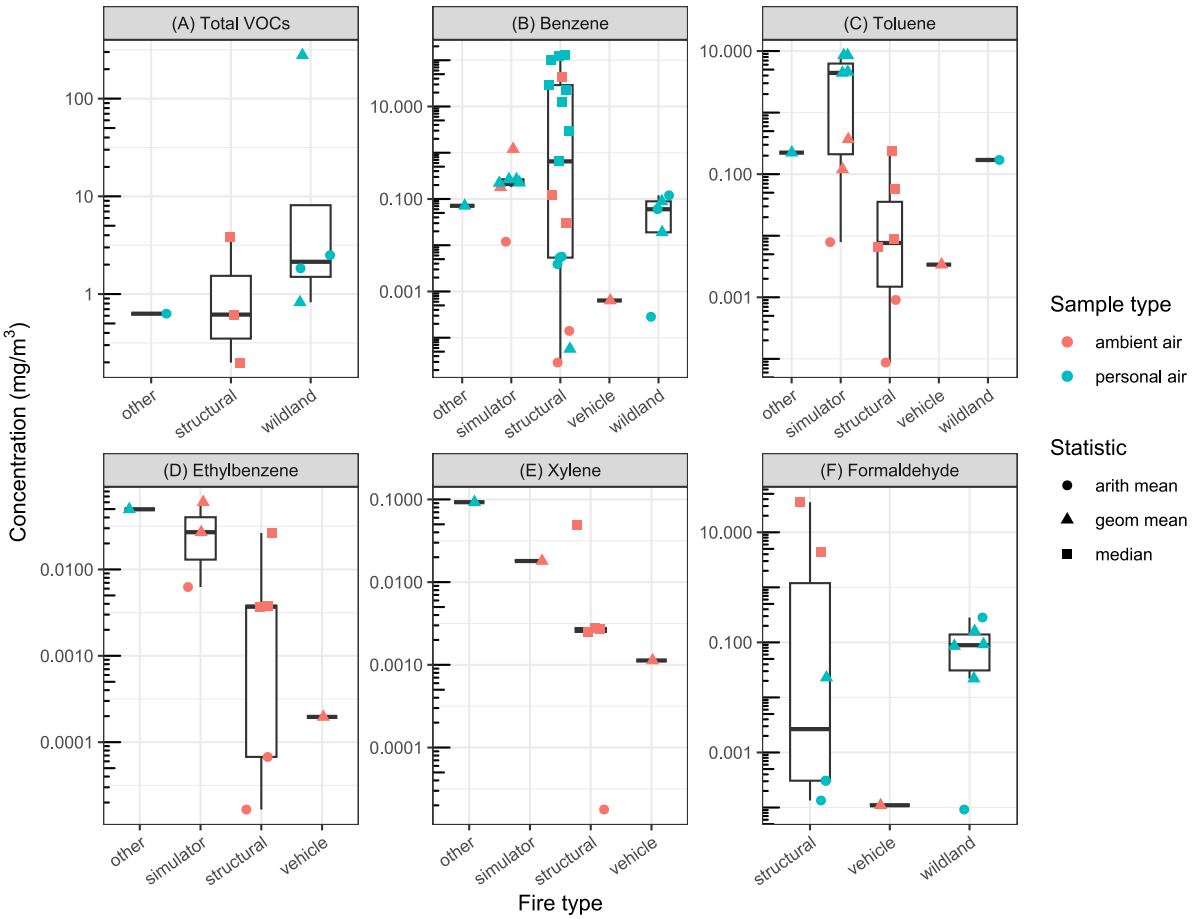
arith, arithmetic; geom, geometric; PAH, polycyclic aromatic hydrocarbon.
[The Working Group compiled information from all studies identified on PubMed until May 2022 that provided measurement data on firefighters' exposure.] Only the mean or median values are plotted in the figures. No data on other firefighting activities were available for skin exposure. Values are presented in a logarithmic scale. [Prescribed burns are usually performed under controlled conditions and so wildland fire exposure data might underestimate the real extent of exposure. See text for more information.]
Created by the Working Group.

single measurement increasing up to 715 mg/m³) during controlled residential fires inside living rooms with modern furnishings (Fent et al., 2018). Regarding total particle count, median levels ranged from 93 152 particles per cm³ during the overhaul phase of live fires (Baxter et al., 2014) to 1 580 000 (range, 102 700–2 970 000) particles per cm³ during controlled residential fires (Fent et al., 2018). Only one study (Baxter et al., 2014) evaluated environmental contamination with particulate matter with a diameter of 2.5 µm or less ($PM_{2.5}$), measuring average concentrations of 0.253–17.53 mg/m³ during firefighting at live overhaul events.

(b) Volatile organic compounds

Structure fires release several VOCs. Concentrations of total VOCs ranging between 0.10 and 107 ppm have been reported during experimental fires burning various materials frequently present in structure fires (Fig. 1.12(a); Table S1.12, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). A study performed in Saudi Arabia demonstrated that firefighters' personal air contained VOCs, including BTEX and CO, at levels that were predominantly higher during firefighting at residential fires than during firefighting at industrial fires (Alharbi et al., 2021; Table S1.12, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Ambient air concentrations of BTEX and formaldehyde ranged between 0.018 and 797 mg/m³ for benzene (maximum single value of 1027 mg/m³ at residential fires); 0.173 and 640 mg/m³ for toluene; 0.0044 and 125 mg/m³ for ethylbenzene; 0.0044 and 80.5 mg/m³ for isomers of xylene; and 0.020 and 35.2 mg/m³

Fig. 1.12 Concentrations of total VOCs, and benzene, toluene, ethylbenzene, xylene, and formaldehyde in the breathable air (ambient or personal) by type of firefighting activity reported in the literature



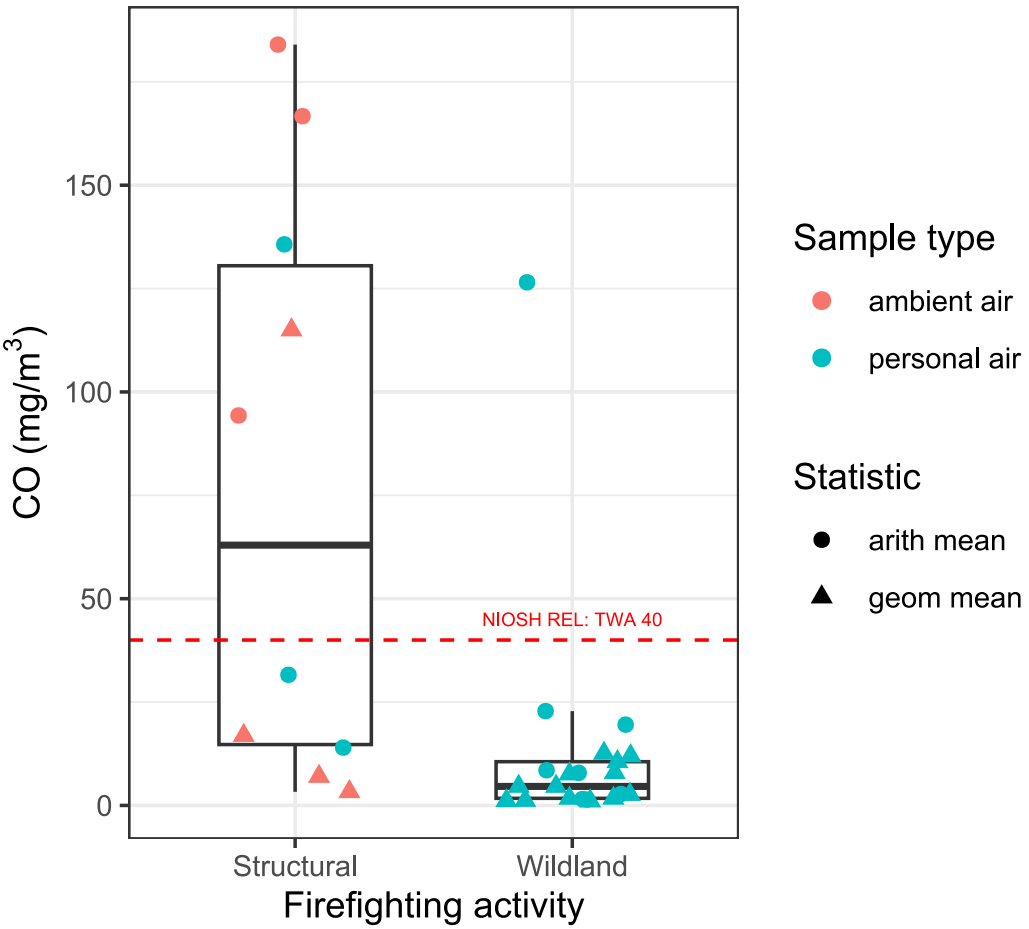
arith, arithmetic; geom, geometric; VOC, volatile organic compound.
[The Working Group compiled information from all studies identified on PubMed until May 2022 that provided measurement data on firefighters' exposure.] Only the mean or median values are plotted in the figure. Values are presented in a logarithmic scale.
Created by the Working Group.

for formaldehyde (Fig. 1.12(b–f) or Table S1.12, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Increased levels of acetaldehyde (up to 291 mg/m³), benzene (up to 101.1 mg/m³), acrolein (up to 60.6 mg/m³), and formaldehyde (up to 35.2 mg/m³) were reported during training exercises burning different fuel packaging materials, including oriented strand board, pallet, and straw, to simulate residential fires (Fent et al., 2019b).

(c) Carbon monoxide

Regarding CO, reported mean values for breathable air (ambient or personal) in structure fire environments were compiled and are presented in Fig. 1.13. Overall reported ranges reached 15 000 ppm [17 250 mg/m³] during live residential fires (Lowry et al., 1985): maximum levels reached 31 050 mg/m³ during structure fires (Burgess & Crutchfield, 1995) (Table S1.12, Annex 1, Supplementary material for Section 1,

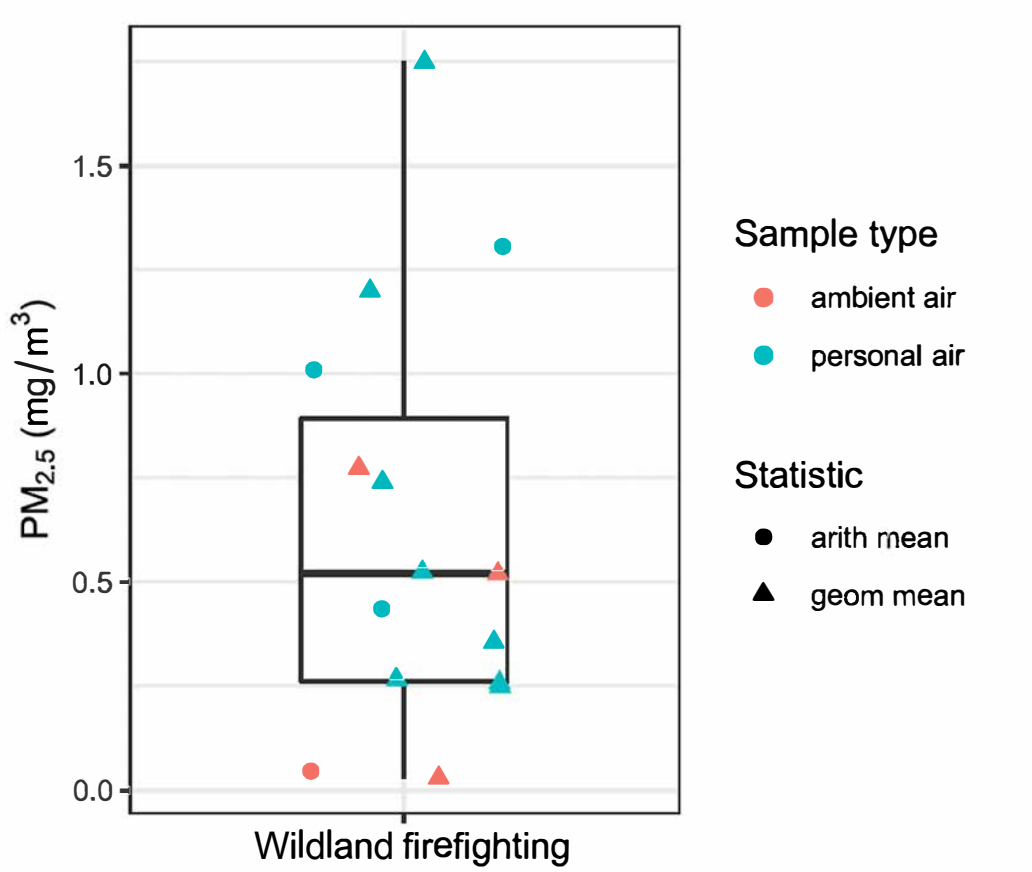
Fig. 1.13 Carbon monoxide concentrations in breathable air (ambient or personal) measured in the context of different firefighting activities



arith, arithmetic; CO, carbon monoxide; geom, geometric; NIOSH REL TWA, National Institute for Occupational Safety and Health recommended exposure limit (8-hour time-weighted average).
[The Working Group compiled information from all studies identified on PubMed until May 2022 that provided measurement data on firefighters' exposure.] Only the mean or median values are plotted in the figure. The NIOSH recommended exposure limit is indicated to allow the reader to put the values into context.
Created by the Working Group.

Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Alharbi et al. (2021) found higher concentrations of CO in the personal air of firefighters attending industrial fires than in those working on residential fires (16.43–384.2 versus 7.89–291.9 mg/m³). Several authors reported high concentrations of CO (> 1000 mg/m³) in the ambient and breathing-zone air of firefighters during firefighting at different structure fires (Table S1.12, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). In emissions from structure fires, the presence of CO was demonstrated at levels that exceeded, for instance, the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (8-hour time-weighted average, TWA) of 40 mg/m³ (Fig. 1.13).

Fig. 1.14 Concentrations of $PM_{2.5}$ in breathable air (ambient and personal) measured in the context of wildland firefighting activities



arith, arithmetic; geom, geometric; $PM_{2.5}$, particulate matter with a diameter of 2.5 µm or less.
[The Working Group compiled information from all studies identified on PubMed until May 2022 that provided measurement data on firefighters' exposure.] Only the mean/median values are plotted in the figure.
Created by the Working Group.

(d) Polycyclic aromatic hydrocarbons

The available literature highlighted structure fires as an important source of exposure to PAHs through inhalation and dermal contact (Fig. 1.11(a) and Fig. 1.11(b)). Firefighters' exposure to total PAHs through breathable air (ambient or personal) varied between 3.6 µg/m³ (geometric mean; training exercises; Sjöström et al., 2019b) and 23.8 mg/m³ (median; maximum single values reached 78.2 mg/m³) during fire combat on residential buildings (Fent et al., 2018; Fig. 1.11(a)). For benzo[*a*]pyrene (IARC Group 1, *carcinogenic to humans*; Table 1.1), personal exposure varied from 8.67 ng/m³ (geometric mean; Sjöström et al., 2019b) to 700 µg/m³ (arithmetic mean; Feunekes et al., 1997) during training firefighting exercises, the latter using heating oil. For PAHs classified by IARC in Group 2B, *possibly carcinogenic to humans* (Table 1.1), the range of exposure values was 1.811300 µg/m³ for naphthalene (maximum up to 15 916 µg/m³), 0.0026–46 µg/m³ for benz[*a*]anthracene (maximum, 236.05 µg/m³), 0.005–23.8 µg/m³ for benzo[*k*]fluoranthene (maximum, 79.2 µg/m³), 0.0108–22.3 µg/m³ for

Table 1.16 Summary of analytes monitored at structure fires, by sample type

Analyte	Sample type	References
Carbon monoxide	Ambient air	Barnard & Weber (1979); Musk et al. (1979); Lowry et al. (1985); Jankovic et al. (1991); Burgess & Crutchfield (1995); Austin et al. (2001a, b); Burgess et al. (2001); Anthony et al. (2007); Cone et al. (2008); Caban-Martinez et al. (2018)
	Personal air	Gold et al. (1978); Brandt-Rauf et al. (1988, 1989); Jankovic et al. (1991); Pośniak (2000); Burgess et al. (2002); Slaughter et al. (2004); Kirkham et al. (2011); Alharbi et al. (2021)
Polycyclic aromatic hydrocarbons (PAHs)	Ambient air	Jankovic et al. (1991); NIOSH (1998a); Austin et al. (2001a, b); Anthony et al. (2007); Kirk & Logan (2015a); Akhtar et al. (2016); Fent et al. (2018); Banks et al. (2021a)
	Personal air	Feunekes et al. (1997); Baxter et al. (2014); Fernando et al. (2016); Fent et al. (2018, 2019b); Sjöström et al. (2019b); Keir et al. (2020); Poutasse et al. (2020)
	Skin	Bolstad-Johnson et al. (2000); Laitinen et al. (2010); Baxter et al. (2014); Fernando et al. (2016); Fent et al. (2014, 2017); Wingfors et al. (2018); Strandberg et al. (2018); Andersen et al. (2018a, b); Sjöström et al. (2019b); Keir et al. (2020); Caban-Martinez et al. (2020); Banks et al. (2021a)
Particulate matter	Ambient air	Musk et al. (1979); Jankovic et al. (1991); Burgess & Crutchfield (1995); NIOSH (1998a); Burgess et al. (2001); Anthony et al. (2007); Baxter et al. (2010, 2014); Fent et al. (2018)
	Personal air	Gold et al. (1978); Brandt-Rauf et al. (1988); Burgess et al. (2002); Sjöström et al. (2019b)
Volatile organic compounds and semi-volatile organic compounds (VOCs and sVOCs)	Ambient air	Lowry et al. (1985); Jankovic et al. (1991); Burgess & Crutchfield (1995); NIOSH (1998a); Austin et al. (2001a, b); Anthony et al. (2007); Caban-Martinez et al. (2018); Fent et al. (2018, 2019b); Kirk & Logan (2019)
	Personal air	Brandt-Rauf et al. (1988); Jankovic et al. (1991); Bolstad-Johnson et al. (2000); Pośniak (2000); Burgess et al. (2001, 2002); Slaughter et al. (2004); Fernando et al. (2016); Fent et al. (2018, 2019b); Sjöström et al. (2019b); Alharbi et al. (2021)

benzo[*b*]fluoranthene (maximum, 218.59 μg/m³), 0.0158–18 μg/m³ for indeno[1,2,3-*c,d*]pyrene (maximum, 146.36 μg/m³), 0.00 457–12.9 μg/m³ for chrysene (maximum, 1062.72 μg/m³), and 0.2–7.0 μg/m³ for benzo[*j*]fluoranthene (Table S1.12, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Firefighters involved in fire combat at structure fires were also exposed to the PAH dibenz[*a,h*]anthracene (IARC Group 2A, *probably carcinogenic to humans*) (Table 1.1) at levels ranging between non-detected and 68 μg/m³ during the overhaul phase of firefighting activities on residential and commercial buildings (Bolstad-Johnson et al., 2000). Over the last few decades, information has slowly emerged related to the contamination of firefighters' skin with PAHs as a result of exposure to fire emissions (Fig. 1.11(b)). Despite being limited in number, all the studies reported increased levels of pollutants on the neck/collarbone, wrists, hands/fingers, face/forehead, back, and scrotum of firefighters after fire combat (Table S1.12, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

(e) Job assignments

[The Working Group highlighted that evidence dedicated to firefighters' exposures based on job assignments is limited.] Caban-Martinez et al. (2018) recorded a reading of 1.5 ppm for total VOCs in firefighters who were fully involved in an arson investigation into a vehicle fire and who were approximately 10 feet [3 m] from the vehicle; the reading persisted throughout the investigation. Moreover, arson investigators may re-aerosolize particulate and experience inhalation and dermal exposures to a variety of contaminants when moving debris during their investigations. Recently, Horn et al. (2022) reported concentrations of different particulate matter fractions (including submicron particles) at increased levels (based on the air quality index) during a 60-minute post-fire investigation of controlled residential fires containing furnishings currently used in the bedroom, kitchen, and living room. Those authors registered median $PM_{2.5}$ concentrations exceeding 0.100 mg/m³ (range, 0.016–0.498 mg/m³), with peak transient values reaching 23.7 mg/m³ (median, 1.090 mg/m³). Similar findings were observed for airborne aldehyde concentrations, with those for formaldehyde (median, 0.356 mg/m³; range, 0.140–0.775 mg/m³) exceeding the NIOSH limit (Horn et al., 2022).

1.4.2 Wildland fires

The available information on levels of exposure during wildland fires is presented in Table 1.17. Most of the available studies characterized prescribed burns and only some reports described participation at live wildfires or experimental/simulated wildfires (Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). [The Working Group noted that prescribed burns are usually performed under controlled conditions; exposure might be higher and much longer in large wildfire incidents. The wildfire exposure scenario presents challenges that make personal sampling complicated. Hence, wildland fire exposure data in the literature might underestimate the real extent of exposure.]

(a) Particulate matter

Studies reported that firefighters were exposed to increased levels of total (0.10–47.6 mg/m³) and respirable (0.02–154 mg/m³) particulate matter during wildland firefighting compared with background levels (overall range of background levels reported: total particulate matter, 0.022–0.63 mg/m³; maximum peak value, 6.9 mg/m³; and respirable particulate matter, 1.39–1.47 mg/m³; maximum peak value,

Table 1.17 Summary of analytes monitored at wildfires, by sample type

Analyte	Sample type	References
Carbon monoxide	Ambient air	Cone et al. (2005)
	Personal air	NIOSH (1991; 1992b, c, 1994a); McMahon & Bush (1992); Materna et al. (1992); Reinhardt et al. (2000); Reinhardt & Ottmar (2004); Edwards et al. (2005); Reisen et al. (2006, 2011); Swiston et al. (2008); De Vos et al. (2009b); Dunn et al. (2009); Neitzel et al. (2009); Reisen & Brown (2009); Carballo-Leyenda et al. (2010); Miranda et al. (2010, 2012); Adetona et al. (2011, 2013a, b, 2017b, 2019); Hejl et al. (2013); Dunn et al. (2013); Gaughan et al. (2014c); Ferguson et al. (2017); Reinhardt & Broyles (2019); Henn et al. (2019); MacSween et al. (2020); Wu et al. (2021)
Polycyclic aromatic hydrocarbons (PAHs)	Ambient air	Navarro et al. (2019a)
	Personal air	Materna et al. (1992); NIOSH (1992b, c, 1994a); Robinson et al. (2008); Navarro et al. (2017); Cherry et al. (2021a)
Particulate matter	Ambient air	NIOSH (1992c); Robinson et al. (2008); Cherry et al. (2019); Navarro et al. (2019a)
	Personal air	NIOSH (1991, 1992b, 1994a); McMahon & Bush (1992); Materna et al. (1992); Reinhardt & Ottmar (2000, 2004); Reinhardt et al. (2000); Slaughter et al. (2004); Edwards et al. (2005); De Vos et al. (2006, 2009b); Naeher et al. (2006); Reisen et al. (2006, 2011); Robinson et al. (2008); Neitzel et al. (2009); Reisen & Brown (2009); Miranda et al. (2010); Adetona et al. (2011, 2013a, b, 2017b, 2019); McNamara et al. (2012); Hejl et al. (2013); Naeher et al. (2013); Gaughan et al. (2014b); Ferguson et al. (2017); Reinhardt & Broyles (2019); Navarro et al. (2021); Wu et al. (2021)
Volatile organic compounds and semi-volatile organic compounds (VOCs and sVOCs)	Ambient air	Toussaint et al. (2010)
	Personal air	NIOSH (1991, 1992b, c, 1994a); Materna et al. (1992); Reinhardt et al. (2000); Reinhardt & Ottmar (2000, 2004); De Vos et al. (2006, 2009a, b); Reisen et al. (2006, 2011); Reisen & Brown (2009); Miranda et al. (2010, 2012); Navarro et al. (2021)

4.38 mg/m³) (Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). However, only few studies included the monitoring of background levels of exposure to particulate matter during the overall work shift of firefighters (Reinhardt et al., 2000; Reinhardt & Ottmar, 2004). Among respirable particulates, $PM_{2.5}$ is the most commonly reported fraction, with ambient values ranging between 0.029 and 435.0 mg/m³; maximum values were found in the personal air of firefighters working on prescribed burns (Fig. 1.14). Moreover, some authors demonstrated that firefighters' personal exposure to particulate matter was higher during wildland firefighting than during the regular work shift (Reinhardt et al., 2000; Reinhardt & Ottmar, 2000, 2004; Booze et al., 2004).

Some studies demonstrated undesirable, unhealthy, or even hazardous levels of exposure to airborne $PM_{2.5}$ based on the United States Environmental Protection Agency (US EPA) ambient air quality index near the fire perimeter of USA wildfire incidents where firefighters camp and rest between work shifts (McNamara et al., 2012; Navarro & Vaidyanathan, 2020).

(b) Volatile organic compounds

Measurements of firefighters' personal levels of total VOCs during wildfires varied between 0.1 and 4.0 ppm (maximum peak level of 88 ppm during an experimental forest fire; Miranda et al., 2010) and from 0.415 to 5.30 mg/m³ (maximum peak level of 7.50 mg/m³ during prescribed and experimental forest burns; Reisen & Brown, 2009) (Fig. 1.12(a); Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Among individual VOCs, toluene (0.038–78 mg/m³), ethylbenzene (0.027–62 mg/m³), benzene (0.01–54 mg/m³), xylene (0.018–54 mg/m³), and formaldehyde (0.010–11 mg/m³) were found at higher concentrations in ambient or breathing-zone air of firefighters (Fig. 1.12(b–f)); Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

(c) Carbon monoxide

Wildland firefighting activities also expose firefighters to CO at personal levels ranging from 0.92 to 345 mg/m³ during wildfires and prescribed burns (Fig. 1.13); maximum ambient air peak values reached 1483 mg/m³ during the fire episode in training forest-fire exercises (Cone et al., 2005). Concentrations of CO were mostly higher during fire attack than during overhaul (Booze et al., 2004; Reinhardt & Ottmar, 2004; Cone et al., 2005; Dunn et al., 2013).

(d) Polycyclic aromatic hydrocarbons

Levels of total PAHs in the ambient air during wildfires and prescribed burns ranged from 56 to 9103 ng/m³ (Fig. 1.11(a)), with benzo[*a*]pyrene concentrations in the breathing (personal) air of firefighters varying between 0.012 and 7 ng/m³ (maximum peak values of up to 140 ng/m³ during live wildfires; Navarro et al., 2017) (Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Exposures to naphthalene (range, 467–6170 ng/m³; maximum peak value, 35 900 ng/m³), benz[*a*]anthracene (range, 8–18 ng/m³; maximum peak value, 192 ng/m³), benzo[*b*]fluoranthene (range, 5–28 ng/m³; maximum peak value, 1700 ng/m³), benzo[*k*]fluoranthene (range, 4–7 ng/m³; maximum peak value, 79 ng/m³), chrysene (range, 11–31 ng/m³; maximum peak value, 250 ng/m³), indeno[1,2,3-*c*,*d*]pyrene (range, 3–21 ng/m³; maximum peak value, 103 ng/m³), and dibenz[*a*,*h*]anthracene (range, 4–10 ng/m³; maximum peak value, 50 ng/m³) were also reported in the breathing air of firefighters during firefighting at wildfires and prescribed burns (Materna et al., 1992; NIOSH, 1992b, c, 1994a; Booze et al., 2004; Robinson et al., 2008;

Table 1.18 Summary of analytes monitored at vehicle fires, by sample type

Analyte	Sample type	References
Carbon monoxide	Ambient air	Caban-Martinez et al. (2018)
Polycyclic aromatic hydrocarbons (PAHs)	Personal air	Fent & Evans (2011)
Particulate matter	Ambient air	Borgerson et al. (2011)
	Personal air	Baxter et al. (2010); Evans & Fent (2015)
Volatile organic compounds and semi-volatile organic compounds (VOCs and sVOCs)	Ambient air	Borgerson et al. (2011); Caban-Martinez et al. (2018)
	Personal air	Fent & Evans (2011)

Navarro et al., 2017, 2019b; Cherry et al., 2021a; Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

[The measured levels of some airborne contaminants during wildfires may appear lower than those observed during structure fires. However, the types of activity sampled, temporal and spatial variability in contamination levels outdoors, duration of the sampling period, the total exposure period, and the type of PPE used need to be taken into consideration when assessing wildland firefighters' exposure.]

1.4.3 Vehicle fires

Vehicle fires occur at very low rates in some countries (e.g. in Liechtenstein and the Russian Federation) but account for up to 13–23% of all fires or incidents in countries such as Australia, France, Japan, New Zealand, Sweden, and the USA (Monash University, 2014; CTIF, 2021). There is a paucity of information on firefighters' exposure to emissions from these fires (Fig. 1.9(a) and Fig. 1.10(a); Table 1.18). Only five studies, all performed in the USA, characterized the levels of pollutants released from these brief fire events during training activities (Table S1.14, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Other authors have also characterized vehicle fire emissions during experimental tests (Lönnermark & Blomqvist, 2006; Caliendo et al., 2013; Krüger et al., 2016; Truchot et al., 2018; Sjöström et al., 2019b). Overall, respirable particle concentrations and counts monitored in the condensed gas phase in the breathing air of firefighting forces were higher during fire combat on passenger cabins fires than on engine area fires (averages, 2.7 versus 0.36 mg/m^3 and 204 × 10^3 versus 54 × 10^3 particles per cm^3); maximum levels reached 170 mg/m^3 and 12 100 × 10^3 particles per cm^3, respectively (Evans & Fent, 2015). These values were determined during firefighting training activities performed on three salvaged vehicles; fires were suppressed with water. Evans & Fent (2015) and Baxter et al. (2010) highlighted the predominance of ultrafine particles during vehicle fire events (principally during overhaul), which may be associated with the complex mixture of materials burned in the vehicle (e.g. rubber, tyres, oil, batteries, foam, steel, electronic devices, fuel).

Ambient levels of some VOCs, including xylene, ethylbenzene, and naphthalene, were predominantly higher in engine fires than in passenger cabin fires (0.35–9.1 versus 0.45–2.7 mg/m^3, 0.15–2.2 versus 0.12–1.4 mg/m^3, and 0.930–2.4 versus 0.170–1.2 mg/m^3, respectively), whereas benzene concentrations were higher in passenger cabin fires (1.6–11 versus 0.38–60 mg/m^3) (Table S1.14, Annex 1,

Table 1.19 Summary of analytes monitored at other fire types, by sampling type

Analyte	Sample type	References
Carbon monoxide	Ambient air	Minty et al. (1985); Markowitz et al. (1989); Sebastião et al. (2021)
Polycyclic aromatic hydrocarbons (PAHs)	Ambient air	Hill et al. (1972); Ruokojärvi et al. (2000); NIOSH (1998a); Banks et al. (2021a)
	Personal air	Strandberg et al. (2018)
Particulate matter	Personal air	Dietrich et al. (2015); Andersen et al. (2017)
Volatile organic compounds and semi-volatile organic compounds (VOCs and sVOCs)	Ambient air	Hill et al. (1972); Markowitz et al. (1989); Etzel & Ashley (1994); NIOSH (1998a); Laitinen et al. (2010, 2012)

Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). [The Working Group noted that differences between VOC and sVOC concentrations may be attributed to the different materials burned in each compartment of the vehicles.]

The literature on the contribution of vehicle fire emissions to environmental levels of CO (up to 4.6 mg/m^3) and PAHs (170–2400 µg/m^3 for naphthalene) remains very limited (Fent & Evans, 2011; Caban-Martinez et al., 2018) (Table S1.14, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

1.4.4 Other types of fire

Table 1.19 presents the information available in the literature on other types of fire, including warehouse and training fires. Among VOCs and sVOCs, BTEX were the most characterized pollutants; concentrations ranged from 0.0091–466 mg/m^3, 0.0231–2.09 mg/m^3, 0.0179–1.66 mg/m^3, and 0.016–2.07 mg/m^3 for benzene, toluene, ethylbenzene, and xylenes, respectively (Fig. 1.12(b–e); Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). The highest ambient values for BTEX were reported during a large warehouse PVC fire (Markowitz et al., 1989) and a diesel-oil firefighting training exercise (Hill et al., 1972). For formaldehyde, ambient levels varied between 0.22 and 11 mg/m^3 during firefighting training exercises at diving simulators and house fires (NIOSH, 1998a; Laitinen et al., 2010) (Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Also, the following compounds were found at concentrations higher than 2 mg/m^3 during fire combat training in a diesel oil fire: acetylene/ethylene, C11 aromatics, diethylbenzene, ethylstyrene, toluene, *ortho*-xylene, and styrene (Hill et al., 1972).

Firefighters' exposure to CO ranged from 115 mg/m^3 during training exercises (Minty et al., 1985) to 10 695 mg/m^3 at a warehouse fire (Markowitz et al., 1989) (Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

Regarding ambient levels of PAHs, exposures to gaseous total PAHs reached 470 mg/m^3 during simulated firefighting activities at apartment fires with pieces of chipboard and old furniture (e.g. armchair, sofas, PVC plastics, etc.) being used as fire load (Ruokojärvi et al., 2000). Ambient concentrations of benzo[*a*]pyrene isomers (0.0045–5200 µg/m^3), naphthalene (1.00–54 000 µg/m^3), benzofluorene isomers (0.0025–1500 µg/m^3), indeno[1,2,3-*c*,*d*]pyrene

(0.0052–2000 μg/m³), and benz[*a*]anthracene plus chrysene (13–390 μg/m³) were also found in the literature; higher values were reported during simulated controlled compartment fires consisting of a diesel pan fire and a particleboard fire (Banks et al., 2021a; Table S1.15, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

Ruokojärvi et al. (2000) reported ambient levels of gaseous chlorinated pollutants, including polychlorinated phenols (14–300 μg/m³), biphenyls (2.8–56 μg/m³), chlorobenzenes (0.5–18 μg/m³), dioxins (12–83 ng/m³), and furans (21–160 ng/m³) during training exercises on simulated apartment fires. Some authors reported increased exposures at firefighting "safe zones", where individuals ease or even remove part of their PPE (e.g. SCBA), because they feel safer and need to relieve thermal and physical discomfort (Burgess et al., 2001; Andersen et al., 2017).

1.4.5 Biomarkers of exposure and considerations regarding absorption, distribution, metabolism, and excretion

Firefighters are exposed to complex mixtures at the fire suppression scene. Personal exposures to these chemicals can take place via dermal contact, inhalation, and non-dietary ingestion; biomonitoring can be used to assess the internal dose of combustion-derived chemicals, and/or their metabolites (see Section 1.3.4(a)) (WHO, 2015). Table 1.20 provides a summary of exposure biomarkers that have been employed to assess firefighters' exposures to noteworthy fire effluents, and a listing of studies that employed a variety of biomarkers.

The informativeness of biomonitoring values depends on factors such as the physical and chemical properties of the substance, the route of chemical exposure (i.e. dermal contact, inhalation, and non-dietary ingestion), as well as factors that influence absorption, distribution, metabolism, and excretion processes. These processes collectively control delivery of the chemical or its metabolite to the site of toxic action (Bessems & Geraets, 2013). In addition, such considerations influence the selection of an appropriate biomarker, the biological matrix to sample, the timing of sample collection, and the appropriate analytical method (OECD, 2022).

(a) Absorption

Absorption, which mechanistically controls bioavailability and internal dose, refers to processes that collectively move chemicals from the site of first contact (e.g. respiratory tract, dermal surface, gastrointestinal tract) to the bloodstream (Derendorf & Schmidt, 2019; Saghir, 2019).

Chemical absorption is affected by the exposure context (e.g. training versus emergency fire suppression), PPE use and post-use handling and storage, PPE design and efficiency (e.g. flash hood textile and design), site of contact (e.g. skin, respiratory tract, gastrointestinal tract), chemical form (e.g. vapour, particulate matter-adsorbed sVOCs), and firefighter duties (e.g. attack and knockdown, command and control).

Many researchers have underscored the importance of dermal absorption of substances such as PAHs and VOCs, including absorption when using turnout gear and SCBA (Feunekes et al., 1997; Laitinen et al., 2010; Baxter et al., 2014; Fent et al., 2014, 2017, 2020b; Pleil et al., 2014; Fernando et al., 2016; Oliveira et al., 2016; Andersen et al., 2017; Andersen et al., 2018a; Stec et al., 2018; Wingfors et al., 2018; Cherry et al., 2019, 2021a; Wallace et al., 2019a; Burgess et al., 2020; Keir et al., 2020; Banks et al., 2021a). Absorption of dermally deposited chemicals encountered during fire suppression, including VOC vapours and sVOCs adsorbed to airborne particulate matter, depends on PPE design and use, location and thickness of exposed skin (e.g. face, neck, wrist, forehead), physical exertion and movement, and environmental temperature

Table 1.20 Biomarkers commonly used to assess firefighters' exposures to selected fire effluents

Biomarker	Fire effluent	Selected references
Urinary biomarkers		
Urinary 2MHA	Xylenes	Fent et al. (2022)
Urinary 3HPMA	Acrolein	Fent et al. (2022)
Urinary 3MHA + 4MHA	Xylenes	Fent et al. (2022)
Urinary 4HBeMA	1,3-Butadiene	Fent et al. (2022)
Urinary BzMA	Toluene or benzyl alcohol	Fent et al. (2022)
Urinary hydroxylated PAHs	Selected PAHs	Feunekes et al. (1997); Moen & Øvrebø (1997); Caux et al. (2002); Edelman et al. (2003); Robinson et al. (2008); Laitinen et al. (2010, 2012); NIOSH (2013a); Fent et al. (2014, 2019a, 2020b); Fernando et al. (2016); Oliveira et al. (2016, 2017a, b, 2020b); Pierrard (2016); Adetona et al. (2017a, 2019); Andersen et al. (2017, 2018a, b); Keir et al. (2017); Hoppe-Jones et al. (2018); Wingfors et al. (2018); Allonneau et al. (2019); Cherry et al. (2019, 2021a); Gill et al. (2019, 2020a); Beitel et al. (2020); Burgess et al. (2020); Kim et al. (2020b); Rossbach et al. (2020); Bader et al. (2021); Banks et al. (2021a); Hoppe-Jones et al. (2021)
Urinary levoglucosan	Levoglucosan	Naeher et al. (2013)
Urinary MADA	Styrene	Fent et al. (2022)
Urinary methoxyphenols	Methoxyphenols (e.g. guaiacol, methylsyringol)	Neitzel et al. (2009); Fernando et al. (2016)
Urinary *para*-chloroaniline	*para*-Chloroaniline	Bader et al. (2014)
Urinary PHEMA	Styrene	Kim et al. (2021)
Urinary phenolic compounds	Phenolic compounds (e.g. bisphenol A, benzophenone-3)	Waldman et al. (2016); Bader et al. (2021)
Urinary PhMA	Benzene	Fent et al. (2022)
Urinary *S*-benzylmercapturic acid	Toluene	Rosting & Olsen (2020); Kim et al. (2021)
Urinary *S*-phenylmercapturic acid	Benzene	NIOSH (2013a); Fent et al. (2014); Bader et al. (2014, 2021); Rosting & Olsen (2020); Kim et al. (2021)
Urinary TZCA	Formaldehyde	Kim et al. (2021)
Urinary *trans,trans*-muconic acid	Benzene	Caux et al. (2002); Laitinen et al. (2010); Bader et al. (2014, 2021); Fent et al. (2022)
Urinary VOCs	BTEX	Bader et al. (2014); Heibati et al. (2018); Allonneau et al. (2019); Bader et al. (2021); Kim et al. (2021)
Haematological biomarkers		
Carboxyhaemoglobin in blood	Carbon monoxide	Levy et al. (1976); Loke et al. (1976); Radford & Levine (1976); NIOSH (1992c); Kales et al. (1994)
Blood cyanide	Cyanide	Jackson & Logue (2017); Edelman et al. (2003)
Blood methanol	Methanol	Aufderheide et al. (1993)
Thiocyanate in serum	Cyanide	Levine & Radford (1978)
Blood sVOCs	Selected sVOC, non-targeted approach	Grashow et al. (2020)
Blood VOCs	Selected VOCs (e.g. xylenes, dichlorobenzene)	Edelman et al. (2003)

Table 1.20 (continued)

Biomarker	Fire effluent	Selected references
Exhaled breath biomarkers		
Carbon monoxide in exhaled breath	Carbon monoxide	Stewart et al. (1976); Brotherhood et al. (1990); Cone et al. (2005); Dunn et al. (2009)
Nitric oxide (NO) in exhaled breath	Nitrogen dioxide (NO_2)	Miranda et al. (2012)
PAHs in exhaled breath	PAHs	Fent et al. (2014); Pleil et al. (2014); Wallace et al. (2017, 2019a, b)
VOCs (e.g. BTEXS) in exhaled breath	VOCs (e.g. BTEXS)	NIOSH (2013a); Fent et al. (2015, 2019a, 2020b); Pleil et al. (2014); Wallace et al. (2017, 2019a); Kim et al. (2021); Mayer et al. (2022)
VOCs and sVOCs in exhaled breath	Selected VOCs and sVOCs, non-targeted approach	Wallace et al. (2017, 2019b)
Saliva biomarkers		
PAHs in saliva	Selected PAHs	Santos et al. (2019)

2MHA, 2-methylhippuric acid; 3HPMA, *N*-acetyl-S-(3-hydroxypropyl)-L-cysteine; 3MHA + 4MHA, 3-methylhippuric acid + 4-methylhippuric acid; 4HBeMA, *N*-acetyl-*S*-(4-hydroxy-2-buten-1-yl)-L-cysteine; BTEX, benzene, toluene, ethylbenzene, and xylene; BTEXS, benzene, toluene, ethylbenzene, xylene, and styrene; BzMA, *N*-acetyl-*S*-(benzyl)-L-cysteine; MADA, mandelic acid; NO, nitric oxide; PAH, polycyclic aromatic hydrocarbon; PHEMA, *N*-acetyl-*S*-(2-phenyl-2-hydroxyethyl)-L-cysteine; PhMA, *N*-acetyl-*S*-(phenyl)-L-cysteine; sVOCs, semi-volatile organic compounds; TZCA, thiazolidine-4-carboxylic acid; VOCs, volatile organic compounds.

and humidity (Wester et al., 1990; WHO, 2006; Laitinen et al., 2010; NIOSH, 2013a; Baxter et al., 2014; Fent et al., 2014, 2017, 2020b; Andersen et al., 2018a; Stec et al., 2018; Sjöström et al., 2019b; Beitel et al., 2020; Keir et al., 2020; Rosting & Olsen, 2020).

Pulmonary absorption of inhaled chemicals, including VOCs (e.g. BTEX, methanol), sVOCs (e.g. PAHs with low molecular weight) and toxic gases (e.g. CO, NO_2) can also occur despite the use of PPE such as SCBA (Aufderheide et al., 1993; Fent et al., 2014, 2015, 2020b; Wallace et al., 2019a). Specifically, pulmonary contact and absorption can occur in situations in which SCBA is less likely to be used (e.g. during overhaul), before donning SCBA, if the SCBA is improperly used, and/or if the SCBA is prematurely doffed (Bolstad-Johnson et al., 2000; Austin et al., 2001c; Burgess et al., 2001; Fent et al., 2014, 2015; Wallace et al., 2019a; Beitel et al., 2020; Burgess et al., 2020; Rosting & Olsen, 2020). Additionally, secondary inhalation exposure can occur via contact with soiled turnout gear (Baxter et al., 2014; Fent et al., 2014, 2015; Pleil et al., 2014; Burgess et al., 2020). With respect to particulate matter and substances adsorbed to particulate matter, absorption is governed by aerodynamic diameter. Large particles (i.e. ≥ 10 µm) are generally retained by the nasopharyngeal system, i.e. they do not enter the lungs. Particulate matter in the 5–10 µm range is generally removed by alveolar macrophages (Geiser, 2010). These particles can also be inadvertently ingested after mucociliary clearance and swallowing, with subsequent absorption in the gastrointestinal tract followed by first-pass hepatic metabolism (Ramesh et al., 2004; Pambianchi et al., 2021). Importantly, small particles (i.e. $PM_{2.5}$) can penetrate the deeper regions of the pulmonary system. Particulate matter in the 1–2.5 µm range can interact with terminal bronchioles; those < 1 µm can readily gain access to alveoli (Schraufnagel, 2020). Particles < 0.1 µm have been shown to readily cross alveolar epithelia, thereby accessing the blood stream and systemic circulation (Schraufnagel, 2020). In comparison with transdermal absorption, pulmonary absorption can be rapid; thus, temporal patterns of excreted metabolites can be

used to determine the relative influence of the different exposure routes (Feunekes et al., 1997; Caux et al., 2002; Laitinen et al., 2012; Pierrard, 2016; Cherry et al., 2019).

(b) Distribution

Distribution refers to the reversible movement of an absorbed chemical from the site of contact (Taveli & Bellera, 2018). Effective distribution is required to permit the use of haematological and urinary biomarkers of exposure (e.g. urinary PAH and benzene metabolites); substances that are absorbed via dermal or pulmonary contact can be rapidly distributed to the sites of metabolism or toxic action. Generally speaking, parent compounds can be detected in the blood; biomonitoring is commonly conducted using serum analyses (e.g. brominated flame retardants and PFAS, see Section 1.5.1(i)) (e.g. Shaw et al., 2013; Rotander et al., 2015a; Trowbridge et al., 2020; Mayer et al., 2021). Metabolites are commonly detected in the urine (for example, metabolites of PAHs and benzene) (see Table 1.20, e.g. Caux et al., 2002; NIOSH, 2013a; Adetona et al., 2017a; Keir et al., 2017; Rosting & Olsen, 2020; Bader et al., 2021; Cherry et al., 2021a). Levels of systemically distributed chemicals can also be monitored via collection and analysis of exhaled breath; particularly for short-term exposures (see Table 1.20, e.g. Pleil et al., 2014; Fent et al., 2015; Wallace et al., 2017; Mayer et al., 2022).

(c) Metabolism and excretion

Metabolism and excretion are controlled by a complex series of dynamic processes influenced by factors such as genotype, sex, age, diet, drug and alcohol consumption, co-exposures to therapeutic products and other chemicals, and disease (Johnson et al., 2012).

The rates of metabolism and excretion (i.e. metabolite terminal half-life) are critically important for determining the appropriate time interval between an exposure event and biomarker sample collection (Bader et al., 2021). Since terminal excretion half-lives of combustion-derived chemicals (e.g. benzene, PAHs, environmental phenols) are generally in the range of 4–16 hours, several research groups have highlighted the importance of rapid post-exposure collection of firefighter biomonitoring samples (Caux et al., 2002; Fent et al., 2015; Waldman et al., 2016; Bader et al., 2021). It can be difficult to evaluate the results of urine samples collected long after the exposure (Caux et al., 2002; Keir et al., 2017; Bader et al., 2021). For example, benzene is rapidly metabolized and cleared from the blood, permitting rapid appearance of metabolites in the urine (Rosting & Olsen, 2020); the terminal half-life of the benzene metabolite *S*-phenylmercapturic acid is only 9 hours (Bader et al., 2021). Similarly, urinary elimination half-lives for hydroxylated metabolites of phenanthrene, fluorene, and naphthalene are in the range of 3–8 hours (Oliveira et al., 2016; Keir et al., 2017). This is consistent with time-course analyses conducted by Rossbach et al. (2020), who reported post-training concentrations of urinary PAH metabolites with half-lives of 3.5–9.3 hours. Consequently, timely collection of biomonitoring samples is of paramount importance (Caux et al., 2002; Keir et al., 2017; Cherry et al., 2019, 2021a; Fent et al., 2020b; Bader et al., 2021). Urine analyses are not commonly used for biomonitoring of exposures to PAHs of higher molecular weight (e.g. benzo[*a*]pyrene), because these substances are primarily excreted via the bile and faeces (Motorykin et al., 2015) and are largely undetectable in the urine (Keir et al., 2017, 2021; Wingfors et al., 2018; Allonneau et al., 2019). Recently, new biomarkers have been used that can provide information on exposure to benzo[*a*]pyrene, such as 3-hydroxybenzo[*a*]-pyrene (3-OH-BaP), the main urinary metabolite of benzo[*a*]pyrene (Alhamdow et al., 2019). However, this requires particularly sensitive analytical procedures, because the pathway for urinary excretion of this metabolite is much less significant than that for faecal excretion; this

permits use of 3-OH-BaP only in settings with high exposures, such as occupational exposure of firefighters (Oliveira et al., 2017c).

A recent published review on biomonitoring in firefighters indicated that the half-lives of noteworthy chemicals range from hours (e.g. PAH, VOC metabolites), to months or even years (e.g. PFAS, chemical flame retardants, see Section 1.5.1(i)) (Engelsman et al., 2020). There is considerable variability or uncertainty in published values for chemical half-lives, and by extension, determination of optimal timing for sample collection (Feunekes et al., 1997; Oliveira et al., 2016; Cherry et al., 2019). [The Working Group noted that there is a paucity of toxicokinetic data for many combustion-derived chemicals. Such data would facilitate interpretation of biomonitoring results in a firefighting context (Li et al., 2012; Oliveira et al., 2016, 2020b; Cherry et al., 2019; Engelsman et al., 2020). In particular, there is a need to critically examine how half-life values vary with different routes of exposure (i.e. transdermal, inhalation, and ingestion) (Li et al., 2012; Oliveira et al., 2016, 2020b).]

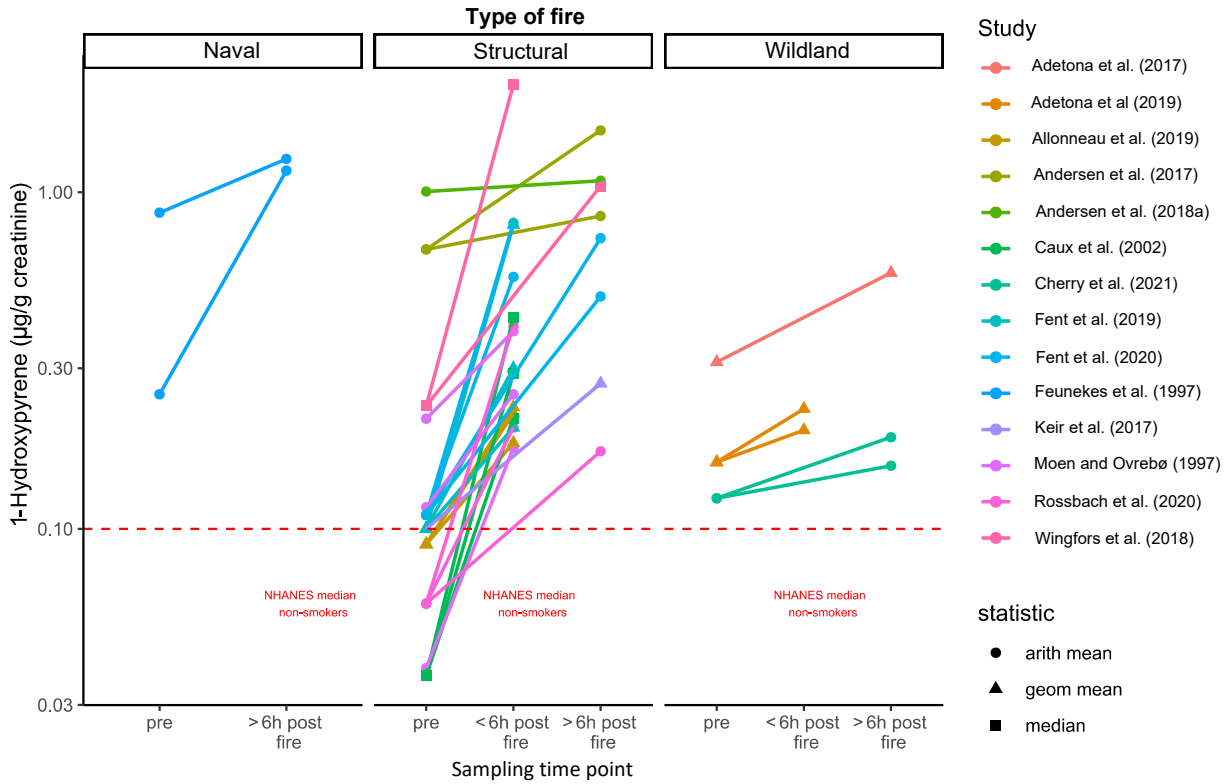
(d) Biomarkers of exposure

The studies listed in Table 1.20 collectively generated a large amount of biomarker data, particularly for urinary PAH metabolites. Although an extensive analysis of the available data was outside the scope of this section, some data patterns and deficiencies are highlighted here. Values for commonly used exposure biomarkers, e.g. 1-hydroxypyrene in urine and benzene in exhaled breath, were available from 67 studies. With respect to the predominant sources of the data, the majority of the studies were conducted in the USA (63%), followed by Canada (14%). Most of the studies (83%) involved career firefighters, and roughly half of the studies investigated structure fires. Almost 60% of the studies considered urinary biomarkers and nearly all the remaining studies examined exhaled breath (16%) or blood (18%).

Fig. 1.15 shows post-exposure changes in urinary 1-hydroxypyrene (μg/g creatinine); all the studies included in the analyses noted post-suppression increases (i.e. a fold-change of > 1.0). Seven studies noted relatively small fold-change increases (i.e. < 2) (Feunekes et al., 1997; Moen & Øvrebø, 1997; Adetona et al., 2017a, 2019; Andersen et al., 2017, 2018a; Cherry et al., 2021a); of those, three examined wildland firefighters (Adetona et al., 2017a, 2019; Cherry et al., 2021a). None of the studies that examined wildland firefighters noted fold-changes of > 2. Five studies noted fold-change increases of > 5 (Caux et al., 2002; Wingfors et al., 2018; Fent et al., 2019a, 2020b; Rossbach et al., 2020); all examined structural firefighters. The majority of studies that noted fold-change values of > 5 measured urinary hydroxypyrene levels in samples collected 3–12 hours post-exposure. This observation is well aligned with the aforementioned half-life range (i.e. 3–9.3 hours) for PAHs of low molecular weight (Oliveira et al., 2016; Keir et al., 2017; Rossbach et al., 2020). Fig. 1.16 shows the distribution of urinary 1-hydroxypyrene levels in firefighters before and after firefighting. The data indicated that, on average, levels post-exposure are 3.3-fold those pre-exposure; pre- and post-exposure levels are significantly different at $P < 0.0001$.

Fig. 1.17 shows post-exposure changes in the level of benzene in exhaled breath. Post-exposure fold-change values (i.e. post- versus pre-exposure) varied from 0.82 to 23.08 μg/m^3; 22 of the 26 values reflect a post-exposure increase (i.e. fold-change > 1.0). Twelve of the 26 values presented indicated a fold-change (i.e. post- versus pre-exposure) > 2; more than half of these (i.e. 7 out of 12) are associated with a sampling time point < 1 hour post-exposure (NIOSH, 2013a; Fent et al., 2020b; Pleil et al., 2014; Mayer et al., 2022). Indeed, all fold-change values for post-exposure sampling < 1 hour are > 1.0 (i.e. post-exposure increase in benzene in exhaled breath), with an average of 7.1 ± 2.3 μg/m^3 (n = 12). The sampling

Fig. 1.15 Urinary concentrations of 1-hydroxypyrene in firefighters before and after suppression of naval, structural, or wildland fires

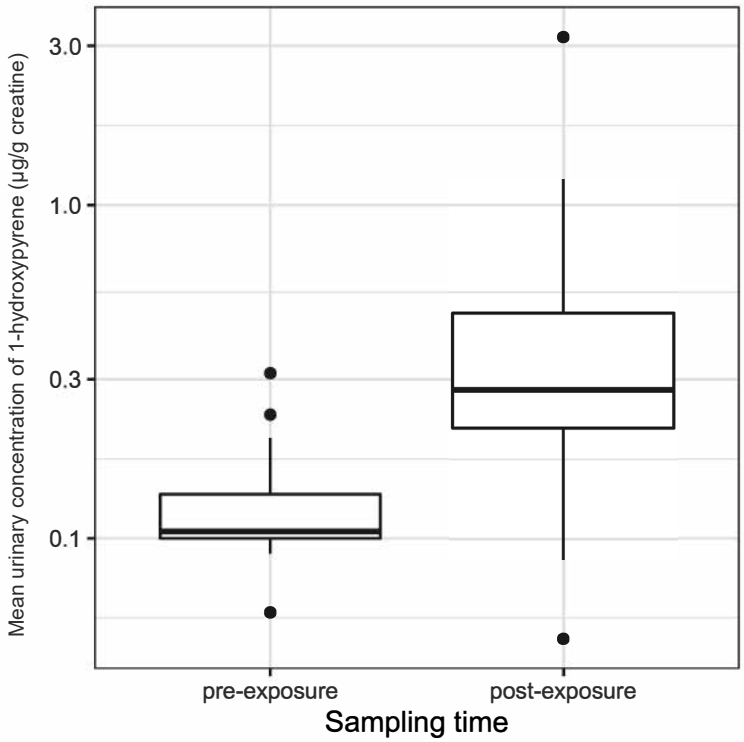


arith, arithmetic; geom, geometric; NHANES, National Health and Nutrition Examination Survey
[The Working Group compiled information from all studies identified on PubMed until May 2022 that provided biomonitoring data of firefighters' exposures.] Values are stratified by post-suppression sampling time and fire type. The median NHANES value for non-smokers is provided for comparison (CDC, 2018). Median values for European non-smokers vary from 0.046 to 0.16 µg/g (HBM4EU, 2022). Average Canadian non-smoker values are in the 0.1 µg/g range (Keir et al., 2021). All values are reported as creatinine-adjusted concentrations. Created by the Working Group.

time-point effect was significant at $P < 0.03$. This is consistent with the rapid absorption, distribution, and exhalation of VOCs such as benzene (US EPA, 1998).

[The Working Group noted that although it is clear that biomonitoring is a valuable tool for assessment of firefighters' exposure to combustion-derived chemicals, it is also clear that numerous factors need to be carefully considered when designing an effective biomonitoring study and when interpreting biomarker measurements in a fire suppression context. Factors that need to be considered when evaluating biomarker responses include sex, hydration level, primary route of exposure, type of fire, and the participant's role in fire suppression, as well as the substance's physical and chemical properties, environmental fate, and biological half-life.]

Fig. 1.16 Distribution of urinary concentrations of 1-hydroxypyrene in firefighters before and after fire suppression



All values are reported as creatinine-adjusted concentrations; values extracted from 11 studies (i.e. Adetona et al., 2017a, 2019; Allonneau et al., 2019; Bader et al., 2021; Cherry et al., 2019, 2021a; Fent et al., 2019a, 2020b; Gill et al., 2019; Keir et al., 2017; Rossbach et al., 2020). All values are arithmetic means, except those from Bader et al. (2021), Cherry et al. (2019), Keir et al. (2017) and Allonneau et al. (2019), Adetona et al. (2017a), which are geometric means. Values are presented in a logarithmic scale. Pre-exposure values (n = 14) range from 0.060 to 0.031, with mean and median values of 0.14 and 0.11, respectively. Post-exposure values (n = 32) range from 0.050 to 3.2, with mean and median values of 0.46 and 0.28, respectively. Post-exposure values include a variety of sampling times and analytical methods. The sampling time effect (i.e. pre-exposure versus post-exposure) on urinary 1-hydroxypyrene concentrations is statistically significant at $P < 0.0001$ [figure and calculations by the Working Group].
Created by the Working Group.

1.5 Exposures other than fire effluents and polycyclic aromatic hydrocarbons

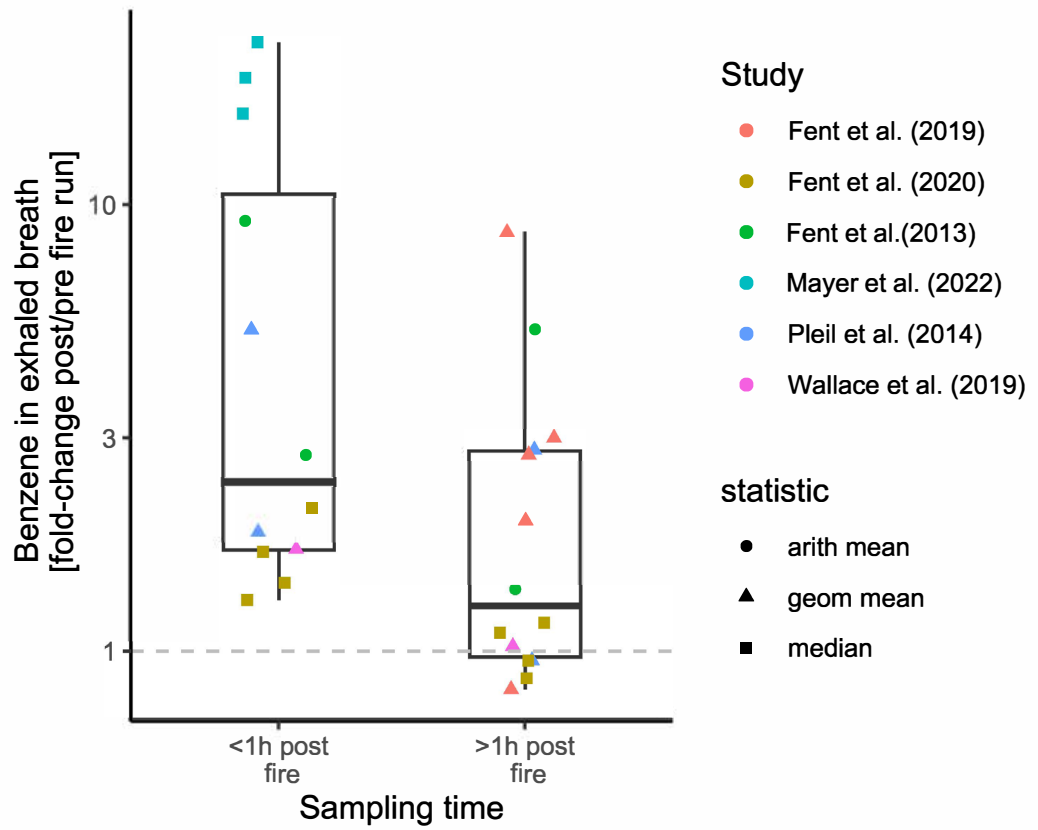
1.5.1 Chemicals and physical factors

(a) Asbestos and other minerals and fibres

Asbestos (IARC Group 1, *carcinogenic to humans*) is a mineral fibre used for its insulating properties in homes, businesses, and other structures that were mostly built before the 1980s. Because asbestos is ubiquitous in so many older structures, it may be encountered by firefighters during fires or other emergency incidents during which building materials are disturbed (see Table 1.21). Fire and high temperature can break down composite materials and liberate the asbestos fibres that they contain. Asbestos fibres directly exposed to high temperatures (> 400 °C) may also break down, resulting in shorter aspect ratios and less pathogenicity (Hoskins & Brown, 1994; Jeyaratnam & West, 1994).

Table S1.22 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615) provides measures of asbestos in air

Fig. 1.17 Changes in benzene concentrations in exhaled breath of firefighters before and before fire suppression



arith, arithmetic; geom, geometric.
[The Working Group compiled information from all studies identified on PubMed until May 2022 that provided biomonitoring data on firefighters' exposures.] Values are stratified by post-suppression sampling time point and presented as fold-change (i.e. post- versus pre-exposure). The average fold-change for a post-exposure sampling time of < 1 hour is 7.1 ± 2.3 (n = 12); the average for sampling time > 1 hour is 2.3 ± 0.59 (n = 14). The sampling time effect is significant at $P < 0.03$. The y-axis is presented on a log 10 scale.
Created by the Working Group.

and on surfaces associated with firefighting. During overhaul, firefighters will commonly tear down walls, ceilings, flooring, and other materials, which could disturb materials containing asbestos. In an evaluation of firefighter exposures during overhaul of structure fires in Arizona, USA, asbestos fibres were detected in 15 of 46 air samples, with an average of 0.073 fibres per cm^3, suggesting that firefighters who were not wearing respiratory protection during overhaul could inhale asbestos fibres (Bolstad Johnson et al., 2000). Asbestos may also be used in roofing materials. A factory fire in England released into the atmosphere chrysotile fibres (contained in asbestos bitumen paper covering the roof), which were later detected on firefighters' clothing and in the surrounding environment (Bridgman, 2001). Another study attempted to measure asbestiform fibres on used firefighter turnout gear from Kentucky, USA, and found evidence of actinolite and chrysotile in four of 29 surface samples, although only one sample quantified asbestos fibres (chrysotile) above the LOD for the method (1570 fibre structures per cm^2) (Hwang et al., 2019b). [Asbestos on firefighting gear could

pose an inhalation hazard if the contamination were to be agitated and become airborne.]

[The Working Group noted that microscopy methods used to measure asbestiform fibres on air filters are vulnerable to interference from other substances that may also have been collected on the filter, which is likely to occur during many firefighting activities.]

Asbestos can also contaminate outdoor sites or soils. A NIOSH evaluation assessed wildland firefighters' exposures to asbestiform fibres in Libby, Montana, USA (a former site for vermiculite mines), and found task-based concentrations of 0.0013–0.13 fibres per cm^3 (NIOSH, 2019). [Contamination of soils with naturally occurring asbestos fibres is not expected to be common in most regions of the world.]

In addition to asbestos, firefighters can be exposed to other minerals, including crystalline silica (see Table 1.21). [The Working Group noted the paucity of literature on silica exposure in municipal firefighters but acknowledges the potential for silica exposure.] A study of wildland firefighters' exposures during prescribed burns and naturally occurring fires found that fire personnel were exposed to respirable quartz at concentrations that frequently exceeded the Occupational Safety and Health Administration (OSHA) permissible exposure limit of 0.05 mg/m^3, especially after adjusting for longer shifts (Reinhardt & Broyles, 2019). Firefighters can also be exposed to man-made vitreous fibres, which are fibrous inorganic materials made from rock, slag, clay, or glass (IARC, 2002). Dust samples collected from the areas surrounding the WTC disaster and from the Grenfell Tower fire contained man-made vitreous fibres (ATSDR, 2002; Lioy et al., 2002; Stec et al., 2019).

(b) Per- and polyfluoroalkyl substances

PFAS are a class of synthetic chemicals that have been used in commercial and industrial products and processes for nearly a century (US EPA, 2021a). By the 1960s, PFAS were integral in the development of a firefighting foam known as AFFF and soon after were incorporated as waterproofing agents into textiles (ITRC, 2020).

AFFFs are often used on fires involving flammable liquids or vapours (known as "class B" fires), such as jet fuel. The PFAS surfactants in AFFFs are designed to lower the surface tension, allowing the foam to quickly spread across and smother the burning liquid. AFFFs are more effective at suppressing liquid fires than is water, and they have the added benefits of reducing the water requirements and runoff potential (Magrabi et al., 2002).

In the past two decades, specific compounds used in the production of AFFFs have shifted from longer carbon chain formulae, such as perfluorooctanesulfonic acid (PFOS), to shorter and alternative formulae, such as perfluorobutane sulfonic acid (PFBS) and hexafluoropropylene oxide-dimer acid (HFPO-DA), because of emerging toxicity data and concerns over the bioaccumulation of longer-chain PFAS (Brase et al., 2021).

Although the contribution of specific pathways to a firefighter's absorbed dose is not fully understood, PFAS exposure could result from dust and products of combustion present at a fire scene; contact with firefighting foam, and PPE in which PFAS is an intentionally added component; or contaminated fire station dust (Tao et al., 2008; Shaw et al., 2013; Leary et al., 2020; Peaslee et al., 2020; Young et al., 2021). There is also the potential for firefighters to be exposed through local contamination of water with AFFF. For example, use of AFFF at fire stations, including those at airports, military bases, and training facilities, has contributed to PFAS contamination in groundwater, soil, and other surfaces (de Solla et al., 2012; Backe et al., 2013; Baduel et al., 2015; Hansen et al., 2016; Hu et al., 2016).

For many firefighters, AFFF may be the most significant source of exposure to PFAS, as supported by several biomonitoring studies in firefighters (Laitinen et al., 2014; Rotander

Table 1.21 Studies in which exposure monitoring was performed for compounds other than fire smoke[a]

Chemical agent or class	Sample type	References
Asbestos	Area air	Bolstad-Johnson et al. (2000)
	Personal air	NIOSH (2019)
	Surface (PPE)	Bridgman (2001)
	Surface (work surfaces)	Hwang et al. (2019b)
Silica	Personal air	Reinhardt & Broyles (2019)
Man-made vitreous fibres	Surface (ambient dust)	ATSDR (2002); Lioy et al. (2002); Stec et al. (2019)
Per- and polyfluoroalkyl substances	Surface (PPE)	Peaslee et al. (2020)
	Surface (work surfaces)	Young et al. (2021)
PBDEs and other brominated flame retardants	Area air	Fent et al. (2020a)
	Surface (PPE)	Easter et al. (2016); Mayer et al. (2019); Fent et al. (2020a); Banks et al. (2021c)
	Surface (work surfaces)	Shen et al. (2018); Gill et al. (2020b)
Organophosphate flame retardants (OPFRs)	Area air	Fent et al. (2020a)
	Surface (PPE)	Mayer et al. (2019); Fent et al. (2020a); Banks et al. (2021c)
	Surface (work surfaces)	Shen et al. (2018); Gill et al. (2020b)
Diesel exhaust (elemental carbon or total particulates)	Area air	NIOSH (2016b); Bott et al. (2017); Chung et al. (2020)
	Personal air	Froines et al. (1987)
Heavy metals (e.g. cadmium, arsenic, lead)	Personal air	Keir et al. (2020)
	Surface (PPE)	Easter et al. (2016); Engelsman et al. (2019)
	Surface (work surfaces)	Engelsman et al. (2019)
PCDD/Fs	Surface (PPE)	Hsu et al. (2011); Fent et al. (2020a)
PBDD/Fs	Surface (PPE)	Fent et al. (2020a)

PBDD/Fs, polybrominated dibenzo-*para*-dioxins/dibenzofurans; PBDEs, polybrominated diphenyl ethers; PCDD/Fs, polychlorinated dibenzo-*para*-dioxins/dibenzofurans; PPE, personal protective equipment.

[a] Exposure results are provided in Supplementary Table S1.22 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

et al., 2015b; Leary et al., 2020). A few studies have suggested a positive association between biological levels of PFAS and years of firefighting (Rotander et al., 2015b; Graber et al., 2021). However, because long-chain PFAS are being removed from AFFF formulations, biological levels of PFAS in firefighters who use class B foams may begin to decline (Rotander et al., 2015b). See Section 1.5.1(i) for more details on biomonitoring studies of firefighters using AFFF.

Because PFAS has been used in various commercial products, including stain-resistant carpeting and furniture, structure fires may also be associated with exposure to and contamination with PFAS. Many of the studies that have evaluated municipal firefighters' exposure to PFAS have involved biological monitoring (Tao et al., 2008; Jin et al., 2011; Shaw et al., 2013; Leary et al., 2020; Trowbridge et al., 2020; Clarity et al., 2021), and a few of these studies found associations between recent fire events or duration of exposure and specific types of PFAS in the blood (Tao et al., 2008; Shaw et al., 2013). See Section 1.5.1(i) for more information on biological levels of PFAS in firefighters.

PFAS could also be present in firefighting textiles either as part of the manufacturing process or as contamination acquired during firefighting. Evaluation of PFAS in turnout gear confirmed measurable levels of several types of PFAS in textiles. The highest levels of PFAS were found in the outer shell and moisture barriers, with evidence of migration across the protective layers in used turnout gear (Peaslee et al., 2020). Studies have also detected PFAS in dust collected from turnout-gear storage areas in fire stations, with some types of PFAS being present in higher concentrations than in dust from living areas of those fire stations (Peaslee et al., 2020; Young et al., 2021) (see Table 1.21, and Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

(c) Chemical flame retardants

Furnishings and other items containing foams, plastics, and other synthetic materials can be highly flammable. One way the furniture, textile, and electronics industries have addressed this flammability issue is by adding chemical flame retardants to their products. PBDEs were one of the first classes of chemical flame retardant to be used, starting in the 1970s (Barbauskas, 1983; McKenna et al., 2018). Use has dwindled and even been banned completely in some countries because of their persistence, ability to accumulate in the body, and toxicological effects. The Stockholm Convention on Persistent Organic Pollutants classified several congeners as persistent organic pollutants in 2009 and decabromodiphenyl ether (BDE-209) in 2017 (Secretariat of the Stockholm Convention, 2019b). Other brominated flame retardants listed for elimination in the Stockholm Convention are hexabromobiphenyl and hexabromocyclododecane (HBCDD). Several countries (e.g. China, India, Japan, and the USA) are making significant strides towards eliminating the use of these compounds. The European Union has almost completely banned the use of PBDEs, hexabromobiphenyl, and HBCDD (Sharkey et al., 2020). However, other chemical flame retardants are still being used globally, including OPFRs and other chlorinated and brominated flame retardants, in products such as foam insulation for buildings (Lee et al., 2016; Chupeau et al., 2020; Estill et al., 2020). The estimated global consumption of flame retardants in Asia, Europe, and the USA was 2.8 million tonnes in 2018 (Yasin et al., 2016).

Table 1.21 provides a summary of flame retardant measurements in area air and on surfaces associated with firefighting (see also Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Firefighters can potentially be exposed to all classes of flame retardant if the fires they respond involve furnishings and other items containing these compounds (such as building insulation), which will depend in part on the rules and regulations of the country where the firefighters work (Sharkey et al., 2020). Fent et al. (2020a) measured a variety of PBDEs, other brominated flame retardants, and OPFRs in the air during the live-fire portion of controlled residential fires containing modern furnishings in the USA; results included BDE-209 (median, 15.6 μg/m^3), 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB; median, 7.71 μg/m^3), and triphenyl phosphate (median, 408 μg/m^3). These substances were also detected in almost every wipe sample collected from the turnout jackets and gloves worn by the responding firefighters. Tris(1,3-dichloro-2-propyl) phosphate (TDCPP) was also detected with high frequency on turnout jackets and gloves (Fent et al., 2020a).

Other studies have measured flame-retardant contaminants on firefighting clothing from the USA and Australia (Alexander & Baxter, 2016; Easter et al., 2016; Mayer et al., 2019; Banks et al., 2021c). Studies have also measured flame retardants in dust collected in fire stations from Australia, Canada, and the USA (Brown et al.,

2014; Shen et al., 2015; Banks et al., 2020; Gill et al., 2020b); some of these studies found higher levels of certain flame retardants (e.g. BDE-209 and TDCPP) than in dust collected from other occupational settings (Shen et al., 2015; Gill et al., 2020b).

Firefighters' turnout gear could also contain flame retardants added during manufacture. Alexander & Baxter (2016) measured BDE-209 from unused gloves and a knit hood available at that time in the USA (< 1 μg/g per sample). In 2019, investigators analysed new knit hoods in the USA and found that they contained no detectable flame retardants (Mayer et al., 2019). More recently, new turnout gear from South Africa was found to contain PBDEs at > 200 μg/g and HBCDD at < 0.1 μg/g (Mokoana et al., 2021). [The Working Group noted that manufacture of turnout gear with textiles containing flame retardants may have been more common in the past than today. However, the study from South Africa suggested that manufacturers may still be producing turnout gear using textiles containing flame retardants in certain regions of the world.]

Biomonitoring has also been used to assess firefighters' exposure to flame retardants. Cross-sectional biomonitoring studies of firefighters in the USA have found elevated serum concentrations of certain PBDEs (e.g. BDE-99 and BDE-209) and elevated urinary concentrations of certain OPFRs (e.g. metabolites of triphenyl phosphate and TDCPP) compared with the general population (Shaw et al., 2013; Park et al., 2015; Jayatilaka et al., 2017). In the study by Fent et al. (2020a), firefighters experienced significant increases in urinary concentrations of metabolites of triphenyl phosphate, TDCPP, and tris(2-chloroethyl) phosphate after firefighting (Mayer et al., 2021). See Section 1.5.1(i) for more information on biological levels of flame retardants measured in firefighters.

(d) Diesel engine exhaust

Firefighters can be exposed to diesel exhaust (IARC Group 1, *carcinogenic to humans*) at the fire station, when fire engines (or apparatus) are started in the bays or return to the bays after a response, and at incidents where fire engines commonly idle. Diesel exhaust is composed of particulate matter, PAHs, inorganic particles, and oxides of carbon, nitrogen, and sulfur (Pronk et al., 2009). The magnitude and composition of diesel exhaust exposures will depend on several factors, including the age and maintenance of the engines, the quality of diesel fuel (e.g. sulfur content), whether the engine includes any filtration systems, the workload or number of runs, whether the engine is running cold or warm, whether diesel-exhaust capture systems are available and being used in the bays, and if not, whether the bays include natural ventilation (e.g. drive-through bays with doors on the front and back) (Chung et al., 2020). Another important factor for living quarters of the station that are attached to the bay is whether they are under positive pressure relative to the bay [if not, there is the potential for diesel exhaust to migrate into the living areas] (NIOSH, 2016b).

Recent studies have quantified diesel exhaust in fire stations by measuring airborne elemental carbon (see Table 1.21, and Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Work-shift concentrations measured in fire stations have varied considerably and are generally higher in engine bays than in other areas of the fire station. One evaluation at fire stations in the USA measured elemental carbon concentrations in the engine bays at < 1–13 μg/m^3, with concentrations in the living areas ranging from 1.2 to 2.7 μg/m^3 (NIOSH, 2016b). A study in Canada measured elemental carbon in vehicle bays at concentrations ranging from < 0.5 to 2.7 μg/m^3 (Chung et al., 2020). A study in Australia measured

elemental carbon at concentrations ranging from 1 to 26 μg/m³ in vehicle bays, with much lower levels in the dormitories (< 2 μg/m³). The same study quantified total PAHs (predominantly naphthalene) at concentrations ranging from ~0.05 to ~1.8 μg/m³ in the engine bays (Bott et al., 2017). No studies have specifically quantified diesel exhaust exposure at emergency incidents, but one study involving controlled residential fires measured particulate matter at > 100 000 particles/m³ before fire ignition, which the investigators attributed to the idling fire apparatus (engine) at the scene (Fent et al., 2018).

(e) Heavy metals

Firefighters can be exposed to heavy metals (some of which are classified as IARC Group 1, *carcinogenic to humans;* see Table 1.1). For example, vehicle fires would be expected to include a variety of heavy metals (present in the engine, battery, frame, and body parts), but metals could also be present in many other fires, especially fires involving older homes with lead paint or pipes or structures containing metal trusses or electronics. Airborne metal particulates or fumes produced during fires may be inhaled.

Table 1.21 provides a summary of air and surface measurements of metals associated with firefighting (see also Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). Keir et al. (2020) measured air concentrations of lead and found levels above the adjusted occupational exposure limit (OEL; 46.9 μg/m³) during two emergency fires in Ottawa, Canada; they also found significant increases in lead and antimony contamination on used turnout gear. Easter et al. (2016) measured metals in used firefighting hoods compared with new hoods in Philadelphia, USA, and found elevated concentrations of numerous metals, including arsenic, cadmium, chromium, and lead. Engelsman et al. (2019) measured metals on surfaces in Australian fire stations and found levels of chromium, lead, copper, zinc, nickel, and manganese that were higher than levels measured in homes or offices.

The presence of metals on firefighter gear and other surfaces does not necessarily mean that firefighters will absorb those contaminants; most metals have relatively low skin permeation coefficients (K_p, 0.001 cm/hour or less). However, there are numerous factors that can impact the permeability of metals through skin, including the valence state, the type of counter ion, and the nature of the chemical bond (organic versus inorganic) and polarity (Hostynek, 2003). [Metals and other contaminants on gear or surfaces could also become aerosolized and inhaled, or transfer to hands and be ingested, depending on hand hygiene practices after firefighting.]

Biomonitoring has also been used to assess firefighters' exposure to metals including lead, e.g. during the WTC disaster and the Notre Dame Cathedral fire, in Paris, France (see Section 1.5.1(i)).

(f) Physical factors

Physical exertion and heat stress are common among municipal and wildland firefighters (Cheung et al., 2010; Bourlai et al., 2012; Lui et al., 2014; Horn et al., 2018). Municipal firefighting ensembles, which are designed to protect firefighters from heat, will also trap metabolic heat energy produced during work and may result in increased core body temperatures (Smith et al., 2013a; Horn et al., 2018; Ghiyasi et al., 2020). Strenuous work under high-stress situations, together with increased body temperature and dehydration, may affect the sympathetic nervous system and result in cardiovascular strain (Shen & Zipes, 2014; Smith et al., 2019). How these physical stressors could impact carcinogenesis is not well understood; however, increased body and skin temperatures may result in increased dermal absorption of toxicants (Chang & Riviere, 1991; Chang et al., 1994), and dehydration can

concentrate hazardous substances in the body and may place additional strain on the kidneys (Baetjer et al., 1960; Baetjer, 1969). In addition, thermoregulatory processes in the body that are part of the immune response against toxicological insults may also be affected by heat strain (Leon, 2008).

[Although the Working Group was unable to identify studies describing firefighters' UV exposure, firefighters working outdoors or working in areas with a high UV index are also likely to be exposed to UV radiation (classified in IARC Group 1) (Peters et al., 2012; Carey et al., 2014; Boniol et al., 2015).] PAHs and UV exposure may have synergistic toxic effects through photoactivation (Ekunwe et al., 2005; Toyooka & Ibuki, 2007). [Wildland firefighters will commonly spend an entire work shift (8 hours or longer) under the sun. Although their arms and legs are typically covered by protective clothing, their necks and faces may be exposed. With the growing wildfire season in various parts of the world, cumulative UV exposure is likely to worsen for wildland firefighters.]

Firefighters are also exposed to radiofrequency electromagnetic fields (IARC Group 2B, *probably carcinogenic to humans*) from the use of hand radios. [The Working Group noted that hand radios are not typically held close to the head, and the effects of radiofrequencies on the human body (e.g. increased skin temperature) drop with increasing distance (Foster & Glaser, 2007).]

In relatively rare situations, firefighters respond to radiological events, such as a dirty bomb, in which their roles could include triage, life support, and decontamination, and during which they could be exposed to ionizing radiation (Rebmann et al., 2019). One of the most well-known radiological disasters was the Chernobyl nuclear power plant disaster in present-day Ukraine in 1986. Numerous studies have documented radiation health effects among firefighters and other workers who responded to the Chernobyl disaster (Junk et al., 1999; Antoniv et al., 2017; Belyi et al., 2019). Fallout from the disaster resulted in radionuclide contamination in the exclusion zone, which presents an additional hazard for wildland firefighters (Yoschenko et al., 2006). Wildland firefighters who responded to a forest fire in the Chernobyl exclusion zone in April–May 2020 were reported to have effective internal dose maximum values of 3.5, 5.1, and 11.8 μSv, depending on the region in which they worked (Bazyka et al., 2020). Radionuclides also occur naturally in soil and vegetation. Carvalho et al. (2014) measured polonium-210 activity in wildfire smoke in Portugal; the average concentration was 70 mBq/m^3, which could theoretically result in a radiation dose for wildland firefighters of ~2.1 μSv per 10-hour workday. However, Viner et al. (2018) conducted modelling of cumulative dose for firefighters in areas of natural and anthropogenic contamination (i.e. Savannah River Site, South Carolina, USA) and found that even under worst-case conditions, the cumulative dose for firefighters exposed to potential fires would not exceed 3% of the annual guidance limit set by the US Department of Energy (0.25 mSv).

Firefighters are also commonly exposed to loud noise from alarms, sirens, personal alert safety systems, and heavy equipment and machinery (Tubbs, 1995; Hong & Samo, 2007; Kirkham et al., 2011; Neitzel et al., 2013). Wildland firefighters may use chainsaws, chippers, and even bulldozers, which can easily exceed OELs for noise (e.g. the NIOSH recommended exposure limit of 85 dB) (Broyles et al., 2017). Wildland firefighters are expected to wear hearing protection when performing tasks using this equipment; however, training on proper use and maintenance of hearing protection may vary throughout the fire service (Broyles et al., 2019).

(g) Building collapse and other catastrophic events

There were few studies reporting on the non-fire exposures received by firefighters at other major natural or man-made disasters. These publications are summarized in Table 1.23. The incidents reported in these studies include: earthquakes (where predominant exposures are assumed to be dust and particulates from collapsed buildings, or release of radioisotopes, e.g. Fukushima, Japan) (Chang et al., 2003; Fushimi, 2012; Caban-Martinez et al., 2021; Ory et al., 2021); explosions (encompassing exposures to dust, particulates, and debris in addition to products of combustion) (Slottje et al., 2005, 2006, 2007, 2008; Witteveen et al., 2007; De Soir et al., 2015); severe weather events, e.g. hurricanes (covering exposure to biologically contaminated floodwater, debris, etc.) (Tak et al., 2007); radiological events (Ory et al., 2021); chemical terrorism (e.g. the sarin nerve-agent attack in the Tokyo subway, Japan, in 1995) (Li et al., 2004); and chemical spills (encompassing exposure to specific chemical agents) (Cho et al., 2013).

Many publications (e.g. Witteveen et al., 2007; Fushimi, 2012) on non-fire exposures in firefighters have also solely focused on assessing firefighters' response to trauma by following the mental health outcomes of those attending the incident.

[The Working Group noted that there was lack of data on exposure during catastrophic events. For the site of the WTC disaster, none of the samples were collected in the immediate aftermath.]

The majority of studies on firefighters' chemical and physical exposures and their health outcomes were focused on the WTC terrorist attack (Claudio, 2001; Landrigan, 2001; Guidotti et al., 2011). Firefighters who responded to the WTC disaster had substantial and repeated exposures to dense, aerosolized dust and smoke (Nordgren et al., 2002). They were exposed to the plume created from the initial fire and building collapses, to ongoing fires that lasted at least 3 months, and to particles that were resuspended during the clean-up and transport of debris. The destruction of the WTC complex pulverized ~1.2 million tonnes of construction material (Klitzman & Freudenberg, 2003; Rom et al., 2010). This material was primarily composed of gypsum and contained calcium carbonate, silicate, and sulfate, as well as various metals. Half of the South Tower had been insulated with chrysotile asbestos (which was found in the rubble) and millions of tonnes of fibrous glass. Collapse of the twin towers (WTC 1 and WTC 2), and then of a third building (WTC 7), produced an enormous dust cloud containing coarse and fine particulate matter (Lioy et al., 2002; Rom et al., 2010).

The predominant sources of toxic gases to which firefighters were exposed included by-products of combustion or pyrolysis from burning jet fuel. The secondary reactions of these combustion products, and of those produced from the burning, vaporization, and pulverization of materials within the towers, produced an array of irritant gases, fumes, and vapours (Landrigan et al., 2004). Specific fire effluent gases measured included VOCs, HCl, PAHs, PCBs, PBDEs, PCDD/Fs), phthalate esters, etc. (Lioy et al., 2002; Litten et al., 2003; McGee et al., 2003; Offenberg et al., 2003; Landrigan et al., 2004; Dahlgren et al., 2007; Guidotti et al., 2011).

Environmental data have shown that particulate matter originating from the WTC disaster differed in composition to ambient particulate matter, being mainly composed of debris from construction buildings and therefore containing concrete, pulverized glass, calcium sulfate (gypsum) and silicates, mineral glass fibres, alkaline metals, wood, paper, cotton, and components of jet fuel (Landrigan, 2001; Lioy et al., 2002; McKinney et al., 2002; Banauch et al., 2003; Landrigan et al., 2004; Lippmann et al., 2015).

Table 1.23 Examples of firefighters' exposures during catastrophic non-fire events

Catastrophe, location, date	Exposed population	Exposures and description of event	Reference
Explosion of reactor at nuclear power plant, Chernobyl, Ukraine, 1986	Firefighters, public	Release of radioisotopes into the atmosphere	Ory et al. (2021)
Amsterdam air disaster, Netherlands, 1992	Firefighters	No specific details on chemicals released Cargo aircraft crashed into apartment buildings; firefighters and police officers assisted with rescue work	Slottje et al. (2005, 2006, 2007, 2008); Huizink et al. (2006); Witteveen et al. (2007)
Earthquake, Taiwan, China, 1999	Firefighters	No specific details on chemicals released The 12-story Tunghsing building collapsed immediately after the earthquake; more than 1500 emergency responders (including firefighters) were involved	Chang et al. (2003)
World Trade Center terrorist attack, USA, 2001	Firefighters	Structural collapse; release of chrysotile asbestos, MMVFs, particulate matter, VOCs, sVOCs, hydrochloric acid, PAHs, PCBs, PBDEs, PCDD/Fs, fire retardants, phthalate esters, and metals	Clark et al. (2001); Claudio (2001); Lioy et al. (2002); McKinney et al. (2002); Banauch et al. (2003); Edelman et al. (2003); Litten et al. (2003); McGee et al. (2003); Offenberg et al. (2003); Landrigan et al. (2004); Moline et al. (2006); Dahlgren et al. (2007); Rom et al. (2010); Guidotti et al. (2011); Lippmann et al. (2015); Weiden et al. (2015)
Ghislenghien gas explosion, Belgium, 2004	Survivors (including firefighters) Public	Debris from gas pipe and buildings projected up to 6 km away from the epicentre; air vibrations registered. Large explosion that instantly killed 24 people; only two firefighters from the first crew survived the initial blast and 132 people were wounded	De Soir et al. (2015)
Tokyo subway disaster, Japan, 1995	Firefighters	Terrorist attack with release of sarin nerve gas	Li et al. (2004)
Hurricanes Katrina and Rita, Louisiana, USA, 2005	Firefighters	Floodwater exposure associated with physical health symptoms 12 weeks after Hurricane Katrina Career firefighters involved in rescue and recovery activities while maintaining normal fire-suppression duties	Tak et al. (2007)
The Great East Japan earthquake, 2011	Firefighters	No specific details on chemicals released	Fushimi (2012)
Fukushima nuclear power plant, north-east Japan, 2011	Plant workers, public	Release radioisotopes into the atmosphere	Ory et al. (2021)

Table 1.23 (continued)

Catastrophe, location, date	Exposed population	Exposures and description of event	Reference
Hydrogen fluoride spill accident, Republic of Korea, 2012	Firefighters	Exposure to hydrogen fluoride [assumed, no measurement/quantification of exposure]	Cho et al. (2013)
Surfside building collapse, Florida, USA, 2021	Firefighters	Exposure to PAHs (from around the building pile)	Caban-Martinez et al. (2021)

MMVFs, man-made vitreous fibres; PAHs, polycyclic aromatic hydrocarbons; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCDD/Fs, polychlorinated dibenzo-*para*-dioxins/dibenzofurans; sVOCs, semi-volatile organic compounds; VOCs, volatile organic compounds.

In data on ambient air pollution reported by nearby regional monitoring stations, airborne particulate matter mass concentrations were measured in only one or two size bands: $PM_{2.5}$ (diameter, ≤ 2.5 μm) and/or PM_{10} (diameter, ≤ 10 μm) (McGee et al., 2003; Guidotti et al., 2011). Concentrations of a mixture of airborne, respirable particulate matter were between 1 and 100 mg/m^3 (Weiden et al., 2015).

Additionally, more than 95% of the mass of WTC dust particles were found to be larger than 10 μm in diameter. The high content of pulverized cement made the dust highly caustic, with a pH in the range of 9 to 11 (Lioy et al., 2002; Banauch et al., 2003; Landrigan et al., 2004). In addition to fibrous and alkaline materials, samples of larger WTC particulate matter also contained various metals (Landrigan et al., 2004; Moline et al., 2006). Samples of smaller particular matter (i.e. $PM_{2.5}$) predominantly contained calcium (or calcium carbonate/bicarbonate), chlorine, and sulfuric oxide compounds originating from construction materials such as cement, concrete aggregate, ceiling tiles, and wallboards (Clark et al., 2001; Edelman et al., 2003; Gavett, 2003).

One study of the building collapse in June 2021 in Surfside, Florida, USA, deployed silicone-based wristbands to measure ambient PAHs around the building pile. Wristbands were placed on the southern, western, and northern perimeters of the building collapse before the controlled demolition. A total of 29 wristbands were deployed for ambient sampling around the collapse, and the PAHs found at highest concentrations were phenanthrene, fluoranthene, and pyrene. Wristbands were found to be a useful passive sampling device to document levels of various PAHs in the immediate environment of the building collapse where urban search and rescue firefighters were working (Caban-Martinez et al., 2021).

(h) Other exposures

Hundreds of combustion by-products may be produced during fires, especially fires that contain various materials and chemistries. This section has covered some of the most common combustion by-products likely to be encountered by firefighters, but there are certainly others that could pose long-term health risks. The locations where firefighters work may result in other occupational exposures. For example, airport firefighters may have additional exposures from aircraft (i.e. jet engines), which are known to produce ultrafine particulate matter and other pollutants (Stacey, 2019).

One area of ongoing research is firefighters' exposure to dioxins and furans. PCDD/Fs and PBDD/Fs may be produced when burning certain types of material, including halogenated polymers and electronics. For example, Organtini et al. (2015) measured several mixed halogenated dibenzofurans (PXDFs) and PBDFs in fire debris (at levels of parts per million) from simulated household fires (which included furnishing and electronics). Electronics may also contain PCBs (some classified in IARC Group 1), which are another class of hazardous compounds to which firefighters may be exposed. See Section 1.3.1 for more information on the possible sources of these compounds during firefighting.

Only a few studies have evaluated firefighters' exposures to PCDD/Fs, PBDD/Fs, and PCBs (see Table 1.21, and Table S1.22, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615), and most involved biological monitoring. 1,2,3,4,6,7,8-Heptachlorodibenzo-*para*-dioxin (HpCDD) has been detected on firefighting equipment and clothing (Hsu et al., 2011) and measured in serum samples from firefighters in California, USA, and fire investigators in Taiwan, China, at concentrations above those for the referent general population (Hsu et al., 2011; Shaw

et al., 2013). Serum concentrations of HpCDD were significantly related to firefighting activity in WTC responders (Edelman et al., 2003). These and other biomonitoring studies evaluating firefighters' exposure to PCDD/Fs, PBDD/Fs, and PCBs are discussed in Section 1.5.1(i).

Other areas of ongoing research pertain to firefighters' exposures from fires involving new technologies or materials, including lithium-ion batteries, nanomaterials, and other new compounds or chemicals. Fires involving lithium-ion batteries, for example, are intense and require tremendous amounts of water and extended time to fully extinguish (Wang et al., 2012; Larsson et al., 2014; US EPA, 2021b). [The Working Group noted that the composition of effluents from these types of fire are not fully understood. The extended response times for these fires may increase firefighters' exposures.]

(i) Biomarkers of exposure

A summary of biomarkers of exposure to agents other than fire smoke and PAHs is provided in the text below and summarized in Table 1.24. Additional details are provided in Table S1.25 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615). General considerations on absorption, distribution, metabolism, and excretion are described in Section 1.4.2(e). Most of these studies involved career firefighters in the USA, with municipal firefighters being the most frequently studied when the type of firefighter was listed; these studies reported mainly on serum measurements, followed by blood and urine.

Inhalation is the major route for asbestos exposure, and asbestos fibres are distributed predominantly into the lungs and pleura. [No studies on biomarkers of asbestos exposure in firefighters were identified by the Working Group, but specific pulmonary abnormalities can indicate exposure. In a study of 212 New York City firefighters (mean age, 57 years), 42 had pleural thickening and/or parenchymal abnormalities on chest radiograph and/or computed tomography, including 20 firefighters without reported prior exposure to asbestos (Markowitz et al., 1991).]

The major exposure route for PBDEs in the general population is ingestion, followed by dermal exposure and inhalation (Lorber, 2008). PBDEs are distributed into lipophilic tissues, and overall metabolism rates are slow; 40% of BDE-47, 16% of BDE-99, 6% of BDE-100, and 2% of BDE-153 is excreted in the urine in mice by 5 days after administration (Staskal et al., 2006). In 12 firefighters in San Francisco, USA, who had responded to a fire within the previous 24 hours, the sum of serum concentrations of PBDE was two- to threefold that reported for the general US population (Shaw et al., 2013). In 101 firefighters in southern California, USA, in 2010–2011, serum concentrations of BDE-28, BDE-47, BDE-100, and BDE-153 were significantly higher than in participants representative of the general US population in the 2003–2004 National Health and Nutrition Examination Survey (NHANES). Lower serum PBDE levels in firefighters were associated with turnout gear cleaning and storage in open rooms after fires (Park et al., 2015). In 36 US firefighters assessed before and after responding to controlled residential fires in 2015, only BDE-209 (out of 12 PBDEs quantified) pre- and post-fire serum concentrations were higher than those in the 2018 NHANES comparison population; the pre- to post-fire change was not significant (Mayer et al., 2021). In 92 male firefighters from Busan, Republic of Korea, compared with 70 male non-firefighters from the same area, the summed concentration of 27 PBDEs was higher in firefighters than in the general population, and there was a positive correlation between PBDE levels and duration of service for firefighters (Ekpe et al., 2021).

PCDD/Fs and PBDD/Fs are generated during combustion. PCDDs and PCDFs distribute predominantly to the liver and adipose tissue;

Table 1.24 Biomarkers used to assess firefighters' exposures to agents other than smoke

Analyte	Sample type	Concentration		References
		Minimum	Maximum	
Polybrominated diphenyl ethers (PBDEs)				
BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-197, BDE-207, BDE-209	Serum	0.1 ng/g lipid	253 ng/g lipid	Shaw et al. (2013); Park et al. (2015)
BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-209	Blood	NR	NR	Mayer et al. (2021)
PBDEs (sum of 27)	Serum	1.58 ng/g lipid	95.2 ng/g lipid	Ekpe et al. (2021)
Polychlorinated dibenzo-para-*dioxins and dibenzofurans (PCDD/Fs)*				
1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,8-HpCDF	Serum	ND	674 pg/g lipid	Shaw et al. (2013)
2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 2,3,4,6,7,8-HxCDF	Serum	2.24 pg/g lipid	NR	Mayer et al. (2021)
PCDD/Fs (sum of 17)	Serum	6.3 pg (TEQ)/g lipid	18 pg (TEQ)/g lipid	Hsu et al. (2011)
Polychlorinated biphenyls (PCBs)				
PCB-66, PCB-74, PCB-99, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, PCB-187, PCB-194, PCB-203	Serum	1.09 ng/g lipid	15.4 ng/g lipid	Park et al. (2015)
PCB-105, PCB-118, PCB-157, PCB-167	Serum	1.02 ng/g lipid	105.76 ng/g lipid	Chernyak et al. (2012)
PCBs (sum of 38)	Serum	36 ng/g lipid	317 ng/g lipid	Shaw et al. (2013)
Organophosphate and other flame retardants				
BCEtP, BDCPP, DPCP, DBuP, TBBPA	Serum	NR	NR	Clarity et al. (2021)
BCEtP, BCPP, BDCPP, DEP, DETP, DEDTP, DMP, DMTP, DMDTP, DBuP, DPhP, IPPPP, TBBA, TBPPP	Urine	< LOD	300 ng/mL	Jayatilaka et al. (2019)
Per- and polyfluoroalkyl substances				
PFHxS	Serum	0.22 ng/mL	326 ng/mL	Jin et al. (2011); Shaw et al. (2013); Laitinen et al. (2014); Dobraca et al. (2015); Rotander et al. (2015a, b); Khalil et al. (2020); Leary et al. (2020); Trowbridge et al. (2020); Clarity et al. (2021); Goodrich et al. (2021); Graber et al. (2021)
PFOS	Serum	< LOD	391 ng/mL	Jin et al. (2011); Shaw et al. (2013); Laitinen et al. (2014); Dobraca et al. (2015); Rotander et al. (2015a, b); Khalil et al. (2020); Leary et al. (2020); Trowbridge et al. (2020); Clarity et al. (2021); Goodrich et al. (2021); Graber et al. (2021)
PFDS	Serum	ND	0.1 ng/mL	Shaw et al. (2013)

Table 1.24 (continued)

Analyte	Sample type	Concentration		References
		Minimum	Maximum	
PFHpA	Serum	< LOD	1 ng/mL	Shaw et al. (2013); Dobraca et al. (2015); Rotander et al. (2015b); Trowbridge et al. (2020)
PFOA	Serum	0.25 ng/mL	7535 ng/mL	Jin et al. (2011); Shaw et al. (2013); Laitinen et al. (2014); Dobraca et al. (2015); Rotander et al. (2015b); Khalil et al. (2020); Leary et al. (2020); Trowbridge et al. (2020); Clarity et al. (2021); Graber et al. (2021); Goodrich et al. (2021)
PFNA	Serum	< 0.06 ng/mL	17.95 ng/mL	Jin et al. (2011); Shaw et al. (2013); Laitinen et al. (2014); Dobraca et al. (2015); Rotander et al. (2015b); Khalil et al. (2020); Leary et al. (2020); Trowbridge et al. (2020); Clarity et al. (2021); Goodrich et al. (2021); Graber et al. (2021)
PFDA	Serum	< LOD	20.7 ng/mL	Shaw et al. (2013); Dobraca et al. (2015); Rotander et al. (2015b); Khalil et al. (2020); Trowbridge et al. (2020); Graber et al. (2021); Clarity et al. (2021); Goodrich et al. (2021)
PFUnDA	Serum	0.1 ng/mL	10.85 ng/mL	Shaw et al. (2013); Dobraca et al. (2015); Khalil et al. (2020); Trowbridge et al. (2020); Clarity et al. (2021); Graber et al. (2021); Goodrich et al. (2021)
PFBS	Serum	< LOD	0.4 ng/mL	Dobraca et al. (2015); Rotander et al. (2015b); Trowbridge et al. (2020); Clarity et al. (2021)
PFOSA	Serum	NR	0.4 ng/mL	Dobraca et al. (2015)
Me-FOSAA	Serum	NR	3.80 ng/mL	Dobraca et al. (2015); Khalil et al. (2020); Goodrich et al. (2021); Graber et al. (2021)
Et-FOSAA	Serum	NR	1.00 ng/mL	Dobraca et al. (2015)
PFTrDA	Serum	< 0.06 ng/mL	28.5 ng/mL	Dobraca et al. (2015); Rotander et al. (2015b)
PFDoA	Serum	0.13 ng/mL	0.15 ng/mL	Dobraca et al. (2015); Graber et al. (2021)
PFBA	Serum	< LOD	0.99 ng/mL	Rotander et al. (2015b); Trowbridge et al. (2020)
PFHxA	Serum	< LOD	< LOD	Trowbridge et al. (2020)
Sb-PFOA	Serum	ND	ND	Goodrich et al. (2021)
Sm-PFOS	Serum	1.91 ng/mL	2.23 ng/mL	Goodrich et al. (2021)
Heavy metals				
Antimony	Serum	NR	NR	Salama & Bashawri (2017)
Arsenic	Serum	NR	NR	Al-Malki (2009)
Cadmium	Blood	0.18 µg/L	0.21 µg/L	Dobraca et al. (2015)
Cadmium	Serum	NR	NR	Al-Malki (2009); Salama & Bashawri (2017)

Table 1.24 (continued)

Analyte	Sample type	Concentration		References
		Minimum	Maximum	
Lead	Blood	0.87 µg/dL	64.7 µg/L	Edelman et al. (2003); Dobraca et al. (2015); Kim et al. (2020b)[a]; Allonneau et al. (2021)
Lead	Serum	NR	NR	Al-Malki (2009); Salama & Bashawri (2017)
Mercury	Blood	2.36 µg/L	3.30 µg/L	Dobraca et al. (2015)
Mercury	Serum	< LOD	16 µg/L	Al-Malki (2009); Smith et al. (2013b); Salama & Bashawri (2017)
Uranium	Urine	NR	NR	Edelman et al. (2003)

[a] [The blood lead levels reported in Kim et al. (2020b) probably have a unit error, as they are reported as mg/dL (not µg/dL), which would exceed reported fatal levels.]

BCPP, bis(1-chloro-2-propyl) phosphate; BCEtP, bis(2-chloroethyl) phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BDE, brominated diphenyl ether; DBuP, dibutyl-*n*-phosphate; DEDTP, diethyl dithiophosphate; DEP, diethyl phosphate; DETP, diethyl thiophosphate; DMDTP, dimethyl dithiophosphate; DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; DpCP, di-*para*-cresyl phosphate; DPhP, diphenyl phosphate; Et-FOSAA, 2-(*N*-ethyl-perfluorooctanesulfonamido) acetic acid; HpCDD, heptachlorodibenzo-*para*-dioxins; HpCDF, 1,2,3,4,6,8,9-heptachlorodibenzofuran; HxCDD, 1,2,3,7,8,9-hexachlorodibenzo-*para*-dioxin; HxCDF, 1,2,4,6,8,9-hexachlorodibenzofuran; IPPPP, 2-((isopropyl)phenyl)phenyl phosphate; LOD, limit of detection; Me-FOSAA, 2-(*N*-methyl-perfluorooctanesulfonamido) acetic acid; ND, not determined; NR, not reported; PFBA, perfluorobutanoic acid; PFBS, perfluorobutane sulfonic acid; PFDA, perfluorodecanoic acid; PFDoA, perfluorododecanoic acid; PFDS, perfluorodecane sulfonate; PFHpA, perfluoroheptanoic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFOSA, perfluorooctane sulfonamide; PFTrDA, perfluorotridecanoic acid; PFUnDA, perfluoroundecanoic acid; Sb-PFOA, branched PFOA isomers; Sm-PFOS, perfluoromethylheptane sulfonate isomers; TBBA, 2,3,4,5-tetrabromobenzoic acid; TBBPA, tetrabromobisphenol A; TBPPP, 4-((*tert*-butyl)phenyl)phenyl phosphate; TEQ, toxic equivalent quantity.

the 2,3,7,8-substituted PCDDs and PCDFs are highly retained in tissues and body, resulting in elimination half-lives of 1–7 years (Van den Berg et al., 1994). PBDD/Fs are also present as contaminants in brominated flame retardants, and their toxicokinetics are generally similar to those of PCDD/Fs (van den Berg et al., 2013). Serum PCDD/F concentrations in 16 male firefighters from Taiwan, China, were not significantly different from those in the male general population, but PCDD/F levels in four fire-scene investigators were higher than those in the general population (Hsu et al., 2011). Comparing 13 current male firefighters, 17 former firefighters, and 10 non-firefighters in eastern Siberia, Russian Federation, serum levels of HpCDD and 1,2,3,7,8,9-hexachlorodibenzofuran (HxCDF) levels were higher in current firefighters than in non-firefighters, and serum levels of octachlorodibenzofuran (OCDF) were higher in current firefighters than in former firefighters and non-firefighters (Chernyak et al., 2012). In 12 firefighters in San Francisco after a fire exposure, serum concentrations of HpCDD exceeded those found in the general population of the USA (Shaw et al., 2013). In 36 US firefighters exposed to controlled structure fires, pre-fire serum concentrations of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (IARC Group 1, *carcinogenic to humans*) were significantly above those in the general population, as were pre- and post-fire serum concentrations of 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 2,3,4,6,7,8-HxCDF (Mayer et al., 2021).

PCBs are distributed into lipophilic tissues. The rate of metabolism varies by congener; metabolism is required before clearance, and elimination is generally slow (Matthews & Dedrick, 1984). After a single dose in humans, measured elimination half-lives for PCB-138, PCB-153, and PCB-180 were 321, 338, and 124 days respectively (Bühler et al., 1988). In current firefighters from eastern Siberia, Russian Federation, previously exposed to the 1992 cable factory fire in the city of Shelekhov involving more than 1000 tonnes of PVC, polyethylene, and other plastics, serum concentrations of PCB-105 and PCB-118 were higher than in non-firefighters, and concentrations of PCB-157 and PCB-167 were higher in both current and former firefighters than in non-firefighters (Chernyak et al., 2012). In 12 firefighters in San Francisco 24 hours after a fire event in 2009, the sum of PCB serum concentrations was lower than that reported for the general population of the USA in 2003–2004 (Shaw et al., 2013). In 101 firefighters in southern California, serum PCB concentrations measured in 2010–2011 were lower than in the 2003–2004 NHANES comparison group (Park et al., 2015). [The Working Group noted that comparison of serum PCB levels in firefighters with those of the general population sampled in a different time-period can introduce a temporal bias.]

Inhalation, dermal contact, and ingestion from the diet are all important routes of exposure to OPFRs (Hou et al., 2016). OPFRs are more rapidly metabolized than PBDEs (Geyer et al., 2004; Hou et al., 2016). In the USA, urine samples collected from firefighters 20 minutes or 3 hours after performing firefighting on controlled structure fires in 2010–2011 were compared with those collected from members of the general population in Atlanta in 2015. Urinary metabolites including bis(2-chloroethyl) phosphate (BCEtP), bis(1-chloro-2-propyl) phosphate, bis(1,3-dichloro-2-propyl) phosphate, di-*n*-butyl phosphate, diphenyl phosphate (DPhP), 2,3,4,5-tetrabromobenzoic acid (TBBA), 2-((isopropyl)phenyl)phenyl phosphate, and 4-((*tert*-butyl)phenyl)phenyl phosphate, and metabolites including dimethyl phosphate, dimethyl thiophosphate, dimethyl dithiophosphate, diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate were measured at higher concentrations in the firefighters than in the general population (Jayatilaka et al., 2019). In 36 US firefighters exposed to controlled structure fires, urinary concentrations of BCEtP and

DPhP measured before the fire were found to be significantly increased 3 hours after the fire (Mayer et al., 2021).

PFAS generally have the highest absorption through ingestion, with lower rates of absorption reported through inhalation or dermal exposure (Pizzurro et al., 2019). The elimination half-lives of PFAS vary, with a range of 44 days to 2.93 years in a study involving AFFF-contaminated drinking-water (Xu et al., 2020). In 12 firefighters in San Francisco after a fire event in 2009, perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) concentrations in serum were twice, and perfluorooctanesulfonic acid (PFOS) and perfluorohexanesulfonic acid (PFHxS) concentrations were half those in the US general population in the NHANES survey in 2003–2004 (Shaw et al., 2013).

Comparing 38 firefighters in Arizona, USA, and matched NHANES participants, firefighters had elevated PFHxS and lower PFNA and perfluoroundecanoic acid serum concentrations (Khalil et al., 2020). In eight airport firefighters training with AFFF in Finland, PFHxS and PFNA levels increased after three consecutive training sessions despite relatively low levels of these PFAS in the AFFF (Laitinen et al., 2014). In 37 firefighters in Ohio and West Virginia, USA, compared with the general population from the same area (selected as part of a PFAS-exposure related lawsuit), serum levels of PFHxS were elevated (Jin et al., 2011). In 101 firefighters in southern California examined in 2010–2011 compared with participants in the 2009 NHANES, perfluorodecanoic acid (PFDA) serum concentrations were three times as high in the firefighters, and perfluoroheptanoic acid (PFHpA) concentrations increased with use of class A firefighting foam (Dobraca et al., 2015). [The Working Group noted that levels of most legacy PFAS are decreasing in the general population of the USA, so levels in 2009 are lower than those measured in 2003–2004.] In samples collected in 2013 from 20 firefighters with AFFF exposure in Queensland, Australia, compared with samples collected in 2011–2012 from 20 non-firefighters, serum PFOS and PFHxS levels were markedly elevated in the firefighters (Rotander et al., 2015a). In 149 firefighters in Australia with AFFF exposure collected in 2013 compared with the general Australian population, serum concentrations of PFOS and PFHxS were positively associated with years of jobs with AFFF contact; study participants who had worked for ≤ 10 years had PFOS levels similar to those of the general population (Rotander et al., 2015b). In 86 female firefighters in San Francisco, USA, compared with female office workers, firefighters had higher serum concentrations of PFHxS, perfluoroundecanoic acid, and PFNA (Trowbridge et al., 2020). In 36 airport and nine suburban firefighters in Ohio, USA, enrolled in 2018–2019 compared with participants in the 2015–2016 NHANES, serum concentrations of PFHxS were elevated in the firefighters, and concentrations of PFOS were higher in airport firefighters than in suburban firefighters (Leary et al., 2020). In 116 volunteer firefighters from New Jersey, USA, in 2019 compared with participants in the 2015–2018 NHANES, serum concentrations of perfluorododecanoic acid (PFDoA), PFNA, and PFDA were elevated among the firefighters, and concentrations of both PFDoA and PFDA were positively associated with years of firefighting (Graber et al., 2021).

[The Working Group noted that for recent fire-suppression events, biomonitoring of firefighters for some organic chemicals with a long elimination half-life (e.g. PFAS or PBDEs) is extremely challenging, particularly since non-occupational exposure can be extensive (Rotander et al., 2015b; Trowbridge et al., 2020).]

The toxicokinetics of metals vary among the individual metals; ingestion and inhalation are generally the most important routes of exposure, but some metals bioaccumulate more than others (Elder et al., 2015). In 49 firefighters in Jeddah and Yanbu cities, Saudi Arabia, compared

with 23 non-firefighters, there were no significant differences in concentrations of any of the metals (i.e. antimony, arsenic, cadmium, lead, and mercury) measured in serum (Al-Malki, 2009). In 66 wildland firefighters compared with 39 non-firefighters in the western USA in 2007–2009, no significant difference in whole-blood mercury concentrations was found (Smith et al., 2013b). In 101 firefighters in southern California, whole-blood mercury concentrations exceeded values for participants in NHANES 2009–2010; higher cadmium concentrations were associated with washing hands less frequently, and higher mercury concentrations with responding to brush fires in the last year (Dobraca et al., 2015). In 100 male firefighters from Dammam and Khobar cities, Saudi Arabia, compared with 50 non-firefighters, there were no differences in whole-blood metal concentrations (Salama & Bashawri, 2017). In a study of 168 firefighters who responded to the Notre Dame cathedral fire in Paris, France, only one quarter had blood lead concentrations above the 95th percentile of the general population of France, and blood lead concentrations had dropped at the 1-month and 6-month follow-up evaluations (Allonneau et al., 2021). Edelman et al. reported increased blood concentrations of lead in firefighters responding to the WTC fire and collapse compared with control firefighters (Edelman et al., 2003)

1.5.2 Organizational and psychosocial factors, and infectious agents

(a) Shift work

Shift work is a schedule of work that includes working hours other than traditional daytime hours (i.e. Monday to Friday from 08:00 to 16:00). Night shift work has been classified by IARC as Group 2A, *probably carcinogenic to humans* (see Section 1.1, Table 1.1). Other associated effects on lifestyle factors (e.g. smoking behaviour, amount of physical activity during leisure time, eating behaviour, and consumption of alcohol (Bøggild & Knutsson, 1999; Bushnell et al., 2010; Pepłońska et al., 2014) have been described in more detail in *IARC Monographs* Volume 124 (IARC, 2020).

Municipal firefighters may work 10-hour day shifts and 14-hour night shifts, 24-hour shifts or 48-hour shifts; thus, firefighters are exposed to night shift work. [There is no internationally standard shift work pattern or rotation for firefighters. Some examples from the literature are provided in this section (Table 1.26; EPSU, 2006).]

Firefighters in the Republic of Korea typically experience 3-, 6-, 9-, or 21-day cycles (Kwak et al., 2020). The 3-day cycle is 24 hours on, 48 hours off. The 6-day cycle consists of two day shifts, two night shifts, and two rest days (days off). The 9-day cycle consists of three day shifts and three night shifts; each night shift is succeeded by one rest day. In the 21-day cycle, the first week consists of five day shifts, followed by two rest days. The second week consists of 12-hour night shifts alternating with a rest day until day 14, which is a 24-hour shift. The third week starts with a rest day, followed by two 12-hour night shifts (each succeeded by one rest day). On day 20, the firefighter works a 24-hour shift. The last day is a rest day (Jeong et al., 2019).

The 1974 Salaries and Working Conditions Survey indicated that 58% of US municipal firefighters work a 24-hour shift, 41% work a 10–14-hour or 9–15-hour shift, and < 1% work a 8–12-hour or 48-hour shift (NIOSH, 1977). [The Working Group noted that schedules have changed over time. Although many schedules exist among firefighters, nowadays almost all US fire departments operate a 24-hour rotation. Typical work schedules are 24 hours on/48 hours off, 48 hours on/96 hours off, and the "Kelly shift" schedule (24 hours on/24 hours off/24 hours on/24 hours off/24 hours on/96 hours off).] In a recent cross-sectional study, 80% of female career firefighters reported schedules that involved working ≥ 24 hours per shift (Jung et al., 2021a).

Table 1.26 Examples of reported standard work shift patterns for firefighters, by country[a]

Country	Work shift pattern and other remarks	Reference
Austria	24 h on/24 h off	EPSU (2006)
Australia and some Canadian provinces	10/14 rotating shift schedule: two consecutive 10-h day shifts followed by two consecutive 14-h night shifts, then 4 days off	Bonnell et al. (2017)
Belgium	8–12-h shifts	EPSU (2006)
Czechia, Denmark	24-h shifts	EPSU (2006)
Estonia, Finland	24 h on/72 h off	EPSU (2006)
France	24-, 12- and 8-h shifts all possible	EPSU (2006)
Germany, Netherlands, Poland, Slovakia, Türkiye	24 h on, 48 h off	EPSU (2006); Demiralp & Özel (2021)
Ireland	9-h days and 15-h nights – with 2 days and 1 night followed by 2 nights and 1 day, followed by 3 days off	EPSU (2006)
Italy, Luxembourg, Slovenia	12-h day/24 h off/12-h night/48 h off	EPSU (2006)
Norway	4–7 and 7–4 shifts Monday to Friday with 24- or 48-h shifts at weekends	EPSU (2006)
Portugal	12-h shifts	EPSU (2006)
Republic of Korea	3-, 6-, 9-, or 21-day cycles	Kwak et al. (2020)
United Kingdom	2 days, 2 nights, and 3 days off	EPSU (2006)
USA and some Canadian provinces	[24-h rotation]	NIOSH (1977); Jung et al. (2021a)

EPSU, European Public Service Union.

[a] Reported standard shift patterns may not apply to wildland firefighters.

[Volunteer, retained, and on-call firefighters may not have a set shift schedule.]

In contrast to those of municipal firefighters, the work schedules of wildland firefighters vary greatly depending on the severity of the fire season. For Canadian and US wildland firefighters, for example, these schedules can go up to 14 consecutive days (up to 16 hours of service per day), with 2 or 3 days of travel at either end, before a minimum of 2 days of rest is mandated (National Multiagency Coordination Group, 2002; McGillis et al., 2017). Incidentally, assignments may be extended up to 30 days (NIFC, 2022b). In Australia, wildland firefighters are typically rostered for a 12-hour day or night shift, but this can go up to 16 hours for 3–5 consecutive days, depending on fire severity and available personnel (Vincent et al., 2016).

Shift work is inevitable in firefighting, and most firefighters work rotating or extended shifts. Firefighters may sleep during the night, unless called out to an emergency event (Pukkala et al., 2014). [However, the opportunity for and quality of sleep during the night may vary by location and employer.] For example, the self-reported sleeping duration of wildland firefighters varies between 3 and 7 hours (Vincent et al., 2018). In a study among 109 US career firefighters, 73% reported poor sleep quality, and sleep disturbance was largest for the Kelly schedule (Billings & Focht, 2016).

(b) Psychosocial factors

The firefighter work environment can be characterized as high stress, high risk, and with low control over job-related tasks and activities (Lourel et al., 2008). Adverse psychological effects of working as a firefighter may arise from working in unsafe physical conditions and witnessing traumatic incidents, and other inherent characteristics of the job (Smith et al., 2001; Brown et al., 2002; Duran et al., 2018). Firefighter working conditions include long periods of inactivity followed by periods of high activity, working night shifts, and organizational issues, including the adequacy of organizational policies, programmes, and practices, and the degree of management and co-worker support.

Research on the psychological impact of firefighting has largely focused on estimating the prevalence of post-traumatic stress disorder, depression, and other psychological illness (i.e. mood and substance-abuse disorders) (Saijo et al., 2012; Armstrong et al., 2014; Fraess-Phillips et al., 2017; Schnell et al., 2020). Prevalence varies substantially depending on the specific group of firefighters studied and the measures used to determine the prevalence of post-traumatic stress disorder. Psychological stressors are associated with an increase in alcohol, tobacco, and drug use (Kimbrel et al., 2011; Smith et al., 2011; Meyer et al., 2012; Gulliver et al., 2018; Lebeaut et al., 2020). Chronic stress can also cause corresponding changes in the body's immune function and inflammatory response; this is significant because a long-term inflammatory response and the decline of the body's immune surveillance capabilities are two out of several potential mechanisms implicated in tumorigenesis (Murphy et al., 1999; Huang et al., 2010b; Huang & Acevedo, 2011).

(c) Exposure to infectious agents

Emergency medical-response duties also put firefighters at risk of exposure to infectious agents, including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), all of which are classified in IARC Group 1, *carcinogenic to humans* (see Table 1.1) (Baker et al., 2020). In the USA, approximately 52% of protective service occupations (i.e. police officers, firefighters, transportation security screeners) are exposed at least once per month to infections in their work environment (Baker et al., 2020). Exposure to infectious agents occurs through either direct or indirect contact (Valdez et al., 2015). Through direct transmission, a pathogen (an agent that causes disease, such as

a virus, bacterium, or fungus) is transmitted directly from an infected patient or victim to the firefighter. Indirect transmission occurs when an inanimate object (e.g. pen, clipboard, disposable resuscitator bag valve mask, etc.) serves as a temporary reservoir for the infectious agent.

A report from the US Centers for Disease Control and Prevention documented that first responders (including firefighters) were not more likely to be exposed to HCV than was the general population (CDC, 2000). The investigators were not able to exclude the possibility that some first responders had acquired HCV infection from job-related exposures. A literature review by Boal et al. also concluded that firefighters and emergency medical services personnel do not have an elevated seroprevalence of HCV compared with the general population (Boal et al., 2005). [The Working Group identified a paucity of scientific articles providing surveillance data on exposure to infectious agents among firefighters.]

1.6 Factors that modify or mediate effects of exposure

1.6.1 Personal protective equipment and other control measures

(a) Hierarchy of controls

The hierarchy of controls is a framework that supports decision-making around implementing feasible and effective control solutions in occupational settings (NIOSH, 2015). Under this hierarchy, control measures are prioritized according to their potential effectiveness. For example, elimination and substitution of occupational hazards are ranked higher than engineering controls (e.g. diesel-exhaust capture), administrative controls (e.g. decontamination of gear or skin), and PPE. PPE is considered to be the least effective type of control measure, mainly because it relies heavily on individuals to properly wear and maintain it. Nevertheless, PPE is a critically important control measure for emergency situations in which other types of controls are difficult to employ and unlikely to eliminate the hazard. Hence, firefighters rely heavily upon PPE (respiratory and dermal protection) to control their exposures to particulate matter, chemicals, and thermal hazards.

(b) Use of personal protective equipment

Variations in firefighting PPE exist across the globe and by job assignment or speciality area. For example, firefighting helmets in Europe differ from those in the USA and Japan in that European helmets are designed to integrate with a SCBA facepiece and do not have a large brim (Lee et al., 2014; Hartin, 2019). The types of PPE worn by fire-cause investigators (IAAI, 2020), industrial firefighters, hazardous material specialists, and other subspecialities of the fire service also differ. Unlike municipal firefighters, wildland firefighters typically wear light protective clothing, such as long-sleeved fire-resistant shirts, trousers, gloves, mid-calf leather boots, and hard hats, but often do not wear respiratory protection (Homeland Security, 2014; Carballo-Leyenda et al., 2018; Navarro et al., 2019a; Koopmans et al., 2022). Some wildland firefighters in certain geographical regions may wear particulate-filtering respirators (NSW Rural Fire Service, 2022); however, these types of respirator are not effective against gases and vapours, including acrolein, formaldehyde, and carbon monoxide (De Vos et al., 2009a), and do not supply oxygen.

(c) Respiratory protection

Firefighters at an incident who do not wear respiratory protection are susceptible to a variety of airborne exposures. However, municipal firefighters will often be wearing pressure-demand SCBA when battling fires, which has an assigned protection factor (APF) of 10 000 (OSHA, 2009) (see Fig. 1.18). An APF is the level of protection that a respirator should provide to employees

Fig. 1.18 Firefighters wearing self-contained breathing apparatus and other personal protective equipment

From Professor Anna A. Stec, Centre for Fire and Hazards Sciences, University of Central Lancashire, UK.

when the employer implements a comprehensive respiratory protection programme (OSHA, 2009). An APF of 10 000 means the respirator will reduce the exposure to one ten-thousandth of the concentration outside the SCBA. Atmosphere-supplying respirators (including SCBA) are the only types permitted for immediately dangerous to life or health (IDLH) environments (OSHA, 2009). On the basis of an analytical model using empirical data, Campbell et al. (1994) estimated that 95% of pressure-demand SCBA wearers would maintain a protection factor two orders of magnitude greater than 10 000. However, another study suggested that firefighters can over-breathe their SCBA during strenuous activities, highlighting the importance of fit-testing (Burgess & Crutchfield, 2015).

SCBA may not always be worn during fire emergencies. Austin et al. (2001c) tracked compressed air usage among firefighters in Montreal, Canada, and estimated that SCBA was worn 50% of the time at structure fires and only 6% of the time at all types of fire. Burgess et al. (2003) found that SCBA was used by firefighters

in Arizona, USA, an average of 98%, 80%, 42%, and 15% of the time during extinguishment, entry/ventilation, overhaul, and support/standby functions, respectively. These studies are older, however, and SCBA usage has probably increased across the fire service (Burgess et al., 2020). Still, in some jurisdictions, SCBA may not be commonly worn by structural [municipal] firefighters during specific activities like vehicle fire suppression, overhaul, fire investigations, command/pump operations, or when conducting horizontal or vertical ventilation (Maglio et al., 2016; Jakobsen et al., 2020). As previously mentioned, wildland firefighters typically do not wear respiratory protection (Navarro, 2020).

Burgess et al. (2020) evaluated the impact of control interventions on exposures for different types of firefighter, including among engineers who typically set up away from the fire and often do not wear respiratory protection. When the engineers wore SCBA in the presence of smoke, they had ~40% lower PAH exposures (urinary metabolites) than they did before the intervention.

Other types of control measures in the hierarchy of controls can be implemented during emergency situations to reduce inhalation exposures for firefighters. For example, engineers, incident commanders, and support personnel may be able to approach and position themselves upwind of the fire and take advantage of natural ventilation (CFRA, 2012). Use of water as a means of controlling dust after a fire or collapse can help control the spread of airborne particles, including asbestos fibres (Kim et al., 2020a). Using fluorine-free foam as a suppression agent instead of AFFFs containing perfluoroalkyl acids can reduce firefighters' exposure to PFAS (EC/ECHA, 2020). Firefighting tactics may also impact exposure levels. For example, tactics that involve exterior suppression as a first step before transitioning to interior attack have been shown to result in less exposure for firefighters than those involving interior attack alone (Fent et al., 2020b). [The Working Group estimated that implementing these control measures together with the use of SCBA and other PPE should help to reduce the overall burden on the protective barriers of the PPE and provide greater protection to the firefighter.]

Even more control options may be available in non-emergency situations. At training academies, fire instructors can rotate positions to minimize their time within burn structures. Fuel packages can be selected to achieve training objectives while minimizing exposures. For example, simulated smoke and digital flames can be used instead of live fire for some types of training (Fent et al., 2019a, b). At fire stations, engineering controls, such as exhaust capture systems in vehicle bays, can be used to reduce firefighters' exposure to diesel exhaust (Chung et al., 2020).

Another source of inhalation exposure is the off-gassing of contaminated turnout gear (Fent et al., 2015, 2017; Kirk & Logan, 2015b; Banks et al., 2021b). This source of exposure can be minimized by quickly removing the gear, rehabilitating away from the gear, bagging or transporting the gear in a compartment other than the passenger cabin of the apparatus (engine) or personal vehicle, laundering the gear after firefighting, and storing the gear in areas outside living quarters of the fire station.

(d) Dermal protection

In addition to the inhalation route, firefighters can ingest particulate matter captured through the mucociliary escalator of the respiratory system (Lippmann et al., 1980) or directly through the oral route from hand-to-mouth transfer of contamination (depending on hygiene practices). Firefighters can also absorb hazardous chemicals via the dermal route (see Section 1.4.5 for more information on the different routes of absorption). Firefighters' skin can pick up contamination when doffing or handling contaminated gear or equipment (Kesler et al., 2021). Some

contaminants may penetrate the protective barriers of the turnout gear and contact skin during the firefight. Studies have shown ingress of benzene, naphthalene, and other PAHs through openings in the turnout gear and have measured PAH contamination on skin, especially on the neck, wrist, and hands (Fent et al., 2014, 2017; Kirk & Logan, 2015b; Keir et al., 2017; Wingfors et al., 2018; Mayer et al., 2020; Banks et al., 2021a). Some chemical vapours may condense on skin as they cool under turnout gear. Compounds with low vapour pressures that contact skin are more likely to be absorbed, although the specific properties of the compounds, such as octanol/water partition coefficient, also play an important role (Frasch, 2002; Rauma et al., 2013). Dermal absorption is generally faster on areas of the body with thinner skin and a high cutaneous blood flow rate, such as the neck (VanRooij et al., 1993; McCarley & Bunge, 2001).

Turnout gear is often designed for the male anatomy, which can have an impact on its fit for female firefighters, leading to larger air spaces under the gear for females and influencing its thermal and vapour resistance (Nawaz & Troynikov, 2018; Jo et al., 2022). [The Working Group concluded that lack of properly fitting turnout gear is likely among female firefighters in general and could result in greater contaminant ingress and dermal exposure.] Tightening the interfaces around the neck, wrists, waist, and boots, and wearing particle-blocking hoods may impede the penetration of some PAH compounds (Ormond et al., 2019; Kesler et al., 2021). However, there is concern that these interventions could also increase the thermal strain for firefighters by trapping metabolic heat energy (Kesler et al., 2021). The micro-environment created under turnout gear (e.g. higher temperature and humidity levels) may facilitate the dermal absorption rate of compounds that penetrate the protective barriers of the gear (Franz, 1984; US EPA, 1992; VanRooij et al., 1993).

Most control interventions aimed at reducing dermal exposure have focused on measures that can be taken after firefighting. These interventions include gross decontamination of turnout gear and other equipment, use of skin-cleansing wipes or washing skin with soap and water at the incident, bagging and laundering of turnout gear and hoods before wearing them again, and showering as soon as possible after returning to the fire station. Fent et al. (2017) found that gross decontamination using water, dish soap, and scrubbing was able to remove a median of 85% of PAH contamination on the exterior of turnout jackets, and that use of skin-cleansing wipes removed a median of 54% of PAH contamination from the skin. Mayer et al. (2019) found a mean reduction in PAH contamination in used knit hoods of 76% after a single laundering; however, results were mixed for removal of PBDEs and OPFRs. Banks et al. (2021c) found that laundering and water-only decontamination did not significantly remove PAHs, PBDEs, or OPFRs contaminating turnout gear, with a few exceptions. Burgess et al. (2020) found that implementing several of these interventions (gross decontamination and segregation of contaminated gear with subsequent laundering, skin cleaning, and showering as soon as possible at the station) resulted in ~36% lower PAH exposures (measured as urinary metabolites) for firefighters compared with before the interventions were implemented.

While many departments have implemented PPE decontamination measures, such as gross on-scene decontamination and laundering of turnout gear that has been worn for a fire response, within the last 10 years (Horn et al., 2021), many fire departments continue to launder turnout gear infrequently (e.g. once or twice per year) as per current minimum standards or because of resource limitations (NFPA, 2020a). SCBAs are also commonly decontaminated after firefighting, but this practice is likely to vary across the fire service (Park et al., 2022). In the USA, wildland firefighters commonly wear the

same protective clothing over weeks and launder these items at home (McQuerry & Easter, 2022).

1.6.2 Other factors, including health behaviours

Inter-individual variability in how chemicals are absorbed, metabolized, and excreted may be related to sex or genetic differences. However, these factors are complex, difficult to study, and are largely beyond the control of the individual. Personal factors that may modify or mediate the effect of exposure that individuals have control over include personal hygiene, use of sunscreen and limiting sun exposure, nutrition, exercise, sleep, limiting alcohol consumption, and not using tobacco.

(a) Personal hygiene factors

Washing or cleaning skin after firefighting will help remove contaminants before they are absorbed into the dermis or deeper layers of skin where blood perfusion occurs. However, skin-cleansing wipes, which are commonly used after firefighting, will not remove all contaminants from the skin (Fent et al., 2017). The longer chemicals stay on the skin (contact time), the more likely they are to be absorbed (Frasch et al., 2014). [The Working Group agreed that showering as soon as possible is critical to remove any residual skin contamination. Washing hands before eating will also help reduce hand-to-mouth ingestion of chemical or biological contaminants. Use of sunscreen, especially by firefighters who spend substantial time outdoors, will help reduce their exposure to harmful UV radiation. Wearing long-brim hats and long-sleeved shirts during extended times outdoors can further minimize UV exposure.]

(b) Health behaviours

Eating nutritious foods, exercising, and maintaining a healthy BMI, while important for overall health, may also help lessen the effects of exposure. Having a strong cardiovascular and respiratory system can lower an individual's breathing rate, which can extend the use of SCBA during operations and reduce the biological uptake of airborne contaminants through the lungs when respiratory protection is not worn (US EPA, 2011). Many hazardous chemicals are lipid-soluble, and increased levels of body fat can act as a reservoir to store these compounds for longer periods (Milbrath et al., 2009). Eating foods that are high in antioxidants, vitamins, and minerals can support the body's natural defences against xenobiotics and oxidative stress (Flora, 2009). Nutrition is especially important for wildland firefighters to provide the necessary calories to support their arduous work, while also providing adequate nutrients for their overall health (Brooks et al., 2021).

Not using tobacco products is also important to maintain the body's normal defence mechanisms against toxicants. Exposure to tobacco smoke has been shown to cause damage to the mucociliary escalator of the respiratory system and lessen the body's ability to clear particles inhaled into the lungs (Xavier et al., 2013).

The human body has several mechanisms in place to repair cellular and DNA damage, regardless of the cause. These mechanisms are especially active during sleep. Hence, getting adequate and consistent sleep, including uninterrupted deep sleep, is important for mitigating the effects of occupational and non-occupational exposures (Atrooz & Salim, 2020; Williams & Naidoo, 2020).

1.7 Regulations and guidelines

1.7.1 Occupational exposure limits

OELs for some fire effluents are presented in Table 1.27. Both the American Conference of Governmental Industrial Hygienists and the European Union (previously via the Scientific Committee on Occupational Exposure Limit

Table 1.27 Examples of occupational exposure limits for some fire effluents[a]

Fire effluents	Units	TLV-TWA		STEL	
		ACGIH	EU[c]	ACGIH	EU[c]
Acetaldehyde[b]	mg/m³		5 (LV)		45 (LV)
Arsenic	mg/m³	0.01	0.01 (IP, BV)		
Asbestos	fibres/cm³	0.1	0.1 (BV)		
Benzene[d] (on NIC)	mg/m³	0.066[e]	0.66 (BV)	0.33[e]	
1,3-Butadiene	mg/m³	4.4[e]	2.2 (BV)		
Cadmium[c]	mg/m³	0.01 TP 0.002 R	0.001 (IP, BV)		
Carbon black	mg/m³	3 IP	3 (LV)		
Carbon monoxide	mg/m³	29[e]	23 (BV)		117 (BV)
Dichloromethane (methylene chloride)	mg/m³	174[e]	353 (IOELV)		706 (IOELV)
Ethylbenzene	mg/m³	88[e]	442 (IOELV)	551[e]	884 (IOELV)
Formaldehyde	mg/m³	0.12[e]	0.37 (BV)	0.37[e]	0.74 (BV)
Tetrahydrofuran	mg/m³	150[e]	150 (IOELV)	590[e]	300 (IOELV)
Isoprene	mg/m³		8.4 (LV)		67.2 (LV)
Lead[d]	mg/m³	0.05	0.15 (BV)	0.0005	
Lead chromate	mg/m³	0.0002 (IP)	0.04 (LV)		
Naphthalene	mg/m³	50[e]	2 (LV)		8 (LV)
Particulate matter (respirable)	mg/m³	No TLV but should be < 3	0.3 (LV)		2.4 (LV)
Particulate matter (total)	mg/m³	No TLV but should be < 10			
Pentachlorophenol	mg/m³	0.5	0.05 (LV)	1	0.1 (LV)
Polychlorinated biphenyls (PCBs) (42% chlorine) (54% chlorine)	mg/m³	 1 0.5			1.5 (IOELV)
Polycyclic aromatic hydrocarbons (PAHs)[d] (benz[*a*]anthracene, benzo[*b*]fluoranthene, chrysene, anthracene, benzo[*a*]pyrene, phenanthrene, acridine, or pyrene)	mg/m³	0.2	0.0005507 (LV)		
Styrene	mg/m³	43[e]	10 (LV)	86[e]	30 (LV)
Sulfuric acid	mg/m³	0.2 TPM	0.05 TPM (IOELV)		
Tetrachloroethylene (perchloroethylene)	mg/m³	170[e]	138 (IOELV)	685[e]	275 (IOELV)
Trichloroethylene	mg/m³	54[e]	54.7 (BV)	135[e]	164.1 (BV)
Trichloromethane (chloroform)	mg/m³	49[e]	10 (IOELV)		5 (LV)

ACGIH, American Conference of Governmental Industrial Hygienists; EU, European Union; IP, inhalable particulate; LV, lowest value; ppm, parts per million; R, respirable; STEL, short-term exposure limits; TLV, threshold limit values; TP, total particulate; TPM, thoracic particulate mass; TWA, time-weighted average.

[a] Adopted from IFA (2022).

[b] Acetaldehyde – ceiling value available: ACGIH (25 ppm); EU (25 ppm, LV).

[c] When a TLV-TWA was not available, an EU binding value (BV) (Directive 2004/37/EC – carcinogens, mutagens or reprotoxic substances at work) the lowest value (LV) in place in a Member State was used or the indicative occupational exposure limit value (IOELV), when available.

[d] Substances with a biological exposure index (BEI) or EU biological limit value (BLV).

[e] Data were converted from ppm to mg/m³.

Values and now via the Committee for Risk Assessment of the European Chemicals Agency, ECHA) provide OELs. [These are both health-based limits but may not have been based on a cancer end-point.] Many countries have lists of OELs to be applied nationally (Schenk et al., 2008). The GESTIS website lists OELs from around the world (IFA, 2022).

[The Working Group noted that only some of the individual components of fire smoke (i.e. aldehydes, acid gases, sulfur dioxide, nitrogen oxides, PAHs, benzene, toluene, styrene, metals, and dioxins) have OELs, and many agents to which firefighters are commonly exposed have no OELs. There is no recommended way of adjusting for the complex and partly unknown mixtures present in fire effluents, some of which are probably composed of agents that act on the same organ and/or have the same effect, e.g. irritancy. Furthermore, OELs are typically set for a work week of 40 hours (8 hours per day for 5 days per week), so may not provide sufficient protection for workers with longer shifts. Some OELs can be arithmetically reduced for longer shifts, perhaps up to 12 hours, so that the total permitted exposure is equivalent. However, for longer shifts, depending on the agent, this may not allow sufficient recovery time between exposure periods. Firefighters often have very intense short-term exposures, during which short-term exposure limits (STELs) or ceiling limits may well be exceeded. In addition, OELs do not consider increased respiratory rates. Some more specific guidance on firefighters' exposure has been provided in Canada, the UK, and Australia (AFAC, 2019a; Government of Ontario, 2022; Government of the United Kingdom, 2022).]

1.7.2 Regulations on use of personal protective equipment

PPE including devices and garments, such as respirators, turnout gear, gloves, blankets, and SCBA are designed to protect firefighters from serious injuries or illnesses resulting from contact with fire and hazardous materials (Smith et al., 2020; McQuerry & Easter, 2022). Regulations on the use of PPE can vary worldwide. Regulation on cleaning, maintenance, and repair of PPE follows BS 8617 in the UK (British Standards Institution, 2019a). Firefighters in the UK should use municipal firefighting PPE as the common default position for fire and rescue activities initially; the PPE is modified by the incident commander based on a joint understanding of risk and information available from other responder agencies (Daniels, 2019). In Australia, PPE must comply with relevant international/Australian standards (AFAC, 2019b).

In the USA, National Fire Protection Association Standard 1971 (NFPA 1971), Standard on Protective Ensembles for Structural Fire Fighting and Proximity Fire Fighting establishes minimum levels of protection from thermal, physical, environmental, and blood-borne pathogen hazards encountered during structural [municipal] and proximity fire-fighting operations (American Public Health Association, 2001; NFPA, 2018). There are several other US NFPA standards that address firefighter PPE, including NFPA 1500 Standard on Fire Department Occupational Safety and Health Program (Loflin, 1989), NFPA 1851 Standard on Selection, Care, and Maintenance of Protective Ensembles for Structural Fire Fighting and Proximity Fire Fighting (NFPA, 2001), NFPA 1951 Standard on Protective Ensembles for Technical Rescue Incidents (NFPA, 2001), NFPA 1975 Station/Work Uniforms for Fire and Emergency Services (NFPA, 2002), NFPA 1977 Standard on Protective Clothing and Equipment for Wildland Fire Fighting (NFPA, 2015), NFPA 1991 Standard on Vapour-Protective Ensembles for Hazardous Materials Emergencies (NFPA, 2005, 2012), NFPA 1992 Standard on Liquid Splash-Protective Clothing for Hazardous Materials Emergencies, NFPA 1994 Standard on Protective Ensembles for First Responders

to CBRN Terrorism Incidents, NFPA 1999 Standard on Protective Clothing for Emergency Medical Operations (EMS), and OSHA Rule 29 CFR 1910.1030 Final rule on Protecting Health Care Workers from Occupational Exposure to Bloodborne Pathogens (Denault & Gardner, 2022).

The use of PPE in Portugal is mandatory for firefighting emergency calls (Moraes et al., 2019a, b); however, different safety gear, devices, and equipment are available based on the fire scenario. There is still limited literature on and systematic investigation of the overall regulatory state of PPE (Kim et al., 2022). In the Republic of Korea, there are no comprehensive regulations governing firefighting PPE, PPE maintenance, and replacement, similar to NFPA 1851 in the USA. In Canada, the Canada Labour Code and Occupational Health and Safety Regulation (Regulation) Part 31: Firefighting, stipulate general PPE requirements, together with protective coats, trousers and hoods, station wear, and personal garments (Frost et al., 2016; Ramsden et al., 2018). [Despite the general use of PPE among firefighters worldwide, there is a need to study the impact of the makeup and design of the various types of PPE, repeated use and exposure to heat and chemicals, maintenance, and cleaning on the protective capabilities of the PPE.]

1.7.3 Regulations on firefighting foams

The use of PFAS in AFFF has been regulated in the European Union since 2006 (Banzhaf et al., 2017), and the Stockholm Convention listed PFAS (i.e. PFOA, its salts, and PFOA-related compounds; PFHxS, its salts, and PFHxS-related compounds, and long-chain perfluorocarboxylic acids, their salts and related compounds) as persistent organic pollutants that are to be phased out in 185 countries (Secretariat of the Stockholm Convention, 2019a; Pinas et al., 2020).

In the European Union, the ECHA has brought forward a restriction proposal for a European Union-wide ban on both the use and production of PFAS. In 2022, ECHA's scientific Committee for Risk Assessment and Committee for Socioeconomic Analysis are assessing the proposed restriction options (ECHA, 2022a). When adopted, the restriction could reduce PFAS emissions into the environment by more than 13 000 tonnes over 30 years (ECHA, 2022b).

1.7.4 Minimum age of firefighters

Requirements and regulations to work as a firefighter vary across countries, but many countries require an individual to be aged at least 18 years (Sluiter & Frings-Dresen, 2007; Evarts & Stein, 2020; Euroinnova, 2022). In Australia, there are no general age requirements; however, the Country Fire Authority, Victoria, has a minimum age of 16 years (16- and 17-year-olds need parental consent) for volunteer firefighters, and some brigades also run a junior programme for 11–15-year-olds (Fire Recruitment Australia, 2015; Fire and Rescue New South Wales, 2021b).

1.7.5 Regulations on maximum worker hours

The majority of US fire departments work a rotating schedule of 24-hour shifts guided by the Fair Labor Standards Act (Cohen & Plecas, 2013). In Canada, firefighters work a minimum of 48 hours per week and become eligible for overtime after working about 56 hours in a week (Ontario Association of Fire Chiefs, 2022). In Australia, working hours are a matter for trade union agreement; working hours average 38 hours per week and shifts vary over an 8-week cycle (ACT Government, 2020).

In the European Union, the Working Time Directive was introduced in 1993 to set rules on maximum weekly working time and other requirements in terms of rest breaks, daily rest periods, and shift work (Rønning, 2002; Sol & Martín, 2015; Risak, 2019). However, there are many differences regarding working time

between and within countries (EPSU, 2006). Working time is negotiated nationally in Denmark, Finland, Slovakia, and the UK, while in other countries there is a combination of national and local negotiation (EPSU, 2006). Furthermore, hours are calculated on an annual basis in Belgium, Denmark, France, Slovak Republic and Spain, while they are weekly in Czechia, Finland, Ireland, Italy, Norway, Sweden and the UK. In the Netherlands, the weekly maximum number of hours is calculated over a 26-week period. The monthly calculation in Estonia is averaged over a 3-month period (EPSU, 2006).

The basic work week – the hours set out in collective agreements or statutes for which firefighters are paid at a basic rate – ranges from 36 hours in Italy and the Netherlands to 42 hours in Sweden and the UK (EPSU, 2006). However, these hours do not necessarily correspond to actual hours normally worked; for example, actual working time averaged 54 hours per week among Dutch firefighters (EPSU, 2006).

There have been a few changes to working time in recent years. In Norway, there has been a new national agreement that allows for 48-hour shifts over weekends and 24-hour shifts during the week (EPSU, 2006). In North Rhine-Westphalia, the biggest region in Germany, firefighters negotiated a reduction in the working week from 54 to 48 hours from 1 January 2007 (EPSU, 2006). The regional government agreed to bring the service into line with the Working Time Directive after pressure from the trade union.

1.8 Quality of exposure assessment in key epidemiological studies of cancer and mechanistic studies in humans

1.8.1 Epidemiological studies of cancer in humans

This section reviews the exposure assessment methods and exposure assessment quality of the epidemiological studies of firefighters. The findings are summarized in Table S1.28, and the criteria for the exposure quality rating are included in Table S1.29 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

As described in Section 1.2, Section 1.4, and Section 1.5, firefighters are exposed to a range of physical and chemical hazards that vary from day to day and have changed over time. Quantitative characterization of all these exposures is not feasible in studies of cancer in humans. The definition of exposure provided by most epidemiological studies is simply having worked as a firefighter. This definition may be refined in a variety of ways to better reflect the extent or intensity of firefighting activities. For example, those with the occupational title of firefighter but who do not actually attend to fires may be excluded. Additionally, the duration of firefighting service (e.g. < 10 years versus ≥ 10 years) may be used under the assumption that longer service will lead to more time spent in direct exposure to fires and related hazards (e.g. Aronson et al., 1994; Ahn & Jeong, 2015; Bigert et al., 2020).

Other exposure assessment metrics have been used to group firefighters by measures of the extent or intensity of exposure and reduce misclassification. For example, individual estimates of firefighting activities including number and/or types of fire (e.g. house, vehicle, etc.), probably better reflect the actual chemical and

physical exposure burdens (e.g. Dahm et al., 2015) than does the simple duration of work. Other studies grouped or selected firefighters by job title or role (active or frontline) (e.g. Demers et al., 1994) and/or provided a measure of busyness, intensity, or type of firefighting role (e.g. Guidotti, 1993; Tornling et al., 1994; Daniels et al., 2015; Glass et al., 2016a).

To assess the quality of the exposure assessment and the extent of misclassification in the epidemiology studies, the following data elements were examined: (i) the study design, location, and era, or exposure period; (ii) ascertainment of firefighter status and years of engagement as a firefighter; (iii) exposure metrics for use in analyses such as a measure of intensity of firefighting work; (iv) timing of exposure relative to the outcome; (v) co-exposures to carcinogens; and (vi) potential for differential exposure misclassification (see also Table S1.28, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

Based on these criteria, an evaluation of the exposure quality of each study is presented in Sections 2.1 to 2.6 and in the accompanying tables in Section 2 and supplementary tables in Annex 2 (Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

(a) Critical review of exposure assessment methods

The 40 cohort studies reviewed all came from high-income countries, including the Republic of Korea (n = 2) (Ahn et al., 2012; Ahn & Jeong, 2015); Canada (n = 5) (Mastromatteo, 1959; Guidotti, 1993; Aronson et al., 1994; Harris et al., 2018; Sritharan et al., 2022); the USA (n = 16) (Musk et al., 1978; Feuer & Rosenman, 1986; Vena & Fiedler, 1987; Grimes et al., 1991; Demers et al., 1992, 1994; Burnett et al., 1994; Ma et al., 2005, 2006; Zeig-Owens et al., 2011; Daniels et al., 2014, 2015; Moir et al., 2016; Colbeth et al., 2020a; Pinkerton et al., 2020; Webber et al., 2021); Oceania (n = 7), (Eliopulos et al., 1984; Giles et al., 1993; Bates et al., 2001; Glass et al., 2016a, b, 2017, 2019); Nordic countries (n = 7) (Tornling et al., 1994; Pukkala et al., 2014; Kullberg et al., 2018; Petersen et al., 2018a, b; Bigert et al., 2020; Marjerrison et al., 2022); and other European countries (n = 3) (Deschamps et al., 1995; Amadeo et al., 2015; Zhao et al., 2020). The case–control studies are also mainly from high-income countries: Europe (n = 1) (Stang et al., 2003); North America (n = 9) (Sama et al., 1990; Muscat & Wynder, 1995; Ma et al., 1998; Kang et al., 2008; Tsai et al., 2015; Muegge et al., 2018; Langevin et al., 2020; Lee et al., 2020; McClure et al., 2021); and one international study that included data from China, Europe, North America, and Oceania (Bigert et al., 2016).

Most cohort studies identified career firefighters from employment records, including general municipal employment records, e.g. Vena & Fiedler (1987). Other reliable sources of employment information used in firefighter epidemiology are professional certification data (Ma et al., 2005, 2006), superannuation (pension contributions), compensation data (Mastromatteo, 1959; Sritharan et al., 2022), and retirement records (Feuer & Rosenman, 1986; Ide, 1998). Studies identifying firefighters from census data rely on self-reported employment information. They may collect data at one point in time, e.g. Zhao et al. (2020) and Harris et al. (2018), or from more than one census, which allows an estimate of employment duration (e.g. Bigert et al., 2020). Mortality studies that use death certificate data on "usual occupation," as reported to the certifying health professional often by the next of kin (for example, Burnett et al., 1994), are probably less reliable than those with employment records, for example. [The limitations of these data as a proxy for occupational exposure are well documented, e.g. Steenland & Beaumont, 1984; Schade & Swanson, 1988; Bidulescu et al., 2007.]

In some case–control studies, firefighters were largely identified from interviews or questionnaires coded to standardized occupational codes and categorized as ever/never firefighters (e.g. Stang et al., 2003; Tsai et al., 2015; Bigert et al., 2016; Langevin et al., 2020). Other sources of information on occupation for case–control studies were cancer registry records (e.g. Tsai et al., 2015), death certificates (e.g. Ma et al., 1998; Muegge et al., 2018), and linkage between cancer registry and census or employment records (e.g. McClure et al., 2021). [Occupational information from cancer and death registries is often incomplete, and there was evidence from at least one registry that the missingness was differentially distributed (McClure et al., 2021). There may also be selection bias in these studies.]

Most employment-based cohorts are from urban areas (e.g. Pinkerton et al., 2020; Webber et al., 2021), whereas other cohorts (e.g. those based on census records) are country-wide and therefore probably include both urban and rural firefighters (e.g. Pukkala et al., 2014; Bigert et al., 2020). [The exposures of rural and urban firefighters differ in type and pattern of exposure. Rural firefighters mainly fight wildland (sometimes called "landscape") fires, whereas municipal firefighters are more likely to attend structure and vehicle fires, hazardous material incidents, and false alarms. Unlike most structure fires, wildland fires can take days or even weeks to extinguish, which means that wildland firefighters may have extended firefighting periods away from home. Their equipment, such as fire trucks, clothing, and respiratory protective equipment may differ from that of municipal firefighters. Wildland firefighters probably use a different mix of fire suppression techniques, such as back burning and aerial spraying of water or flame retardants, and are less likely to use respiratory protective equipment. Section 1.2 provides further information on differences in exposure between different groups of firefighters and types of fire.]

Most cohort studies are of career firefighters, but some also included volunteers (Guidotti, 1993; Bates et al., 2001; and Petersen et al., 2018b). One study included only volunteer firefighters (Glass et al., 2017). Glass et al. (2019) included a relatively small number of career female firefighters; most of the analyses focused on volunteer female firefighters. [Assessing quality of the exposure assessment requires that firefighters be accurately identified. For career firefighters, employment records are an accurate way to identify firefighters, but similar documentation for volunteer or wildland firefighters may be unavailable in many countries. Volunteer records may not be a reliable source of duration of active firefighting, since volunteer rolls may not be updated, and volunteers may remain in the organization but not actively fight fires.]

Employment duration was often captured from employment records and used as a proxy for exposure (e.g. Petersen et al., 2018a; Glass et al., 2019; Marjerrison et al., 2022). Employment duration inferred from periodic census data is probably less reliable than that from employment records (e.g. Bigert et al., 2020). In many other studies, employment was characterized qualitatively as ever/never a firefighter, and in some cases the status was known only at a specific time point (e.g. Amadeo et al., 2015). An improvement on employment duration used by several authors (e.g. Demers et al., 1994; Ahn & Jeong, 2015; Petersen et al., 2018a) was to count only years of service in direct firefighting roles.

A few studies specified a minimum period of service as a firefighter: 1 day (Daniels et al., 2014), 1 month (Ahn & Jeong, 2015), 3 months (Glass et al., 2016b), and 1 year (Demers et al., 1992; Tornling et al., 1994; Bates et al., 2001; Kullberg et al., 2018). [This could mean that firefighters with a relatively short duration of service were included in analyses together with those with longer service, and studies were included that did not report duration of employment.]

Among the strongest exposure assessments were studies that used various sources of information to improve upon duration of service, including indicators of likelihood of high exposures from actual firefighting activities. These included Guidotti (1993), who used an exposure opportunity matrix to weigh the duration of work by proximity to the fire for various job categories. Glass et al. (2016b, 2017, 2019) grouped firefighters by the recorded number of incidents and type of fire attended (although records were incomplete and were estimated for early years). Tornling et al. (1994) grouped firefighters by the estimated number of fires they had fought. One of the exposure assessments of the highest quality was conducted for an epidemiological study of firefighters in three cities in the USA. The investigators developed a job-exposure matrix linked to participants' work history records to calculate several proxy exposure measures, including duration of exposure (cumulative time classified by exposed job title and assignment), fire-runs (cumulative events of potential fire exposure) and time at fire (cumulative hours of potential fire exposure) (Dahm et al., 2015; Daniels et al., 2015; Pinkerton et al., 2020), or specific exposures (e.g. Baris et al., 2001) assessed on diesel engine emissions.

The earliest cohort studies reviewed here included firefighters who were employed before 1930 (Musk et al., 1978; Guidotti, 1993), and the most recent studies included firefighters working in 2014 (Petersen et al., 2018a, b). A preponderance of studies examined cancer rates among firefighters working between 1980 and 2000. Analysis by era of employment may help to investigate changes in exposure over time (Glass et al., 2016a, 2017, 2019). [The wide range of eras indicated that there would have been differences in exposures between cohorts, for example, changes in the number of vehicle fires and extent of exposure to burning plastics, shift-work patterns, use of firefighting foams, and type of PPE availability and use (see Section 1.2 and Section 1.5(b) for further information.]

Information on PPE use was mentioned in only few studies. Tornling et al. (1994) included the use of SCBA in their exposure index. Wolfe et al. (2012) considered clothing in a case report of non-melanoma skin cancers. The quality and use of PPE, including respiratory protective equipment, has varied over time and so may affect the extent of exposure of individuals (Austin et al., 2001c; Austin, 2008).

Some studies examined the risk of cancer among firefighters who attended the aftermath of the WTC disaster in 2001 and were employed by the Fire Department of New York City (FDNY) (e.g. Colbeth et al., 2020a), or firefighters employed by other cities (Webber et al., 2021). Zeig-Owens et al. (2011), Colbeth et al. (2020a), and Webber et al. (2021) used earlier-developed ordinal exposure categories based on period of arrival at the scene: (1) (highest) arrived on the morning of 11 September 2001; (2) arrived afternoon of 11 September 2001; (3) arrived on 12 September 2001; (4) arrived between 13 and 24 September 2001; and (5) (lowest) arrived between 25 September 2001 and 25 July 2002. [None of these studies considered firefighting exposure that preceded the WTC response.]

The case reports and case series reviewed included limited information on exposure and are not discussed further here (Bates & Lane, 1995; Cucchi, 2003; Wolfe et al., 2012; Cormack, 2013; Schrey et al., 2013; Sugi et al., 2013; Antoniv et al., 2017; Landgren et al., 2018; Geiger et al., 2020).

(b) Other occupational exposures to carcinogens

Both career firefighters and volunteers are likely to hold or have held other jobs, either different positions within the fire service, or entirely separate occupations (Ma et al., 2006; Glass et al., 2017). For example, in a cohort of Danish paid [career] and volunteer firefighters

(Petersen et al., 2018a), more than 10% of firefighters had held jobs potentially exposing them to additional hazardous exposures in construction-related jobs, laundry or dry cleaning, the automobile industry, and rubber and plastic production. Compared with full-time firefighters, part-time or volunteer firefighters had more frequently been employed in the machine industry, fabricated metal production, the wood and furniture industry, and farming (Elbaek Pedersen et al., 2020). In a survey of career firefighters in Florida, USA, 29.7% had a second job; the most frequently reported second jobs were in education, health care, and sales (Baikovitz et al., 2019). [Most seasonal wildland firefighters also hold other jobs. These other jobs may result in exposure to other occupational carcinogens, e.g. asbestos or paint during construction work, or pesticides or solar UV in farming or forestry. Data on exposures in other jobs were not adjusted for in any cohort studies identified in the present monograph.]

1.8.2 Mechanistic studies in humans

This section reviews the exposure assessment methods used in and exposure assessment quality of the mechanistic studies of firefighters. The findings are summarized in Table S1.30 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

There is no single best method for assessing exposure of firefighters for the study of key characteristics of carcinogens (Smith et al., 2016) in humans. Assessment of the quality and informativeness of the exposure assessment requires understanding the research question, the study design, and the temporal characteristics of markers of exposure and effect. To be useful, the assessment should be unbiased, temporally appropriate, sufficiently quantitatively precise to allow demonstration of a dose–response relationship, and produce a summary measure of exposure that is credibly associated with the key characteristic of interest.

The studies of firefighters selected for assessing the key characteristics of carcinogens can largely be grouped into four different study types: cross-sectional (with a single measurement), repeated measurements (without a pre-exposure measurement), pre/post comparisons, and pre/post trials (where comparisons were done on exposures in a controlled setting), each with different strengths and limitations.

Many of the key characteristics studies used cross-sectional designs in which exposure was measured at a single point in time, and reflect all previous exposures, both recent and in the distant past. These studies usually involve an exposure contrast between exposed and unexposed groups, for example, comparing firefighters and non-firefighters. A major challenge to validity in this approach is that there are likely to be many differences in health-related characteristics of the compared groups, such that the fact that one is "exposed" and the other "not exposed" may be only one of many reasons why the two groups experience different health outcomes.

The cross-sectional design may also be used to compare different groups of firefighters with varying amounts of exposure, for example, different numbers of years of employment, or time spent at fires. This is an improvement, but there are still important limitations. One of the challenges of these designs is that it is often difficult to explicitly consider exposures that have occurred at different times in the past. If the outcome measure is thought to be affected only by very recent exposures, then there may be substantial misclassification of exposure if a long-term measure of exposure such as the number of years of employment is used. In an attempt to avoid this problem, participants may be asked about their recent exposures, but these reports may be subject to recall bias, particularly if participants are aware that the hypothesis is that their recent exposures are hazardous.

Comparing groups of firefighters with varying amounts of exposure is nearly always a retrospective exercise, and it is usually not possible to estimate with any confidence the long-term or cumulative exposures to specific agents that are expected to be proportional to chronic biological effects. Even good administrative records, when they are available, will rarely provide information on PPE (what was used and how effectively). Additionally, the number of years employed as a firefighter is usually strongly correlated with age, making it difficult to disentangle exposure and age effects.

Cross-sectional designs are often used in studies of high exposures under extreme conditions after firefighters have participated in catastrophic events, such as the collapse of the WTC or certain out-of-control wildfires. These are, of necessity, post hoc, effectively prohibiting direct measurement of pre-exposure effect markers and, to a large degree (such as at the WTC), excluding contemporary measures of exposure. Moreover, the exposure experienced may have little relevance to the day-to-day exposures of the great majority of firefighters.

Studies with a repeated-measurement design examine the contrast between exposures for individuals across time. These studies have many names, but the term "repeated measurements design" will be used here for studies with two or more measurements for the same person but without a measurement before the exposure. In contrast, the term "pre/post" will be used here for studies that contrast a measurement before exposure with one or more measurements after exposure. The pre/post time interval between samples may be a work shift (8 hours, for example), but may also be many weeks or months. It is important that the exposure time window defined by the two or more time points is appropriately matched to the temporal dynamics of the outcome measure. Considerations include the half-life of circulating cells or biomarkers and any latency between exposure and response that arises from the biological mechanism of the key characteristic. The pre/post design has the strong advantage that each participant "serves as his/her own control", because it is the change in exposure over time that is studied for its association with the change in outcome, reducing risk of confounding.

An example of a good application of the pre/post design, used mainly with wildland firefighters, is the monitoring of pollutants (particles from smoke) in the breathing zone during a work shift, relating these measures to biomarkers of exposure (such as urinary 1-hydroxypyrene, reflecting PAH exposure) and to effect markers that appear rapidly (within at most 24 hours) and may have some long-term relevance to the key characteristic of interest. While in principle this design could also be used in the urban setting, it is logistically challenging, because municipal firefighters respond to fire calls only infrequently and, of course, not on a predictable schedule that would allow setting up the sampling equipment. Such a design may not take account of prior exposures over months or years of firefighting. Better studies concentrate on changes in measured biomarkers between the beginning and end of shift; although relatively straightforward to design, the importance and interpretation of changes in transient effect biomarkers may be less obvious in these studies.

The fourth type of study is the "pre/post trial"; again, a measurement before exposure is compared with one or more measurements after exposure, but in these studies the investigators assign exposures or interventions rather than simply observing whatever exposures their study participants experience. Such trials have the strong advantage of minimizing the risk of most biases since the exposure is well defined and assigned, but they are limited in their applicability, because many of the exposures of firefighters cannot ethically be delivered to human subjects. Trials have most often been conducted to evaluate effects of exposures other than

breathing smoke and other combustion products, and include such factors as sleep restriction, heat exposure, physical exercise, and nutrition. Although these potentially important risk factors for cancer among firefighters can be studied in a controlled setting, findings must be interpreted cautiously, because the trial conditions may not correspond well to the actual exposures experienced by firefighters on the job.

(a) Is genotoxic

The most common approach to exposure assessment in studies of genotoxicity end-points in firefighters was to identify firefighters by employment records, sometimes supplemented with information on the duration of exposure (e.g. Ray et al., 2005). These studies are of limited use because of lack of information on the frequency or recency of firefighting activities, the timing and intensity of exposures to toxic chemicals, and the use of protective equipment.

Three studies with genotoxicity end-points involved special populations with unique exposures that are of limited relevance to the hazards of typical firefighters, and included teams who were brought to Kuwait to fight oil fires after the first Gulf War ("Operation Desert Storm") in 1990–1991 (Darcey et al., 1992), responders to a chemical plant explosion in Germany (Hengstler et al., 1995), and emergency technicians who responded to the sarin gas attack in the Tokyo subway, Japan (Li et al., 2004). Min et al. (2020) conducted a study of several mechanistic end-points among a population of firefighters on different work shifts. The hypotheses investigated were about the effects of shift work, and no other exposure information was gathered.

Higher-quality exposure assessments gathered information on the frequency or intensity of firefighting activities. Rothman et al. (1993, 1995) studied a cohort of California wildland firefighters twice, 2 months apart. Information was collected from self-reports on total hours of firefighting activity in the recent past, number of previous seasons of firefighting activity, and duration of daily exposure to diesel exhaust. Information on potential confounding exposures (including consumption of charcoal-broiled meat) was also collected by questionnaire. Self-reports of mask-wearing were also gathered. Liou et al. (1989) gathered self-reported information from firefighters on the frequency of firefighting activities in an effort to improve upon the basic firefighter/non-firefighter comparison used in the primary analyses in their papers.

(b) Induces epigenetic alterations

Four studies assessing the associations between measures of DNA methylation and firefighters' exposures used cross-sectional designs (Ouyang et al., 2012; Kuan et al., 2019; Zhou et al., 2019; Goodrich et al., 2021). There were variations in exposure assessment methods that may affect study quality. Ouyang et al. (2012) used the simplest approach, comparing firefighters to non-firefighters. Zhou et al. (2019) improved upon this simple contrast by comparing new recruits to incumbent firefighters (14 years of service, on average), and comparing incumbents by duration of service. Goodrich et al. (2021) studied only active-duty firefighting. The principle exposure contrast was created using serum concentrations of PFAS compounds, rather than any measure of firefighting experience. This approach to exposure assessment avoided problems of selection or recall bias, and even inaccuracies of official records that are found in most of the studies on firefighters. In the fourth cross-sectional study of epigenetic alterations, Kuan et al. (2019) constructed an innovative exposure metric, the exposure-ranking index, to summarize many dimensions of the exposure histories of WTC first responders. The exposure-ranking index incorporated information on the duration of exposures, as well as exposure-related tasks and use of PPE on 11 September 2001 and in the subsequent months. The information was gathered from detailed exposure questionnaires completed

by firefighters and other first responders some time after the event, at enrolment into the WTC cohort. The index does not include quantitative data on specific airborne substances but should represent the inhaled burden of pollutants from the WTC event.

Among the strongest of the exposure assessments was the study of both incumbent (previously employed) and newly hired firefighters in Tucson, Arizona, USA (by Jeong et al., 2018; Zhou et al., 2019; Jung et al., 2021b; Goodrich et al., 2022). The newly-hired firefighters were followed for 2 years, and data were gathered from department records documenting for each participant the cumulative fire-hours, fire-runs (number of fires to which a participant responds), and days since the last fire call. These data were also stratified by type of fire, to attempt to distinguish different broad types of fire smoke.

(c) Induces oxidative stress

One set of studies adopted a pre/post cross-shift design, with measurement of exposure during a single work shift. Several of these came from one group (Adetona et al., 2013b, 2019; Wu et al., 2020a, b) and used data on US wildland firefighters at prescribed burns. Personal exposure to $PM_{2.5}$ was measured in the breathing zone, and exposure was also characterized by type of activity during the prescribed burn and/or by urinary markers of exposure. The exposure assessment for these was of good quality but was limited by the inclusion of only exposures during a single shift. Studies of municipal firefighters, using call-out to fire activities rather than prescribed burns, have been carried out in Denmark (Andersen et al., 2018a) and Canada (Keir et al., 2017) using a similar design but over three to five shifts. Again, particulate exposures were measured and urinary biomarkers of exposure (1-hydroxypyrene) were analysed, together with skin-wipe samples.

A second set of studies used a cross-sectional design in which exposure information was limited to being currently employed as a firefighter (Al-Malki et al., 2008; Gündüzöz, et al., 2018), or using self-reported duration of employment (Abreu et al., 2017). Such studies included wildland firefighters (Abreu et al., 2017) and firefighters carrying out more general duties (Al-Malki et al., 2008), using comparison data from non-exposed volunteers (Oliveira et al., 2020b). Gaughan et al. (2014a) studied firefighters cross-sectionally but used individual urinary levoglucosan concentrations as a measure of smoke exposure. Another group of studies used a pre/post trial design to assess the effect on oxidative stress markers of PPE-wearing (Park et al., 2016), heat exposure (McAllister et al., 2018), training (Gurney et al., 2021), physical fitness test (Macedo et al., 2015), or woodsmoke exposure among apparent non-firefighter subjects (Ferguson et al., 2016; Peters et al., 2018).

(d) Induces chronic inflammation

Pre/post trials were used for the assessment of physical and psychological stress (Huang et al., 2010a; Webb et al., 2011), heat exposure (Wright-Beatty et al., 2014; Walker et al., 2015, 2017; Wolkow et al., 2017; Kim et al., 2018; Watkins et al., 2019a, b), and sleep restriction (Wolkow et al., 2015a, b, 2016a, b), as well as interventions on time-restricted feeding (McAllister et al., 2020, 2021). [The settings were controlled, so the impact of potential confounding was limited in these studies.]

Another common design for studies evaluating chronic inflammation used measurements of an outcome pre- and post-exposure, but these were observational studies, not trials, and the investigators could not control or manipulate the exposures occurring between the two time points. This design was used in eight studies (Burgess et al., 2001, 2002; Swiston et al., 2008; Hejl et al., 2013; Main et al., 2013, 2020; Andersen et al., 2018a; Wu et al., 2020a).

There were several studies carried out during and after specific incidents: four studies on firefighters attending the WTC-site in New York after the collapse on 11 September 2001 (Fireman et al., 2004; Cho et al., 2014; Tsukiji et al., 2014; Loupasakis et al., 2015; Aldrich et al., 2016; Hena et al., 2018; Singh et al., 2018; Cleven et al., 2019; Lam et al., 2020; Goldfarb et al., 2021; Weiden et al., 2021); firefighters attending the "Black Saturday" natural disaster involving bush fires that destroyed more than 450 000 hectares in south-eastern Australia in 2009 (Main et al., 2020); and a study after the Fort McMurray fire that destroyed almost 600 000 hectares in Alberta, Canada, in 2016 (Cherry et al., 2021b; Adu et al., 2022). For the WTC studies, either presence or time of arrival was used as the measure of exposure. No further information was collected, and exposures may have varied widely. In the Black Saturday event, no further information on individual exposure was collected. In the Canadian study, environmental monitoring data were considered for $PM_{2.5}$, although these were only informative at the group level and did not allow for differentiation between workers. [For all these specific incident studies, events before and after the incident that were unmeasured may also have been of influence.]

The exposure assessment in many cross-sectional studies was simply based on being a firefighter (Orris et al., 1986; Kern et al., 1993; Bergström et al., 1997; Almeida et al., 2007; Josyula et al., 2007; Yucesoy et al., 2008; Gaughan et al., 2014b; Gianniou et al., 2016, 2018). [These studies were of limited use regarding exposure assessment, because no information was included on specific firefighting activities, or the timing and intensity of exposures experienced.] Other cross-sectional studies were based on self-reported exposures to heat (Watkins et al., 2021) and fire smoke (Greven et al., 2011, 2012). Self-reported exposures are prone to bias and misclassification, particularly with regard to identifying frequency (e.g. number of fires fought). [Among the strongest assessments of exposure were those that employed quantitative (individual) exposure measurements (Burgess et al., 2002; Swiston et al., 2008; Hejl et al., 2013; Ferguson et al., 2016; Adetona et al., 2017b; Andersen et al., 2018a, b).]

(e) Is immunosuppressive

Pre/post approaches were used to assess the immunosuppressive effects of engagement in firefighting (Smith et al., 2004, 2005) and exposure to specific firefighting-associated hazards, including heat (Walker et al., 2015, 2017), physical stress (Santos et al., 2020), and physical stress in combination with psychological stress (Huang et al., 2010a, b). The impact of potential confounding firefighting and non-firefighting exposures on the results of these studies is limited, because conditions were well-controlled in trials. The exposure–response relationships were assessed only on the basis of the presence or absence of the hazard(s). Watt et al. (2016) had high quality data on heat exposure obtained by collecting the rectal temperatures of the study participants, but these data were not used in quantitative exposure–response analyses of the study outcomes.

Potential confounding by smoking or other non-workplace exposures was not assessed in other cross-sectional studies (Bodienkova & Ivanskaia, 2003; Kudaeva & Budarina, 2005, 2007; Borges et al., 2021; Ricaud et al., 2021) or in the repeated measurement design (Montague et al., 2021). Finally, the methods used to collect exposure information and/or the metric used for quantifying exposure were not specified in three cross-sectional studies (Bodienkova & Ivanskaia, 2003; Kudaeva & Budarina, 2005, 2007).

(f) Modulates receptor-mediated effects

Exposure was limited to firefighting activity in an observational pre/post comparison study conducted by Christison et al. (2021). Qualitative categorization was used to assess the impact of job rotation (Kazemi et al., 2018; Lim et al., 2020),

a semiquantitative questionnaire-based index score was used to assess repeated exposures to psychological stress, and biological monitoring was used to assess the effects of exposure to components of smoke in other observational studies (Beitel et al., 2020; Chernyak & Grassman, 2020). The potential impact of confounders was reduced in these studies by the employment of the pre/post comparison or repeated measurement study design across work-shift periods or by controlling for confounders in the analyses. However, residual confounding from non-firefighting exposures (e.g. diet) in the intervening period (17–18 years) between the exposure of interest and the measurement of effects was likely in the study that assessed the impact of exposures to PCDD/Fs and PCBs at a cable factory fire (Chernyak & Grassman, 2020). Moreover, information about the relationship between serum concentrations of the contaminants and exposures of the firefighters to smoke during the event of interest was apparently not obtained. The impact of physical stress alone (Diaz-Castro et al., 2020a) and physical stress in combination with psychological stress (Webb et al., 2011) was investigated in a randomized control trial of nutritional supplements and a pre/post trial, respectively, with exposures to equal quantities of the hazard(s) of interest under controlled conditions. Although the exposure–response relationships were assessed only on the basis of changes across specified exposures to the hazard(s) in these cases, confounding was minimized, as the participants served as their own controls.

(g) Causes immortalization, and alters cell proliferation, cell death, or nutrient supply

Quantitative assessment of exposure to constituents of smoke, including PFAS and PBDEs by biomonitoring was conducted in a cross-sectional study with appropriate control for potential confounders (Clarity et al., 2021). The biomarkers were considered appropriate for assessing the relationship between firefighting-related exposures and telomere length in the study because of the relatively long half-lives of the compounds of interest and the minimum career length of 5 years for the firefighters in the study (Clarity et al., 2021). Occupation and organophosphate flame-retardant concentration in spot urine samples were used to assess exposure in another cross-sectional study but without control for potential non-workplace exposures to products containing these chemicals (Trowbridge et al., 2022). No firefighting exposures were considered in another cross-sectional study that was available (Ranadive et al., 2021). A combination of equal exposures to physical and psychological stress under controlled conditions was investigated in a randomized control trial of a nutritional supplement (Diaz-Castro et al., 2020b). Confounding in this study was minimized since the participants served as their own controls.

References

Abrard S, Bertrand M, De Valence T, Schaupp T (2019). French firefighters exposure to benzo[*a*]pyrene after simulated structure fires. *Int J Hyg Environ Health*. 222(1):84–8. doi:10.1016/j.ijheh.2018.08.010 PMID:30172597

Abreu A, Costa C, Pinho E Silva S, Morais S, do Carmo Pereira M, Fernandes A, et al. (2017). Wood smoke exposure of Portuguese wildland firefighters: DNA and oxidative damage evaluation. *J Toxicol Environ Health A*. 80(13–15):596–604. doi:10.1080/15287394.2017.1286896 PMID:28524757

ACT Government (2020). Act Public Sector Act Fire and Rescue Enterprise Agreement 2020–2024. Canberra (ACT), Australia: Government of the Australian Capital Territory. Available from: https://www.cmtedd.act.gov.au/__data/assets/pdf_file/0006/1552524/ACT-Fire-and-Rescue-Enterprise-Agreement-2020-2024.pdf, accessed March 2023.

Adetona AM, Adetona O, Gogal RM Jr, Diaz-Sanchez D, Rathbun SL, Naeher LP (2017b). Impact of work task-related acute occupational smoke exposures on select proinflammatory immune parameters in wildland firefighters. *J Occup Environ Med*. 59(7):679–90. doi:10.1097/JOM.0000000000001053 PMID:28692002

Adetona AM, Martin WK, Warren SH, Hanley NM, Adetona O, Zhang JJ, et al. (2019). Urinary mutagenicity and other biomarkers of occupational smoke exposure of wildland firefighters and oxidative stress. *Inhal Toxicol*. 31(2):73–87. doi:10.1080/08958378.2019.1600079 PMID:30985217

Adetona O, Dunn K, Hall DB, Achtemeier G, Stock A, Naeher LP (2011). Personal $PM_{2.5}$ exposure among wildland firefighters working at prescribed forest burns in southeastern United States. *J Occup Environ Hyg*. 8(8):503–11. doi:10.1080/15459624.2011.595257 PMID:21762011

Adetona O, Reinhardt TE, Domitrovich J, Broyles G, Adetona AM, Kleinman MT, et al. (2016). Review of the health effects of wildland fire smoke on wildland firefighters and the public. *Inhal Toxicol*. 28(3):95–139. doi:10.3109/08958378.2016.1145771 PMID:26915822

Adetona O, Simpson CD, Li Z, Sjodin A, Calafat AM, Naeher LP (2017a). Hydroxylated polycyclic aromatic hydrocarbons as biomarkers of exposure to wood smoke in wildland firefighters. *J Expo Sci Environ Epidemiol*. 27(1):78–83. doi:10.1038/jes.2015.75 PMID:26555473

Adetona O, Simpson CD, Onstad G, Naeher LP (2013a). Exposure of wildland firefighters to carbon monoxide, fine particles, and levoglucosan. *Ann Occup Hyg*. 57(8):979–91. PMID:23813888

Adetona O, Zhang JJ, Hall DB, Wang JS, Vena JE, Naeher LP (2013b). Occupational exposure to woodsmoke and oxidative stress in wildland firefighters. *Sci Total Environ*. 449:269–75. doi:10.1016/j.scitotenv.2013.01.075 PMID:23434577

Adu MK, Eboreime E, Shalaby R, Sapara A, Agyapong B, Obuobi-Donkor G, et al. (2022). Five years after the Fort McMurray wildfire: prevalence and correlates of low resilience. *Behav Sci (Basel)*. 12(4):96. doi:10.3390/bs12040096 PMID:35447668

AFAC (2019a). Managing bushfire smoke exposure. Version 1.0. AFAC Publication No. 3062. East Melbourne, Australia: Australasian Fire and Emergency Service Authorities Council Limited. Available from: https://www.afac.com.au/auxiliary/article/managing-bushfire-smoke-exposure, accessed July 2022.

AFAC (2019b). Selection, use, care and maintenance of personal protective equipment (PPE). Guideline. Version 2.0. 30 April 2019. Report No. FES.004.001.0011_002. East Melbourne (VIC), Australia: Australasian Fire and Emergency Service Authorities Council Limited. Available from: https://naturaldisaster.royalcommission.gov.au/system/files/2020-07/FES.004.001.0011.pdf.

AFAC (2021). Seasonal bushfire outlook. Summer 2021. East Melbourne, Australia: Australasian Fire and Emergency Service Authorities Council Limited. Available from: https://www.afac.com.au/docs/default-source/bushfire-seasonal-outlook/seasonaloutlook_summer_2021_v1-0.pdf.

Ahn YS, Jeong KS (2015). Mortality due to malignant and non-malignant diseases in Korean professional emergency responders. *PLoS One*. 10(3):e0120305. doi:10.1371/journal.pone.0120305 PMID:25756281

Ahn YS, Jeong KS, Kim KS (2012). Cancer morbidity of professional emergency responders in Korea. *Am J Ind Med*. 55(9):768–78. doi:10.1002/ajim.22068 PMID:22628010

Ahrens M, Evarts B (2021). Fire loss in the United States during 2020. National Fire Protection Association. Available from: https://www.maine.gov/dps/fmo/sites/maine.gov.dps.fmo/files/inline-files/Fire%20Loss%20in%20the%20US%20during%202020.pdf, accessed November 2022.

Akhtar US, Keir JL, Matschke D, White P, Blais JM (2016). Occupational exposure to polycyclic aromatic hydrocarbons (PAHs) by firefighters. *Toxicol Lett*. 259:S211. doi:10.1016/j.toxlet.2016.07.505

Al-Malki AL (2009). Serum heavy metals and hemoglobin related compounds in Saudi Arabia firefighters. *J Occup Med Toxicol*. 4(1):18. doi:10.1186/1745-6673-4-18 PMID:19583874

Al-Malki AL, Rezq AM, Al-Saedy MH (2008). Effect of fire smoke on some biochemical parameters in firefighters of Saudi Arabia. *J Occup Med Toxicol*. 3(1):33. doi:10.1186/1745-6673-3-33 PMID:19077241

Aldrich TK, Weakley J, Dhar S, Hall CB, Crosse T, Banauch GI, et al. (2016). Bronchial reactivity and lung function after World Trade Center exposure. *Chest*. 150(6):1333–40. doi:10.1016/j.chest.2016.07.005 PMID:27445092

Alexander BM, Baxter CS (2016). Flame-retardant contamination of firefighter personal protective clothing - a potential health risk for firefighters. *J Occup Environ Hyg*. 13(9):D148–55. doi:10.1080/15459624.2016.1183016 PMID:27171467

Alhamdow A, Tinnerberg H, Lindh C, Albin M, Broberg K (2019). Cancer-related proteins in serum are altered in workers occupationally exposed to polycyclic aromatic hydrocarbons: a cross-sectional study. *Carcinogenesis*. 40(6):771–81. doi:10.1093/carcin/bgz022 PMID:30753342

Alharbi BH, Pasha MJ, Al-Shamsi MAS (2021). Firefighter exposures to organic and inorganic gas emissions in emergency residential and industrial fires. *Sci Total Environ*. 770:145332. doi:10.1016/j.scitotenv.2021.145332 PMID:33515879

Allcorn M, Bluteau T, Corfield J, Day G, Cornelsen M, Holmes NJC, et al. (2018). Fluorine-free firefighting foams (3F) viable alternatives to fluorinated aqueous film-forming foams (AFFF). Independent expert panel convened by IPEN. Stockholm Convention POPRC-14. Rome, Italy, 17–21 September 2018. Available from: https://ipen.org/sites/default/files/documents/IPEN_F3_Position_Paper_POPRC-14_12September2018d.pdf, accessed March 2023.

Allonneau A, Mercier S, Maurin O, Robardet F, Menguy-Fleuriot A, Luu SC, et al. (2021). Lead contamination among Paris Fire Brigade firefighters who fought the Notre Dame Cathedral fire in Paris. *Int J Hyg Environ Health*. 233:113707. doi:10.1016/j.ijheh.2021.113707 PMID:33631659

Allonneau A, Mercier S, Menguy-Fleuriot A, Luu SC, Louyot C, Nicolas A, et al. (2019). Exposure to fire smoke in firefighters suppressing controlled structure fires. *Arch Mal Prof Environ*. 80:257–72. doi:10.1016/j.admp.2019.03.008

Almeida AG, Duarte R, Mieiro L, Paiva AC, Rodrigues AM, Almeida MH, et al. (2007). [Pulmonary function in Portuguese firefighters]. *Rev Port Pneumol*. 13(3):349–64. [Portuguese] doi:10.1016/S0873-2159(15)30354-8 PMID:17632674

Amadeo B, Marchand JL, Moisan F, Donnadieu S, Gaëlle C, Simone MP, et al. (2015). French firefighter mortality: analysis over a 30-year period. *Am J Ind Med*. 58(4):437–43. doi:10.1002/ajim.22434 PMID:25708859

American Public Health Association (2001). Public health role of the National Fire Protection Association in setting codes and standards for the built environment. *Am J Public Health*. 91(3):503–4. doi:10.2105/AJPH.91.3.503 PMID:11236442

Andersen MHG, Saber AT, Clausen PA, Pedersen JE, Løhr M, Kermanizadeh A, et al. (2018a). Association between polycyclic aromatic hydrocarbon exposure and peripheral blood mononuclear cell DNA damage in human volunteers during fire extinction exercises. *Mutagenesis*. 33(1):105–15. doi:10.1093/mutage/gex021 PMID:29045708

Andersen MHG, Saber AT, Pedersen JE, Pedersen PB, Clausen PA, Løhr M, et al. (2018b). Assessment of polycyclic aromatic hydrocarbon exposure, lung function, systemic inflammation, and genotoxicity in peripheral blood mononuclear cells from firefighters before and after a work shift. *Environ Mol Mutagen*. 59(6):539–48. doi:10.1002/em.22193 PMID:29761929

Andersen MHG, Saber AT, Pedersen PB, Loft S, Hansen ÅM, Koponen IK, et al. (2017). Cardiovascular health effects following exposure of human volunteers during fire extinction exercises. *Environ Health*. 16(1):96. doi:10.1186/s12940-017-0303-8 PMID:28877717

Andrews DQ, Hayes J, Stoiber T, Brewer B, Campbell C, Naidenko OV (2021). Identification of point source dischargers of per- and polyfluoroalkyl substances in the United States. *AWWA Water Sci*. 3(5):e1252. doi:10.1002/aws2.1252

Angerer J, Bird MG, Burke TA, Doerrer NG, Needham L, Robison SH, et al. (2006). Strategic biomonitoring initiatives: moving the science forward. *Toxicol Sci*. 93(1):3–10. doi:10.1093/toxsci/kfl042 PMID:16785253

Angerer J, Ewers U, Wilhelm M (2007). Human biomonitoring: state of the art. *Int J Hyg Environ Health*. 210(3-4):201–28. doi:10.1016/j.ijheh.2007.01.024 PMID:17376741

Angerer J, Gündel J, Knecht U, Korn M (1994). Benzene and alkylbenzenes (BTX aromatics). In: Angerer J, Schaller KH, Greim H, editors. Analyses of hazardous compounds in biological materials. Volume 4. Weinheim, Germany: Deutsche Forschungsgemeinschaft, Wiley-VCH Weinheim.

Angerer J, Rauscher D, Will W, Blaszkewicz M (1997). *t,t*-Muconic acid. In: Angerer J, Schaller KH, Greim H, editors. Analyses of hazardous compounds in biological materials. Weinheim, Germany: Wiley-VCH.

Anthony TR, Joggerst P, James L, Burgess JL, Leonard SS, Shogren ES (2007). Method development study for APR cartridge evaluation in fire overhaul exposures. *Ann Occup Hyg*. 51(8):703–16. PMID:17989124

Antoniv VF, Popaduyk VI, Antoniv TV (2017). [Ionizing radiation and laryngeal cancer]. *Vestn Otorinolaringol*. 82(2):19–23. [Russian]doi:10.17116/otorino201782219-23 PMID:28514358

Armstrong D, Shakespeare-Finch J, Shochet IJAJP (2014). Predicting post-traumatic growth and post-traumatic stress in firefighters. *Aust J Psychol*. 66(1):38–46. doi:10.1111/ajpy.12032

Arnold SM, Angerer J, Boogaard PJ, Hughes MF, O'Lone RB, Robison SH, et al. (2013). The use of biomonitoring data in exposure and human health risk assessment: benzene case study. *Crit Rev Toxicol*. 43(2):119–53. doi:10.3109/10408444.2012.756455 PMID:23346981

Aronson KJ, Tomlinson GA, Smith L (1994). Mortality among fire fighters in metropolitan Toronto. *Am J Ind Med*. 26(1):89–101. doi:10.1002/ajim.4700260108 PMID:8074127

Atrooz F, Salim S (2020). Sleep deprivation, oxidative stress and inflammation. *Adv Protein Chem Struct Biol*. 119:309–36. doi:10.1016/bs.apcsb.2019.03.001 PMID:31997771

ATSDR (2002). Final technical report of the public health investigation to assess potential exposures to airborne and settled surface dust in residential areas of lower Manhattan. Atlanta (GA), USA: Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services, New York Department of Health and Mental Hygiene and Agency for Toxic Substances and Disease Registry. Available from: https://www.atsdr.cdc.gov/asbestos/asbestos/types_of_exposure/_downloads/final-report-lowermanhattan-02.pdf, accessed 26 August 2022.

Aufderheide TP, White SM, Brady WJ, Stueven HA (1993). Inhalational and percutaneous methanol toxicity in two firefighters. *Ann Emerg Med*. 22(12):1916–8. doi:10.1016/S0196-0644(05)80423-8 PMID:8239116

Austin C (2008). Wildland firefighter health risks and respiratory protection. IRSST Report R-572. Montreal, Canada: Institut de recherche Robert-Sauvé en santé et en sécurité du travail. Available from: https://www.irsst.qc.ca/en/publications-tools/publication/i/100404/n/wildland-firefighter-health-risks-and-respiratory-protection-r-572, accessed 30 March 2022.

Austin CC, Dussault G, Ecobichon DJ (2001c). Municipal firefighter exposure groups, time spent at fires and use of self-contained-breathing-apparatus. *Am J Ind Med*. 40(6):683–92. doi:10.1002/ajim.10023 PMID:11757045

Austin CC, Ecobichon DJ, Dussault G, Tirado C (1997). Carbon monoxide and water vapor contamination of compressed breathing air for firefighters and divers. *J Toxicol Environ Health*. 52(5):403–23. doi:10.1080/00984109708984073 PMID:9388533

Austin CC, Wang D, Ecobichon DJ, Dussault G (2001a). Characterization of volatile organic compounds in smoke at municipal structural fires. *J Toxicol Environ Health A*. 63(6):437–58. doi:10.1080/152873901300343470 PMID:11482799

Austin CC, Wang D, Ecobichon DJ, Dussault G (2001b). Characterization of volatile organic compounds in smoke at experimental fires. *J Toxicol Environ Health A*. 63(3):191–206. doi:10.1080/15287390151101547 PMID:11405415

Australian Government Productivity Commission (2022). Emergency services for fire and other events. Report on Government Services 2022. Part D. Melbourne, Australia: Australian Government Productivity Commission. Available from: https://www.pc.gov.au/research/ongoing/report-on-government-services/2022/emergency-management, accessed June 2022.

Backe WJ, Day TC, Field JA (2013). Zwitterionic, cationic, and anionic fluorinated chemicals in aqueous film forming foam formulations and groundwater from US military bases by nonaqueous large-volume injection HPLC-MS/MS. *Environ. Sci. Technol.* 47(10):5226–5234. doi:10.1021/es3034999 PMID:23590254

Bader M, Bäcker S, Jäger T, Webendörfer S, Van Bortel G, Van Mieghem F, et al. (2021). Preparedness as a key factor for human biomonitoring programs after chemical incidents. *J Expo Sci Environ Epidemiol*. 31(5):867–75. doi:10.1038/s41370-021-00320-w PMID:33774650

Bader M, Van Weyenbergh T, Verwerft E, Van Pul J, Lang S, Oberlinner C (2014). Human biomonitoring after chemical incidents and during short-term maintenance work as a tool for exposure analysis and assessment. *Toxicol Lett*. 231(3):328–36. doi:10.1016/j.toxlet.2014.09.015 PMID:25290578

Baduel C, Paxman CJ, Mueller JF (2015). Perfluoroalkyl substances in a firefighting training ground (FTG), distribution and potential future release. *J Hazard Mater*. 296:46–53. doi:10.1016/j.jhazmat.2015.03.007 PMID:25966923

Bae MJ, Song YM, Shin JY, Choi BY, Keum JH, Lee EA (2017). The association between shift work and health behavior: findings from the Korean National Health and Nutrition Examination Survey. *Korean J Fam Med*. 38(2):86–92. doi:10.4082/kjfm.2017.38.2.86 PMID:28360984

Baetjer AM (1969). Effects of dehydration and environmental temperature on antimony toxicity. *Arch Environ Health*. 19(6):784–92. doi:10.1080/00039896.1969.10666931 PMID:5351679

Baetjer AM, Joardar SN, McQUARY WA (1960). Effect of environmental temperature and humidity on lead poisoning in animals. *Arch Environ Health*. 1(6):463–77. doi:10.1080/00039896.1960.10662721 PMID:13685821

Baikovitz J, Caban-Martinez A, Lee D, Koru-Sengul T, Fent K, Santiago K, et al. (2019). Estimating predictors and types of second jobs among Florida firefighters: evidence from the Sylvester Firefighter Cancer Initiative. APHA Annual Meeting and Expo, Philadelphia, 2–6 November 2019. Washington (DC), USA: American Public Health Association. Available from: https://apha.confex.com/apha/2019/meetingapp.cgi/Paper/444729, accessed November 2022.

Bakali U, Baum JLR, Killawala C, Kobetz EN, Solle NS, Deo SK, et al. (2021). Mapping carcinogen exposure across urban fire incident response arenas using passive silicone-based samplers. *Ecotoxicol Environ Saf.* 228:112929. doi:10.1016/j.ecoenv.2021.112929 PMID:34768049

Baker MG, Peckham TK, Seixas NS (2020). Estimating the burden of United States workers exposed to infection or disease: a key factor in containing risk of COVID-19 infection. *PLoS One*. 15(4):e0232452. doi:10.1371/journal.pone.0232452 PMID:32343747

Banauch GI, Alleyne D, Sanchez R, Olender K, Cohen HW, Weiden M, et al. (2003). Persistent hyperreactivity and reactive airway dysfunction in firefighters at the World Trade Center. *Am J Respir Crit Care Med*. 168(1):54–62. doi:10.1164/rccm.200211-1329OC PMID:12615613

Banks APW, Engelsman M, He C, Wang X, Mueller JF (2020). The occurrence of PAHs and flame-retardants in air and dust from Australian fire stations. *J Occup Environ Hyg*. 17(2–3):73–84. doi:10.1080/15459624.2019.1699246 PMID:31910147

Banks APW, Thai P, Engelsman M, Wang X, Osorio AF, Mueller JF (2021a). Characterising the exposure of Australian firefighters to polycyclic aromatic hydrocarbons generated in simulated compartment fires. *Int J Hyg Environ Health*. 231:113637. doi:10.1016/j.ijheh.2020.113637 PMID:33080523

Banks APW, Wang X, Engelsman M, He C, Osorio AF, Mueller JF (2021c). Assessing decontamination and laundering processes for the removal of polycyclic aromatic hydrocarbons and flame retardants from firefighting uniforms. *Environ Res*. 194:110616. doi:10.1016/j.envres.2020.110616 PMID:33321140

Banks APW, Wang X, He C, Gallen M, Thomas KV, Mueller JF (2021b). Off-gassing of semi-volatile organic compounds from fire-fighters' uniforms in private vehicles-a pilot study. *Int J Environ Res Public Health*. 18(6):3030. doi:10.3390/ijerph18063030 PMID:33809422

Banzhaf S, Filipovic M, Lewis J, Sparrenbom CJ, Barthel R (2017). A review of contamination of surface-, ground-, and drinking water in Sweden by perfluoroalkyl and polyfluoroalkyl substances (PFASs). *Ambio*. 46(3):335–46. doi:10.1007/s13280-016-0848-8 PMID:27844420

Barbauskas V (1983). Upholstered furniture heat release rates: measurements and estimation. *J Fire Sci*. 1(1):9–32. doi:10.1177/073490418300100103

Baris D, Garrity TJ, Telles JL, Heineman EF, Olshan A, Zahm SH (2001). Cohort mortality study of Philadelphia firefighters. *Am J Ind Med*. 39(5):463–76. doi:10.1002/ajim.1040 PMID:11333408

Barnard RJ, Weber JS (1979). Carbon monoxide: a hazard to fire fighters. *Arch Environ Health*. 34(4):255–7. doi:10.1080/00039896.1979.10667410 PMID:475470

Barni PE, Rego ACM, Silva FCF, Lopes RAS, Xaud HAM, Xaud MR, et al. (2021). Logging Amazon forest increased the severity and spread of fires during the 2015–2016 El Niño. *For Ecol Manage*. 500:119652. doi:10.1016/j.foreco.2021.119652

Bates MN, Fawcett J, Garrett N, Arnold R, Pearce N, Woodward A (2001). Is testicular cancer an occupational disease of fire fighters? *Am J Ind Med*. 40(3):263–70. doi:10.1002/ajim.1097 PMID:11598972

Bates MN, Lane L (1995). Testicular cancer in fire fighters: a cluster investigation. *N Z Med J*. 108(1006):334–7. PMID:7566760

Baum JLR, Bakali U, Killawala C, Santiago KM, Dikici E, Kobetz EN, et al. (2020). Evaluation of silicone-based wristbands as passive sampling systems using PAHs as an exposure proxy for carcinogen monitoring in firefighters: evidence from the firefighter cancer initiative. *Ecotoxicol Environ Saf*. 205:111100. doi:10.1016/j.ecoenv.2020.111100 PMID:32911453

Baxter CS, Hoffman JD, Knipp MJ, Reponen T, Haynes EN (2014). Exposure of firefighters to particulates and polycyclic aromatic hydrocarbons. *J Occup Environ Hyg*. 11(7):D85–91. doi:10.1080/15459624.2014.890286 PMID:24512044

Baxter CS, Ross CS, Fabian T, Borgerson JL, Shawon J, Gandhi PD, et al. (2010). Ultrafine particle exposure during fire suppression–is it an important contributory factor for coronary heart disease in firefighters? *J Occup Environ Med*. 52(8):791–6. doi:10.1097/JOM.0b013e3181ed2c6e PMID:20657302

Bazyka DA, Fedirko PA, Vasylenko VV, Kolosynska OO, Yaroshenko ZS, Kuriata MS, et al. (2020). Results of WBC-monitoring of firefighters participating in response to Chornobyl forest fires in April-May 2020. *Probl Radiac Med Radiobiol*. 25:177–87. doi:10.33145/2304-8336-2020-25-177-187 PMID:33361834

Beaton RD, Murphy SA (1993). Sources of occupational stress among firefighter/EMTs and firefighter/paramedics and correlations with job-related outcomes. *Prehosp Disaster Med*. 8(2):140–50. doi:10.1017/S1049023X00040218 PMID:10155458

Beitel SC, Flahr LM, Hoppe-Jones C, Burgess JL, Littau SR, Gulotta J, et al. (2020). Assessment of the toxicity of firefighter exposures using the PAH CALUX bioassay. *Environ Int*. 135:105207. doi:10.1016/j.envint.2019.105207 PMID:31812113

Belcher CM, Brown I, Clay GD, Doerr SH, Elliott A, Gazzard R, et al. (2021). UK wildfires and their climate challenges: expert-led report prepared for the third climate change risk assessment. Exeter, UK: Global Sysytems Institute, University of Exeter. Available from: https://www.ukclimaterisk.org/wp-content/uploads/2021/06/UK-Wildfires-and-their-Climate-Challenges.pdf, accessed March 2023.

Belfiglio G (2022). How to become a fire investigator. Resource center. Interfire online. Available from: https://www.interfire.org/features/become_fire_investigator.asp, accessed November 2022.

Belval EJ, Wei Y, Calkin DE, Stonesifer CS, Thompson MP, Tipton JRJI (2017). Studying interregional wildland fire engine assignments for large fire suppression. *Int J Wildland Fire*. 26(7):642–53. doi:10.1071/WF16162

Belyi D, Nastina O, Sydorenko G, Kursina N, Bazyka O, Gabulavichene Z, et al. (2019). The development of hypertension disease and ischemic heart disease in emergency workers of the Chornobyl accident and influence on it conditions of being under radiation. *Probl Radiac Med Radiobiol*. 24:350–66. doi:10.33145/2304-8336-2019-24-350-366 PMID:31841479

Bendix S (1979). Firefighter exposure to environmental carcinogens. *J Combust Toxicol*. 6:127–35.

Bergström CE, Eklund A, Sköld M, Tornling G (1997). Bronchoalveolar lavage findings in firefighters. *Am J Ind Med*. 32(4):332–6. doi:10.1002/(SICI)1097-0274(199710)32:4<332::AID-AJIM2>3.0.CO;2-W PMID:9258385

Bessems JG, Geraets L (2013). Proper knowledge on toxicokinetics improves human hazard testing and subsequent health risk characterisation. A case study approach. *Regul Toxicol Pharmacol*. 67(3):325–34. doi:10.1016/j.yrtph.2013.08.010 PMID:24051162

Bidulescu A, Rose KM, Wolf SH, Rosamond WD (2007). Occupation recorded on certificates of death compared with self-report: the Atherosclerosis Risk in Communities (ARIC) Study. *BMC Public Health*. 7(1):229. doi:10.1186/1471-2458-7-229 PMID:17764567

Bigert C, Gustavsson P, Straif K, Taeger D, Pesch B, Kendzia B, et al. (2016). Lung cancer among firefighters: smoking-adjusted risk estimates in a pooled analysis of case-control studies. *J Occup Environ Med*.

58(11):1137–43. doi:10.1097/JOM.0000000000000878 PMID:27820764

Bigert C, Martinsen JI, Gustavsson P, Sparén P (2020). Cancer incidence among Swedish firefighters: an extended follow-up of the NOCCA study. *Int Arch Occup Environ Health*. 93(2):197–204. doi:10.1007/s00420-019-01472-x PMID:31463517

Billings J, Focht W (2016). Firefighter shift schedules affect sleep quality. *J Occup Environ Med*. 58(3):294–8. doi:10.1097/JOM.0000000000000624 PMID:26949880

Birch ME (2002). Occupational monitoring of particulate diesel exhaust by NIOSH Method 5040. *Appl Occup Environ Hyg*. 17(6):400–5. doi:10.1080/10473220290035390 PMID:12049428

Blocker K (2020). Aircraft rescue and fire fighting capabilities: are today's standards protecting passenger's futures? [MSc thesis] Scholarly Commons. Prescott (AZ), USA: Embry-Riddle Aeronautical University. Available from: https://commons.erau.edu/student-works/151/, accessed November 2022.

Blomqvist P McNamee M, Stec AA, Gylestam D, Karlsson D (2010). Characterisation of fire generated particles. Fire technology. SP Technical Research Institute of Sweden.

Blomqvist P, McNamee MS, Stec AA, Gylestam D, Karlsson D (2014). Detailed study of distribution patterns of PAHs and isocyanates under different fire conditions. *Fire Mater*. 38:125–44. doi:10.1002/fam.2173

Blomqvist P, Rosell L, Simonson M (2004a). Emissions from fires part I: fire retarded and non-fire retarded TV-sets. *Fire Technol*. 40(1):39–58. doi:10.1023/B:FIRE.0000003315.47815.cb

Blomqvist P, Rosell L, Simonson M (2004b). Emissions from fires part II: simulated room fires. *Fire Technol*. 40(1):59–73. doi:10.1023/B:FIRE.0000003316.63475.16

Boal WL, Hales T, Ross CS (2005). Blood-borne pathogens among firefighters and emergency medical technicians. *Prehosp Emerg Care*. 9(2):236–47. doi:10.1080/10903120590924915 PMID:16036853

Bodienkova GM, Ivanskaia TI (2003). [Nervous system pathology and disruption of immunoreactivity in firefighters]. *Gig Sanit*. (2):29–31. [Scientific Research Institute of Occupational Medicine and Human Ecology – the Angar Filial State Institute Scientific Centre of Medical Ecology, East Siberian Scientific Centre, Siberian division of the Russian Academy of Medical Sciences.] [Russian] PMID:12861686

Bøggild H, Knutsson A (1999). Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health*. 25(2):85–99. doi:10.5271/sjweh.410 PMID:10360463

Bolstad-Johnson DM, Burgess JL, Crutchfield CD, Storment S, Gerkin R, Wilson JR (2000). Characterization of firefighter exposures during fire overhaul. *AIHAJ*. 61(5):636–41. doi:10.1080/15298660008984572 PMID:11071414

Boniol M, Koechlin A, Boniol M, Valentini F, Chignol MC, Doré JF, et al. (2015). Occupational UV exposure in French outdoor workers. *J Occup Environ Med*. 57(3):315–20. doi:10.1097/JOM.0000000000000354 PMID:25742537

Bonnell EK, Huggins CE, Huggins CT, McCaffrey TA, Palermo C, Bonham MP (2017). Influences on dietary choices during day versus night shift in shift workers: a mixed methods study. *Nutrients*. 9(3):193. doi:10.3390/nu9030193 PMID:28245625

Booze TF, Reinhardt TE, Quiring SJ, Ottmar RD (2004). A screening-level assessment of the health risks of chronic smoke exposure for wildland firefighters. *J Occup Environ Hyg*. 1(5):296–305. doi:10.1080/15459620490442500 PMID:15238338

Borgerson JL, Fabian TZ, Gandhi PD (2011). Investigation of the gas effluents and smoke particulates generated during automobile passenger and engine compartment fires. 12th International Conference and Exhibition on Fire and Materials 2011, 31 January to 2 February 2011. San Francisco (CA), USA: Interscience Communications Ltd; pp. 147–158.

Borges LP, Nascimento LC, Heimfarth L, Souza DRV, Martins AF, de Rezende Neto JM, et al. (2021). Estimated SARS-CoV-2 infection and seroprevalence in firefighters from a northeastern Brazilian state: a cross-sectional study. *Int J Environ Res Public Health*. 18(15):8148. doi:10.3390/ijerph18158148 PMID:34360442

Bott RC, Kirk KM, Logan MB, Reid DA (2017). Diesel particulate matter and polycyclic aromatic hydrocarbons in fire stations. *Environ Sci Process Impacts*. 19(10):1320–6. doi:10.1039/C7EM00291B PMID:28861557

Bourlai T, Pryor RR, Suyama J, Reis SE, Hostler D (2012). Use of thermal imagery for estimation of core body temperature during precooling, exertion, and recovery in wildland firefighter protective clothing. *Prehosp Emerg Care*. 16(3):390–9. doi:10.3109/10903127.2012.670689 PMID:22510022

Bowler RG (1944). The determination of thiocyanate in blood serum. *Biochem J*. 38(5):385–8. doi:10.1042/bj0380385 PMID:16747819

Braithwaite GR (2001). Aviation rescue and firefighting in Australia is it protecting the customer? *J Air Transp Manage*. 7(2):111–8. doi:10.1016/S0969-6997(00)00037-5

Bralewska K, Rakowska J (2020). Concentrations of particulate matter and PM-bound polycyclic aromatic hydrocarbons released during combustion of various types of materials and possible toxicological potential of the emissions: the results of preliminary studies. *Int J Environ Res Public Health*. 17(9):E3202. doi:10.3390/ijerph17093202 PMID:32380661

Brandt-Rauf PW, Cosman B, Fallon LF Jr, Tarantini T, Idema C (1989). Health hazards of firefighters: acute pulmonary effects after toxic exposures. *Br J Ind Med*. 46(3):209–11. doi:10.1136/oem.46.3.209 PMID:2930733

Brandt-Rauf PW, Fallon LF Jr, Tarantini T, Idema C, Andrews L (1988). Health hazards of fire fighters: exposure assessment. *Br J Ind Med*. 45(9):606–12. doi:10.1136/oem.45.9.606 PMID:3179235

Brase RA, Mullin EJ, Spink DC (2021). Legacy and emerging per- and polyfluoroalkyl substances: analytical techniques, environmental fate, and health effects. *Int J Mol Sci*. 22(3):995. doi:10.3390/ijms22030995 PMID:33498193

Bridgman S (2001). Community health risk assessment after a fire with asbestos containing fallout. *J Epidemiol Community Health*. 55(12):921–7. doi:10.1136/jech.55.12.921 PMID:11707487

British Standards Institution (2006). BS EN 469:2005: Protective clothing for firefighters. Performance requirements for protective clothing for firefighting. Available from: https://shop.bsigroup.com/ProductDetail/?pid=000000000030161108, accessed November 2022.

British Standards Institution (2019a). BS 8617:2019. Personal protective equipment for firefighters. Cleaning, maintenance and repair. Code of practice. Available from: https://www.en-standard.eu/bs-8617-2019-personal-protective-equipment-for-firefighters-cleaning-maintenance-and-repair-code-of-practice/, accessed November 2022.

British Standards Institution (2019b). BS 8617:2019 - Personal protective equipment for firefighters. Cleaning, maintenance and repair. Code of practice. Available from: https://shop.bsigroup.com/ProductDetail?pid=000000000030379245, accessed November 2022.

British Standards Institution (2020). BS EN 469:2020 - Protective clothing for firefighters. Performance requirements for protective clothing for firefighting activities. Available from: https://shop.bsigroup.com/ProductDetail/?pid=000000000030374480, accessed November 2022.

Brooks SJ, West MR, Domitrovich JW, Sol JA, Holubetz H, Partridge C, et al. (2021). Nutrient intake of wildland firefighters during arduous wildfire suppression: macronutrient and micronutrient consumption. *J Occup Environ Med*. 63(12):e949–56. doi:10.1097/JOM.0000000000002413 PMID:34654035

Brotherhood JR, Budd GM, Jeffery SE, Hendrie AL, Beasley FA, Costin BP, et al. (1990). Fire fighters' exposure to carbon monoxide during Australian bushfires. *Am Ind Hyg Assoc J*. 51(4):234–40. doi:10.1080/15298669091369583 PMID:2327333

Brown FR, Whitehead TP, Park JS, Metayer C, Petreas MX (2014). Levels of non-polybrominated diphenyl ether brominated flame retardants in residential house dust samples and fire station dust samples in California. *Environ Res*. 135:9–14. doi:10.1016/j.envres.2014.08.022 PMID:25261858

Brown J, Mulhern G, Joseph S (2002). Incident-related stressors, locus of control, coping, and psychological distress among firefighters in Northern Ireland. *J Trauma Stress*. 15(2):161–8. doi:10.1023/A:1014816309959 PMID:12013068

Broyles G, Butler CR, Kardous CA (2017). Noise exposure among federal wildland fire fighters. *J Acoust Soc Am*. 141(2):EL177–83. doi:10.1121/1.4976041 PMID:28253638

Broyles G, Kardous CA, Shaw PB, Krieg EF (2019). Noise exposures and perceptions of hearing conservation programs among wildland firefighters. *J Occup Environ Hyg*. 16(12):775–84. doi:10.1080/15459624.2019.1668001 PMID:31658434

Bühler F, Schmid P, Schlatter Ch (1988). Kinetics of PCB elimination in man. *Chemosphere*. 17(9):1717–26. doi:10.1016/0045-6535(88)90099-9

Burgess JL, Crutchfield CD (1995). Tucson fire fighter exposure to products of combustion: a risk assessment. *Appl Occup Environ Hyg*. 10(1):37–42. doi:10.1080/1047322X.1995.10387609

Burgess JL, Crutchfield CD (2015). Quantitative respirator fit tests of Tucson fire fighters and measurement of negative pressure excursions during exertion. *Appl Occup Environ Hyg*. 10(1):29–36. doi:10.1080/1047322X.1995.10387608

Burgess JL, Hoppe-Jones C, Griffin SC, Zhou JJ, Gulotta JJ, Wallentine DD, et al. (2020). Evaluation of interventions to reduce firefighter exposures. *J Occup Environ Med*. 62(4):279–88. doi:10.1097/JOM.0000000000001815 PMID:31977921

Burgess JL, Nanson CJ, Bolstad-Johnson DM, Gerkin R, Hysong TA, Lantz RC, et al. (2001). Adverse respiratory effects following overhaul in firefighters. *J Occup Environ Med*. 43(5):467–73. doi:10.1097/00043764-200105000-00007 PMID:11382182

Burgess JL, Nanson CJ, Hysong TA, Gerkin R, Witten ML, Lantz RC (2002). Rapid decline in sputum IL-10 concentration following occupational smoke exposure. *Inhal Toxicol*. 14(2):133–40. doi:10.1080/089583701753403953 PMID:12122576

Burgess JL, Witten ML, Nanson CJ, Hysong TA, Sherrill DL, Quan SF, et al. (2003). Serum pneumoproteins: a cross-sectional comparison of firefighters and police. *Am J Ind Med*. 44(3):246–53. doi:10.1002/ajim.10269 PMID:12929144

Burnett CA, Halperin WE, Lalich NR, Sestito JP (1994). Mortality among fire fighters: a 27 state survey. *Am J Ind Med*. 26(6):831–3. doi:10.1002/ajim.4700260612 PMID:7892834

Buser H-R (1985). Formation, occurrence and analysis of polychlorinated dibenzofurans, dioxins and related compounds. *Environ Health Perspect*. 60:259–67. doi:10.1289/ehp.8560259 PMID:3928352

Bushfire and Natural Hazards CRC (2019). Lessons and insights from significant bushfires in Australia and overseas. Informing the 2018 Queensland Bushfires Review. Prepared by Burrows N. East Melbourne, Australia: Bushfire and Natural Hazards CRC. Available from: https://www.igem.qld.gov.au/sites/default/files/2019-12/IGEM%20QBR%20BNHCRC%20-%20lessons%20and%20insights.pdf, accessed March 2023.

Bushnell PT, Colombi A, Caruso CC, Tak S (2010). Work schedules and health behavior outcomes at a large manufacturer. *Ind Health*. 48(4):395–405. doi:10.2486/indhealth.MSSW-03 PMID:20720331

Butler C, Marsh S, Domitrovich JW, Helmkamp J (2017). Wildland firefighter deaths in the United States: a comparison of existing surveillance systems. *J Occup Environ Hyg*. 14(4):258–70. doi:10.1080/15459624.2016.1250004 PMID:27754819

Caban-Martinez AJ, Bakali U, Urwin D, et al. (2021). Environmental/occupational exposures among first responders of the surfside building collapse. *Ann Epidemiol*. 67:107.

Caban-Martinez AJ, Kropa B, Niemczyk N, Moore KJ, Baum J, Solle NS, et al. (2018). The "warm zone" cases: environmental monitoring immediately outside the fire incident response arena by firefighters. *Saf Health Work*. 9(3):352–5. doi:10.1016/j.shaw.2017.12.003 PMID:30370169

Caban-Martinez AJ, Louzado-Feliciano P, Santiago KM, Baum J, Schaefer Solle N, Rivera G, et al. (2020). Objective measurement of carcinogens among Dominican Republic firefighters using silicone-based wristbands. *J Occup Environ Med*. 62(11):e611–5. doi:10.1097/JOM.0000000000002006 PMID:32826549

Cai K, Song Q, Yuan W, Ruan J, Duan H, Li Y, et al. (2020). Human exposure to PBDEs in e-waste areas: a review. *Environ Pollut*. 267:115634. doi:10.1016/j.envpol.2020.115634 PMID:33254638

Caliendo C, Ciambelli P, De Guglielmo ML, Meo MG, Russo P (2013). Simulation of fire scenarios due to different vehicle types with and without traffic in a bi-directional road tunnel. *Tunn Undergr Space Technol*. 37:22–36. doi:10.1016/j.tust.2013.03.004

Campbell DL, Noonan GP, Merinar TR, Stobbe JA (1994). Estimated workplace protection factors for positive-pressure self-contained breathing apparatus. *Am Ind Hyg Assoc J*. 55(4):322–9. doi:10.1080/15428119491018961 PMID:8209837

Canadian Centre for Occupational Health and Safety (2022). Occupations and workplaces: firefighter fact sheet. Hamilton (ON), Canada: Government of Canada, Canadian Centre for Occupational Health and Safety (CCOHS). Available from: https://www.ccohs.ca/oshanswers/occup_workplace/firefighter.html, accessed 13 June 2022.

Carballo-Leyenda B, Rodríguez-Marroyo JA, López-Satué J, Avila Ordás C, Pernía Cubillo R, Villa Vicente JG (2010). [Exposure to carbon monoxide in wildland firefighters during wildfires suppression]. *Rev Esp Salud Pública*. 84(6):799–807. [Spanish] doi:10.1590/S1135-57272010000600010 PMID:21327314

Carballo-Leyenda B, Villa JG, López-Satué J, Collado PS, Rodríguez-Marroyo JA (2018). Fractional contribution of wildland firefighters' personal protective equipment on physiological strain. *Front Physiol*. 9:1139. doi:10.3389/fphys.2018.01139 PMID:30154736

Carballo-Leyenda B, Villa JG, López-Satué J, Rodríguez-Marroyo JA (2017). Impact of different personal protective clothing on wildland firefighters' physiological strain. *Front Physiol*. 8:618. doi:10.3389/fphys.2017.00618 PMID:28894421

Cardoso Castro Rego FM, Moreno Rodríguez JM, Calzada VRV, Xanthopoulos G (2018). Forest fires: sparking firesmart policies in the EU. Available from: https://data.europa.eu/doi/10.2777/181450, accessed November 2022.

Carey RN, Glass DC, Peters S, Reid A, Benke G, Driscoll TR, et al. (2014). Occupational exposure to solar radiation in Australia: who is exposed and what protection do they use? *Aust N Z J Public Health*. 38(1):54–9. doi:10.1111/1753-6405.12174 PMID:24494947

Carrico CM, Prenni AJ, Kreidenweis SM, Levin EJT, McCluskey CS, DeMott PJ, et al. (2016). Rapidly evolving ultrafine and fine mode biomass smoke physical properties: comparing laboratory and field results. *J Geophys Res Atmos*. 121(10):5750–68. doi:10.1002/2015JD024389

Carvalho FP, Oliveira JM, Malta M (2014). Exposure to radionuclides in smoke from vegetation fires. *Sci Total Environ*. 472:421–4. doi:10.1016/j.scitotenv.2013.11.073 PMID:24295758

Caton SE, Hakes RSP, Gorham DJ, Zhou A, Gollner MJ (2017). Review of pathways for building fire spread in the wildland urban interface Part I: exposure conditions. *Fire Technol*. 53(2):429–73. doi:10.1007/s10694-016-0589-z

Caux C, O'Brien C, Viau C (2002). Determination of firefighter exposure to polycyclic aromatic hydrocarbons and benzene during fire fighting using measurement of biological indicators. *Appl Occup Environ Hyg*. 17(5):379–86. doi:10.1080/10473220252864987 PMID:12018402

CBS (2022). [Fire brigade; professionals and volunteers, rank level, education, region 2000–2019]. Statistics Netherlands. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/71482ned/table, accessed November 2022. [Dutch]

CDC (2000). Hepatitis C virus infection among firefighters, emergency medical technicians, and paramedics – selected locations, United States, 1991–2000. *MMWR Morb Mortal Wkly Rep*. 49(29):660–5. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4929a3.htm, accessed November 2022.

CDC (2012). NHANES 2011–2012 laboratory methods. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2011, accessed 23 November 2021.

CDC (2018). Fourth national report on human exposure to environmental chemicals, updated tables, March 2018, Volume Two. National Health and Nutrition Examination Survey. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: http://e.hormone.tulane.edu/PDFs/FourthReport_UpdatedTables_Volume2_Mar2018.pdf, accessed May 2022.

CDC (2022). NHANES questionnaires, datasets, and related documentation. National Health and Nutrition Examination Survey. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx, accessed 13 June 2022.

CEN (2020). CSN EN 469. Protective clothing for firefighters - performance requirements for protective clothing for firefighting activities. Brussels, Belgium: Comite européen de normalisation [European Committee for Standardization]. Available from: https://www.en-standard.eu/csn-en-469-protective-clothing-for-firefighters-performance-requirements-for-protective-clothing-for-firefighting-activities/, accessed November 2022.

CFRA (2012). Fire and Rescue Service. Operational guidance. Incidents involving hazardous materials. Norwich, England: Chief Fire and Rescue Adviser, Department for Communities and Local Government. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/15082/GRA_Hazmat_Manual_part_1.pdf, accessed March 2023.

Chang CM, Lee LC, Connor KM, Davidson JRT, Jeffries K, Lai TJ (2003). Posttraumatic distress and coping strategies among rescue workers after an earthquake. *J Nerv Ment Dis*. 191(6):391–8. doi:10.1097/01.NMD.0000071588.73571.3D PMID:12826921

Chang SK, Brownie C, Riviere JE (1994). Percutaneous absorption of topical parathion through porcine skin: in vitro studies on the effect of environmental perturbations. *J Vet Pharmacol Ther*. 17(6):434–9. doi:10.1111/j.1365-2885.1994.tb00274.x PMID:7707488

Chang SK, Riviere JE (1991). Percutaneous absorption of parathion in vitro in porcine skin: effects of dose, temperature, humidity, and perfusate composition on absorptive flux. *Fundam Appl Toxicol*. 17(3):494–504. doi:10.1016/0272-0590(91)90200-N PMID:1794653

Chernyak YI, Grassman JA (2020). Impact of AhRR (565C > G) polymorphism on dioxin dependent CYP1A2 induction. *Toxicol Lett*. 320:58–63. doi:10.1016/j.toxlet.2019.12.002 PMID:31805342

Chernyak YI, Shelepchikov AA, Brodsky ES, Grassman JA (2012). PCDD, PCDF, and PCB exposure in current and former firefighters from eastern Siberia. *Toxicol Lett*. 213(1):9–14. doi:10.1016/j.toxlet.2011.09.021 PMID:21979175

Cherry N, Aklilu YA, Beach J, Britz-McKibbin P, Elbourne R, Galarneau JM, et al. (2019). Urinary 1-hydroxypyrene and skin contamination in firefighters deployed to the Fort McMurray fire. *Ann Work Expo Health*. 63(4):448–58. doi:10.1093/annweh/wxz006 PMID:30753267

Cherry N, Barrie JR, Beach J, Galarneau JM, Mhonde T, Wong E (2021b). Respiratory outcomes of firefighter exposures in the Fort McMurray fire: a cohort study from Alberta Canada. *J Occup Environ Med*. 63(9):779–86. doi:10.1097/JOM.0000000000002286 PMID:34491965

Cherry N, Galarneau JM, Kinniburgh D, Quemerais B, Tiu S, Zhang X (2021a). Exposure and absorption of PAHs in wildland firefighters: a field study with pilot interventions. *Ann Work Expo Health*. 65(2):148–61. doi:10.1093/annweh/wxaa064 PMID:32572446

Cheung SS, Petersen SR, McLellan TM (2010). Physiological strain and countermeasures with firefighting. *Scand J Med Sci Sports*. 20(Suppl 3):103–16. doi:10.1111/j.1600-0838.2010.01215.x PMID:21029197

Cho SJ, Echevarria GC, Kwon S, Naveed B, Schenck EJ, Tsukiji J, et al. (2014). One airway: biomarkers of protection from upper and lower airway injury after World Trade Center exposure. *Respir Med*. 108(1):162–70. doi:10.1016/j.rmed.2013.11.002 PMID:24290899

Cho SY, Woo KH, Kim JS, Yoon SY, Na JY, Yu JH, et al. (2013). Acute symptoms in firefighters who participated in collection work after the community hydrogen fluoride spill accident. *Ann Occup Environ Med*. 25(1):36. doi:10.1186/2052-4374-25-36 PMID:24472575

Christison KS, Gurney SC, Sol JA, Williamson-Reisdorph CM, Quindry TS, Quindry JC, et al. (2021). Muscle damage and overreaching during wildland firefighter critical training. *J Occup Environ Med*. 63(4):350–6. doi:10.1097/JOM.0000000000002149 PMID:33769401

Chung J, Demers PA, Kalenge S, Kirkham TL (2020). Career fire hall exposures to diesel engine exhaust in Ontario, Canada. *J Occup Environ Hyg*. 17(1):38–46. doi:10.1080/15459624.2019.1691729 PMID:31851590

Chupeau Z, Bonvallot N, Mercier F, Le Bot B, Chevrier C, Glorennec P (2020). Organophosphorus flame retardants: a global review of indoor contamination and human exposure in Europe and epidemiological

evidence. *Int J Environ Res Public Health*. 17(18):6713. doi:10.3390/ijerph17186713 PMID:32942622

Clarity C, Trowbridge J, Gerona R, Ona K, McMaster M, Bessonneau V, et al. (2021). Associations between polyfluoroalkyl substance and organophosphate flame retardant exposures and telomere length in a cohort of women firefighters and office workers in San Francisco. *Environ Health*. 20(1):97. doi:10.1186/s12940-021-00778-z PMID:34454526

Clark RN, Green RO, Swayze GA, Meeker G, Sutley S, Hoefen TM, et al. (2001). Environmental studies of the World Trade Center after the September 11, 2001 attack. 18 December 2001. Reston (VA), USA: United States Geological Survey. Available from: https://pubs.usgs.gov/of/2001/ofr-01-0429, accessed 5 September 2022.

Claudio L (2001). Environmental aftermath. *Environ Health Perspect*. 109(11):A528–36. doi:10.1289/ehp.109-a528 PMID:11713010

Cleven KL, Ye K, Zeig-Owens R, Hena KM, Montagna C, Shan J, et al. (2019). Genetic variants associated with FDNY WTC-related sarcoidosis. *Int J Environ Res Public Health*. 16(10):E1830. doi:10.3390/ijerph16101830 PMID:31126090

Cohen IM, Plecas D (2013). A review of the research literature on 24-hour shifts for firefighters. University of the Fraser Valley, School of Criminology & Criminal Justice.

Colbeth HL, Genere N, Hall CB, Jaber N, Brito JP, El Kawkgi OM, et al. (2020a). Evaluation of medical surveillance and incidence of post-September 11, 2001, thyroid cancer in World Trade Center-exposed firefighters and emergency medical service workers. *JAMA Intern Med*. 180(6):888–95. doi:10.1001/jamainternmed.2020.0950 PMID:32310290

Cone DC, MacMillan D, Parwani V, Van Gelder C (2008). Threats to life in residential structure fires. *Prehosp Emerg Care*. 12(3):297–301. doi:10.1080/10903120802104029 PMID:18584495

Cone DC, MacMillan DS, Van Gelder C, Brown DJ, Weir SD, Bogucki S (2005). Noninvasive fireground assessment of carboxyhemoglobin levels in firefighters. *Prehosp Emerg Care*. 9(1):8–13. doi:10.1080/10903120590891912 PMID:16036821

Coogan SCP, Daniels LD, Boychuk D, Burton PJ, Flannigan MD, Gauthier S, et al. (2020). Fifty years of wildland fire science in Canada. *Can J For Res*. 51(2):283–302. doi:10.1139/cjfr-2020-0314

Corbally MA, Williams MR, Chappell JN, Sigman ME (2021). Detecting chemical vapor diffusion through firefighter turnout gear. *Int J Environ Res Public Health*. 18(9):4833. doi:10.3390/ijerph18094833 PMID:33946547

Cormack S (2013). Case report: malignant peritoneal mesothelioma. *Lung Cancer*. 79:S34–5. doi:10.1016/S0169-5002(13)70099-0

Cruz MG, Gould JS, Hollis JJ, McCaw WL (2018). A hierarchical classification of wildland fire fuels for Australian vegetation types. *Fire (Basel)*. 1(1):13. doi:10.3390/fire1010013

CTIF (2021). World Fire Statistics. No. 26. International Association of Fire and Rescue Services. Available from: https://ctif.org/sites/default/files/2021-06/CTIF_Report26.pdf.

Cucchi G (2003). [Primary mesothelioma of the pericardium]. *Ital Heart J Suppl*. 4(3):241–3. [Italian] PMID:12784760

Daeid NN (2005). Fire investigation. Florida. CRC Press. Partly available from: https://aboutforensics.co.uk/fire-investigation/, accessed November 2022.

Dahlgren J, Cecchini M, Takhar H, Paepke O (2007). Persistent organic pollutants in 9/11 World Trade Center rescue workers: reduction following detoxification. *Chemosphere*. 69(8):1320–5. doi:10.1016/j.chemosphere.2006.05.127 PMID:17234251

Dahm MM, Bertke S, Allee S, Daniels RD (2015). Creation of a retrospective job-exposure matrix using surrogate measures of exposure for a cohort of US career firefighters from San Francisco, Chicago and Philadelphia. *Occup Environ Med*. 72(9):670–7. doi:10.1136/oemed-2014-102790 PMID:26163543

Daniels C (2019). Emergency services architecture. In: Wankhade P, McCann L, Murphy P, editors. Critical perspectives on the management and organization of emergency services. Routledge. Critical Studies in Public Management.

Daniels RD, Bertke S, Dahm MM, Yiin JH, Kubale TL, Hales TR, et al. (2015). Exposure-response relationships for select cancer and non-cancer health outcomes in a cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). *Occup Environ Med*. 72(10):699–706. doi:10.1136/oemed-2014-102671 PMID:25673342

Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, et al. (2014). Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). *Occup Environ Med*. 71(6):388–97. doi:10.1136/oemed-2013-101662 PMID:24142974

Darcey DJ, Everson RB, Putman KL, Randerath K (1992). DNA adducts and exposure to burning oil. *Lancet*. 339(8791):489. doi:10.1016/0140-6736(92)91092-M PMID:1346835

Darques RJAG (2015). Mediterranean cities under fire. A critical approach to the wildland–urban interface. *Appl Geogr*. 59:10–21. doi:10.1016/j.apgeog.2015.02.008

De Soir E, Zech E, Versporten A, Van Oyen H, Kleber R, Mylle J, et al. (2015). Degree of exposure and peritraumatic dissociation as determinants of PTSD symptoms in the aftermath of the Ghislenghien gas explosion. *Arch Public Health*. 73(1):21. doi:10.1186/s13690-015-0069-9 PMID:25897400

de Solla ST, et al. (2012). Highly elevated levels of perfluorooctane sulfonate and other perfluorinated acids found in biota and surface water downstream of an international airport, Hamilton, Ontario, Canada. *Environment International*. 39(1):19-26. doi:10.1016/j.envint.2011.09.011

De Vos AJ, Cook A, Devine B, Thompson PJ, Weinstein P (2006). Effect of protective filters on fire fighter respiratory health during simulated bushfire smoke exposure. *Am J Ind Med*. 49(9):740–50. doi:10.1002/ajim.20369 PMID:16847937

De Vos AJ, Cook A, Devine B, Thompson PJ, Weinstein P (2009a). Effect of protective filters on fire fighter respiratory health: field validation during prescribed burns. *Am J Ind Med*. 52(1):76–87. doi:10.1002/ajim.20651 PMID:18946878

De Vos AJ, Reisen F, Cook A, Devine B, Weinstein P (2009b). Respiratory irritants in Australian bushfire smoke: air toxics sampling in a smoke chamber and during prescribed burns. *Arch Environ Contam Toxicol*. 56(3):380–8. doi:10.1007/s00244-008-9209-3 PMID:18712497

Decker JA, DeBord DG, Bernard B, Dotson GS, Halpin J, Hines CJ, et al. (2013). Recommendations for biomonitoring of emergency responders: focus on occupational health investigations and occupational health research. *Mil Med*. 178(1):68–75. doi:10.7205/MILMED-D-12-00173 PMID:23356122

Dellinger B, Lomnicki S, Khachatryan L, Maskos Z, Hall RW, Adounkpe J, et al. (2007). Formation and stabilization of persistent free radicals. *Proc Combust Inst*. 31(1):521–8. doi:10.1016/j.proci.2006.07.172 PMID:25598747

Demers PA, Checkoway H, Vaughan TL, Weiss NS, Heyer NJ, Rosenstock L (1994). Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). *Cancer Causes Control*. 5(2):129–35. doi:10.1007/BF01830258 PMID:8167259

Demers PA, Heyer NJ, Rosenstock L (1992). Mortality among firefighters from three northwestern United States cities. *Br J Ind Med*. 49(9):664–70. doi:10.1136/oem.49.9.664 PMID:1390274

Demiralp N, Özel F (2021). Evaluation of metabolic syndrome and sleep quality in shift workers. *Occup Med (Lond)*. 71(9):453–9. doi:10.1093/occmed/kqab140 PMID:34791382

Denault D, Gardner H (2022). OSHA Bloodborne Pathogen Standards Last update: 14 April 2022. StatPearls [Internet]. Treasure Island (FL), USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570561/#_NBK570561_pubdet_, accessed November 2022.

Department of Interior (2022). DOI fires - wildland fire jobs. FIRES Program Office, United States Department of the Interior. Available from https://www.firejobs.doi.gov/crews, accessed November 2022.

Derendorf H, Schmidt S (2019). Rowland and Tozer's clinical pharmacokinetics and pharmacodynamics: concepts and applications. 5th ed. Philadelphia (PA), USA: Wolters Kluwer Health.

Deschamps S, Momas I, Festy B (1995). Mortality amongst Paris fire-fighters. *Eur J Epidemiol*. 11(6):643–6. doi:10.1007/BF01720297 PMID:8861847

Diaz-Castro J, Mira-Rufino PJ, Moreno-Fernandez J, Chirosa I, Chirosa JL, Guisado R, et al. (2020a). Ubiquinol supplementation modulates energy metabolism and bone turnover during high intensity exercise. *Food Funct*. 11(9):7523–31. doi:10.1039/D0FO01147A PMID:32797125

Diaz-Castro J, Moreno-Fernandez J, Chirosa I, Chirosa LJ, Guisado R, Ochoa JJ (2020b). Beneficial effect of ubiquinol on hematological and inflammatory signalling during exercise. *Nutrients*. 12(2):E424. doi:10.3390/nu12020424 PMID:32041223

Dietrich J, Yermakov M, Reponen T, Kulkarni P, Qi C, Grinshpun SA (2015). Protection of firefighters against combustion aerosol particles: simulated workplace protection factor of a half-mask respirator (pilot study). *J Occup Environ Hyg*. 12(6):415–20. doi:10.1080/15459624.2015.1006637 PMID:25625543

Dills RL, Beaudreau M (2008). Chemical composition of overhaul smoke after use of three extinguishing agents. *Fire Technol*. 44(4):419–37. doi:10.1007/s10694-007-0035-3

Dills RL, Paulsen M, Ahmad J, Kalman DA, Elias FN, Simpson CD (2006). Evaluation of urinary methoxyphenols as biomarkers of woodsmoke exposure. *Environ Sci Technol*. 40(7):2163–70. doi:10.1021/es051886f PMID:16646448

Dills RL, Zhu X, Kalman DA (2001). Measurement of urinary methoxyphenols and their use for biological monitoring of wood smoke exposure. *Environ Res*. 85(2):145–58. doi:10.1006/enrs.2000.4107 PMID:11161664

Dixon HM, Armstrong G, Barton M, Bergmann AJ, Bondy M, Halbleib ML, et al. (2019). Discovery of common chemical exposures across three continents using silicone wristbands. *R Soc Open Sci*. 6(2):181836. doi:10.1098/rsos.181836 PMID:30891293

Dobraca D, Israel L, McNeel S, Voss R, Wang M, Gajek R, et al. (2015). Biomonitoring in California firefighters: metals and perfluorinated chemicals. *J Occup Environ Med*. 57(1):88–97. doi:10.1097/JOM.0000000000000307 PMID:25563545

Doerr SH, Santín C (2016). Global trends in wildfire and its impacts: perceptions versus realities in a changing world. *Philos Trans R Soc Lond B Biol Sci*. 371(1696):20150345. doi:10.1098/rstb.2015.0345 PMID:27216515

Dunn KH, Devaux I, Stock A, Naeher LP (2009). Application of end-exhaled breath monitoring to assess carbon monoxide exposures of wildland firefighters

at prescribed burns. *Inhal Toxicol*. 21(1):55–61. doi:10.1080/08958370802207300 PMID:18946764

Dunn KH, Shulman S, Stock AL, Naeher LP (2013). Personal carbon monoxide exposures among firefighters at prescribed forest burns in the southeastern United States. *Arch Environ Occup Health*. 68(1):55–9. doi:10.1080/19338244.2011.633126 PMID:23298425

Duran F, Woodhams J, Bishopp DJER, Journal R (2018). An interview study of the experiences of firefighters in regard to psychological contract and stressors. *Employee Responsib Rights J*. 30(3):203–26. doi:10.1007/s10672-018-9314-z

Easter E, Lander D, Huston T (2016). Risk assessment of soils identified on firefighter turnout gear. *J Occup Environ Hyg*. 13(9):647–57. doi:10.1080/15459624.2016.1165823 PMID:27027971

EC/ECHA (2020). The use of PFAS and fluorine-free alternatives in fire-fighting foams. Final report. Specific contracts No 07.0203/2018/791749/ENV.B.2 and ECHA/2018/561. European Commission DG Environment/European Chemicals Agency (ECHA). Available from: https://echa.europa.eu/documents/10162/28801697/pfas_flourine-free_alternatives_fire_fighting_en.pdf/d5b24e2a-d027-0168-cdd8-f723c675fa98, accessed November 2022.

ECHA (2022a). Perfluoroalkyl chemicals (PFASs). Available from: https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas, accessed November 2022.

ECHA (2022b). Proposal to ban 'forever chemicals' in firefighting foams throughout the EU. ECHA/NR/22/05. Available from: https://echa.europa.eu/-/proposal-to-ban-forever-chemicals-in-firefighting-foams-throughout-the-eu, accessed November 2022.

Edelman P, Osterloh J, Pirkle J, Caudill SP, Grainger J, Jones R, et al. (2003). Biomonitoring of chemical exposure among New York City firefighters responding to the World Trade Center fire and collapse. *Environ Health Perspect*. 111(16):1906–11. doi:10.1289/ehp.6315 PMID:14644665

Edwards R, Johnson M, Dunn KH, Naeher LP (2005). Application of real-time particle sensors to help mitigate exposures of wildland firefighters. *Arch Environ Occup Health*. 60(1):40–3. doi:10.3200/AEOH.60.1.40-43 PMID:16961007

Ekpe OD, Sim W, Choi S, Choo G, Oh JE (2021). Assessment of exposure of Korean firefighters to polybrominated diphenyl ethers and polycyclic aromatic hydrocarbons via their measurement in serum and polycyclic aromatic hydrocarbon metabolites in urine. *Environ Sci Technol*. 55(20):14015–25. doi:10.1021/acs.est.1c02554 PMID:34435767

Ekunwe SIN, Hunter RD, Hwang HM (2005). Ultraviolet radiation increases the toxicity of pyrene, 1-aminopyrene and 1-hydroxypyrene to human keratinocytes. *Int J Environ Res Public Health*. 2(1):58–62. doi:10.3390/ijerph2005010058 PMID:16708424

Elbaek Pedersen J, Ugelvig Petersen K, Hansen J (2020). Full employment history of Danish firefighters potentially involving additional exposures, 1964-2015. *Am J Ind Med*. 63(4):328–36. doi:10.1002/ajim.23089 PMID:31953961

Elder A, Nordberg GF, Kleinman M (2015). Routes of exposure, dose, and toxicokinetics of metals. Chapter 3. In: Nordberg GF, Fowler BA, Nordberg M, editors. Handbook on the Toxicology of Metals. 4th ed. Amsterdam, the Netherlands: Academic Press; pp. 45–74.

Eliopulos E, Armstrong BK, Spickett JT, Heyworth F (1984). Mortality of fire fighters in Western Australia. *Br J Ind Med*. 41(2):183–7. doi:10.1136/oem.41.2.183 PMID:6722044

Engel R (2020). What are the firefighter ranks? Fire Careers Jul 24. Available from: https://www.firerescue1.com/fire-careers/articles/what-are-the-firefighter-ranks-hvwaU0z1FF6xkIE8/, accessed November 2022.

Engelsman M, Snoek MF, Banks APW, Cantrell P, Wang X, Toms LM, et al. (2019). Exposure to metals and semivolatile organic compounds in Australian fire stations. *Environ Res*. 179(Pt A):108745. doi:10.1016/j.envres.2019.108745 PMID:31546131

Engelsman M, Toms LL, Banks APW, Wang X, Mueller JF (2020). Biomonitoring in firefighters for volatile organic compounds, semivolatile organic compounds, persistent organic pollutants, and metals: A systematic review. *Environ Res*. 188:109562. doi:10.1016/j.envres.2020.109562 PMID:32526498

Environmental Litigation Group PC (2020). Industrial uses and potential impact of PFAS-based fire suppressants, 6 March 2020. Available from: https://www.ishn.com/articles/112383-industrial-uses-and-potential-impact-of-pfas-based-fire-suppressants, accessed November 2022.

EPSU (2006). European firefighters' network. Report on working time and retirement. Brussels, Belgium: European Public Service Union (EPSU). Available from: https://www.epsu.org/sites/default/files/article/files/EN_Firefighters_Working_Time.pdf, accessed March 2023.

Estill CF, Slone J, Mayer A, Chen IC, La Guardia MJ (2020). Worker exposure to flame retardants in manufacturing, construction and service industries. *Environ Int*. 135:105349. doi:10.1016/j.envint.2019.105349 PMID:31810010

Etzel RA, Ashley DL (1994). Volatile organic compounds in the blood of persons in Kuwait during the oil fires. *Int Arch Occup Environ Health*. 66(2):125–9. doi:10.1007/BF00383368 PMID:7806395

Euroinnova (2022). ¿Cuáles son los requisitos para ser bombero? Available from: https://www.euroinnova.pe/oposiciones/seguridad/bomberos/, accessed March 2023. [Spanish]

Evans DE, Fent KW (2015). Ultrafine and respirable particle exposure during vehicle fire suppression. *Environ Sci Process Impacts*. 17(10):1749–59. doi:10.1039/C5EM00233H PMID:26308547

Evarts B, Stein GP (2020). US fire department profile 2018. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/News-and-Research/Data-research-and-tools/Emergency-Responders/US-fire-department-profile, accessed March 2023.

Fabian T, Borgerson JL, Kerber SI, Baxter CS, Ross CS, Lockey JE, et al. (2010). Firefighter exposure to smoke particulates. Northbrook (IL), USA: Underwriters Laboratories. Final Report Project Number: 08CA31673; File Number: IN 15941.

Fabian TZ, Borgerson JL, Gandhi PD, Baxter CS, Ross CS, Lockey JE, et al. (2014). Characterization of firefighter smoke exposure. *Fire Technol*. 50(4):993–1019. doi:10.1007/s10694-011-0212-2

Fahy R, Evarts B, Stein GP (2021). US fire department profile 2019. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/-/media/Files/News-and-Research/Fire-statistics-and-reports/Emergency-responders/osfdprofile.pdf, accessed March 2023.

Fent KW, Alexander B, Roberts J, Robertson S, Toennis C, Sammons D, et al. (2017). Contamination of firefighter personal protective equipment and skin and the effectiveness of decontamination procedures. *J Occup Environ Hyg*. 14(10):801–14. doi:10.1080/15459624.2017.1334904 PMID:28636458

Fent KW, Eisenberg J, Snawder J, Sammons D, Pleil JD, Stiegel MA, et al. (2014). Systemic exposure to PAHs and benzene in firefighters suppressing controlled structure fires. *Ann Occup Hyg*. 58(7):830–45. PMID:24906357

Fent KW, Evans DE (2011). Assessing the risk to firefighters from chemical vapors and gases during vehicle fire suppression. *J Environ Monit*. 13(3):536–43. doi:10.1039/c0em00591f PMID:21274476

Fent KW, Evans DE, Babik K, Striley C, Bertke S, Kerber S, et al. (2018). Airborne contaminants during controlled residential fires. *J Occup Environ Hyg*. 15(5):399–412. doi:10.1080/15459624.2018.1445260 PMID:29494297

Fent KW, Evans DE, Booher D, Pleil JD, Stiegel MA, Horn GP, et al. (2015). Volatile organic compounds off-gassing from firefighters' personal protective equipment ensembles after use. *J Occup Environ Hyg*. 12(6):404–14. doi:10.1080/15459624.2015.1025135 PMID:25751596

Fent KW, LaGuardia M, Luellen D, McCormick S, Mayer A, Chen IC, et al. (2020a). Flame retardants, dioxins, and furans in air and on firefighters' protective ensembles during controlled residential firefighting. *Environ Int*. 140:105756. doi:10.1016/j.envint.2020.105756 PMID:32388249

Fent KW, Mayer A, Bertke S, Kerber S, Smith D, Horn GP (2019b). Understanding airborne contaminants produced by different fuel packages during training fires. *J Occup Environ Hyg*. 16(8):532–43. doi:10.1080/15459624.2019.1617870 PMID:31169466

Fent KW, Mayer AC, Toennis C, Sammons D, Robertson S, Chen I-C, et al. (2022). Firefighters' urinary concentrations of VOC metabolites after controlled-residential and training fire responses. *Int J Hyg Environ Health*. 242:113969. doi:10.1016/j.ijheh.2022.113969 PMID:35421664

Fent KW, Toennis C, Sammons D, Robertson S, Bertke S, Calafat AM, et al. (2019a). Firefighters' and instructors' absorption of PAHs and benzene during training exercises. *Int J Hyg Environ Health*. 222(7):991–1000. doi:10.1016/j.ijheh.2019.06.006 PMID:31272797

Fent KW, Toennis C, Sammons D, Robertson S, Bertke S, Calafat AM, et al. (2020b). Firefighters' absorption of PAHs and VOCs during controlled residential fires by job assignment and fire attack tactic. *J Expo Sci Environ Epidemiol*. 30(2):338–49. doi:10.1038/s41370-019-0145-2 PMID:31175324

Ferguson MD, Semmens EO, Dumke C, Quindry JC, Ward TJ (2016). Measured pulmonary and systemic markers of inflammation and oxidative stress following wildland firefighter simulations. *J Occup Environ Med*. 58(4):407–13. doi:10.1097/JOM.0000000000000688 PMID:27058482

Ferguson MD, Semmens EO, Weiler E, Domitrovich J, French M, Migliaccio C, et al. (2017). Lung function measures following simulated wildland firefighter exposures. *J Occup Environ Hyg*. 14(9):739–48. doi:10.1080/15459624.2017.1326700 PMID:28609218

Fernandez-Anez N, Krasovskiy A, Müller M, Vacik H, Baetens J, Hukić E, et al. (2021). Current wildland fire patterns and challenges in Europe: a synthesis of national perspectives. *Air Soil Water Res*. 14:1–19. doi:10.1177/11786221211028185

Fernando S, Shaw L, Shaw D, Gallea M, VandenEnden L, House R, et al. (2016). Evaluation of firefighter exposure to wood smoke during training exercises at burn houses. *Environ Sci Technol*. 50(3):1536–43. doi:10.1021/acs.est.5b04752 PMID:26726952

Ferreira-Leite F, Lourenço L, Bento-Gonçalves AJMR (2013). Large forest fires in mainland Portugal, brief characterization. *Méditerranée*. 121(121):53–65. doi:10.4000/mediterranee.6863

Feuer E, Rosenman K (1986). Mortality in police and firefighters in New Jersey. *Am J Ind Med*. 9(6):517–27. doi:10.1002/ajim.4700090603 PMID:3488681

Feunekes FD, Jongeneelen FJ, vd Laan H, Schoonhof FH (1997). Uptake of polycyclic aromatic hydrocarbons among trainers in a fire-fighting training facility. *Am Ind Hyg Assoc J*. 58(1):23–8. doi:10.1080/15428119791013035 PMID:9018833

Fine PM, Cass GR, Simoneit BR (2001). Chemical characterization of fine particle emissions from fireplace combustion of woods grown in the northeastern United States. *Environ Sci Technol*. 35(13):2665–75. doi:10.1021/es001466k PMID:11452590

Fire and Emergency New Zealand (2021). Annual report for the year ended 30 June 2021. Available from: https://www.fireandemergency.nz/assets/Documents/About-FENZ/Key-documents/FENZ-Annual-Report-2020-2021.pdf, accessed March 2023.

Fire and Rescue New South Wales (2021a). About the role of being a firefighter. Sydney (NSW), Australia: Fire and Rescue New South Wales, State Government. Available from: https://www.fire.nsw.gov.au/page.php?id=9067#:~:text=Responding%20to%20rescue%20calls%20throughout,such%20as%20the%20NSW%20Ambulance, accessed 13 June 2022.

Fire and Rescue New South Wales (2021b). Permanent firefighter recruitment FAQ's. Sydney (NSW), Australia: Fire and Rescue New South Wales, State Government. Available from: https://www.fire.nsw.gov.au/page.php?id=924, accessed November 2022.

Fire Recruitment Australia (2015). Firefighter age requirements - Fire Recruitment Australia. 12 January 2015. Available from: https://firerecruitmentaustralia.com.au/age-requirements-to-join-fire-services-in-australia/, accessed November 2022.

Firefighter Connection (2022). A day in the life of a career firefighter. 13 May 2022. Available from: https://firefighterconnection.com/a-day-in-the-life-of-a-career-firefighter/, accessed November 2022.

Firefighter Insider (2022). How long does a fire investigation take? Available from: https://firefighterinsider.com/how-long-does-a-fire-investigation-take/, accessed November 2022.

Fireman EM, Lerman Y, Ganor E, Greif J, Fireman-Shoresh S, Lioy PJ, et al. (2004). Induced sputum assessment in New York City firefighters exposed to World Trade Center dust. *Environ Health Perspect*. 112(15):1564–9. doi:10.1289/ehp.7233 PMID:15531443

Fleming RS, Zhu FX (2009). Managerial responsibilities of the contemporary fire chief: EBSCOhost. *J Global Business Issues*. 3(2):57–68. Available from: https://www.proquest.com/openview/beeac59c8f675a8b2743daca8616eb34/1?cbl=39974&pq-origsite=gscholar&parentSessionId=HBsWrWD5uQrhrR7CbC7YoVL7OdI0%2Br6gvaHrLXg4t4c%3D, accessed November 2022.

Flora SJ (2009). Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure. *Oxid Med Cell Longev*. 2(4):191–206. doi:10.4161/oxim.2.4.9112 PMID:20716905

Forest Fire Management Victoria (2022). Firefighting and employment. Available from: https://www.ffm.vic.gov.au/who-we-are/firefighting-and-employment, accessed 13 June 2022.

Foster KR, Glaser R (2007). Thermal mechanisms of interaction of radiofrequency energy with biological systems with relevance to exposure guidelines. *Health Phys*. 92(6):609–20. doi:10.1097/01.HP.0000262572.64418.38 PMID:17495663

Fraess-Phillips A, Wagner S, Harris L (2017). Firefighters and traumatic stress. *Int J Emerg Serv*. 6:67–80. doi:10.1108/IJES-10-2016-0020

Franz TJ (1984). Percutaneous absorption of benzene. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., editors. Advances in modern environmental toxicology, Vol. VI, Applied toxicology of petroleum hydrocarbons. Princeton (NJ), USA: Princeton Scientific Publishers Inc; pp 61–70.

Frasch HF (2002). A random walk model of skin permeation. *Risk Anal*. 22(2):265–76. doi:10.1111/0272-4332.00024 PMID:12022675

Frasch HF, Dotson GS, Bunge AL, Chen CP, Cherrie JW, Kasting GB, et al. (2014). Analysis of finite dose dermal absorption data: implications for dermal exposure assessment. *J Expo Sci Environ Epidemiol*. 24(1):65–73. doi:10.1038/jes.2013.23 PMID:23715085

Froines JR, Hinds WC, Duffy RM, Lafuente EJ, Liu WC (1987). Exposure of firefighters to diesel emissions in fire stations. *Am Ind Hyg Assoc J*. 48(3):202–7. doi:10.1080/15298668791384634 PMID:2437785

Frost DM, Beach TA, Crosby I, McGill SM (2016). The cost and distribution of firefighter injuries in a large Canadian Fire Department. *Work*. 55(3):497–504. doi:10.3233/WOR-162420 PMID:27768003

Fushimi M (2012). Posttraumatic stress in professional firefighters in Japan: rescue efforts after the Great East Japan Earthquake (Higashi Nihon Dai-Shinsai). *Prehosp Disaster Med*. 27(5):416–8. doi:10.1017/S1049023X12001070 PMID:22877787

Gaudreau É, Bérubé R, Bienvenu JF, Fleury N (2016). Stability issues in the determination of 19 urinary (free and conjugated) monohydroxy polycyclic aromatic hydrocarbons. *Anal Bioanal Chem*. 408(15):4021–33. doi:10.1007/s00216-016-9491-2 PMID:27098935

Gaughan DM, Christiani DC, Hughes MD, Baur DM, Kobzik L, Wagner GR, et al. (2014b). High hsCRP is associated with reduced lung function in structural firefighters. *Am J Ind Med*. 57(1):31–7. doi:10.1002/ajim.22260 PMID:24115029

Gaughan DM, Piacitelli CA, Chen BT, Law BF, Virji MA, Edwards NT, et al. (2014c). Exposures and cross-shift lung function declines in wildland firefighters. *J Occup Environ Hyg*. 11(9):591–603. doi:10.1080/15459624.2014.895372 PMID:24568319

Gaughan DM, Siegel PD, Hughes MD, Chang CY, Law BF, Campbell CR, et al. (2014a). Arterial stiffness, oxidative stress, and smoke exposure in wildland firefighters. *Am J Ind Med*. 57(7):748–56. doi:10.1002/ajim.22331 PMID:24909863

Gavett SH (2003). World Trade Center fine particulate matter–chemistry and toxic respiratory effects: an overview. *Environ Health Perspect*. 111(7):971. doi:10.1289/ehp.111-1241533 PMID:12782500

Geiger KW, Wright TJ, Deters L (2020). Renal cell carcinoma as an incidental finding in firefighters: a case series. *Cureus*. 12(7):e9259. doi:10.7759/cureus.9259 PMID:32821605

Geiser M (2010). Update on macrophage clearance of inhaled micro- and nanoparticles. *J Aerosol Med Pulm Drug Deliv*. 23(4):207–17. doi:10.1089/jamp.2009.0797 PMID:20109124

Genuis SK, Birkholz D, Genuis SJ (2017). Human excretion of polybrominated diphenyl ether flame retardants: blood, urine, and sweat study. *BioMed Res Int*. 2017:3676089. doi:10.1155/2017/3676089 PMID:28373979

German Network of Female Firefighters (2022). Available from: https://www.feuerwehrfrauen.de/english/, accessed November 2022.

Geyer HJ, Schramm KW, Darnerud PO, Aune M, Feicht EA, Fried K, et al. (2004). Terminal elimination half-lives (T1/2H) of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans. *Organohalogen Compd*. 66:3867–71.

Ghasemi F, Zarei H, Babamiri M, Kalatpour O (2021). Fatigue profile among petrochemical firefighters and its relationship with safety behavior: the moderating and mediating roles of perceived safety climate. *Int J Occup Saf Ergon*. 9:1–7. PMID:34042558

Ghiyasi S, Nabizadeh H, Jazari MD, Soltanzadeh A, Heidari H, Fardi A, et al. (2020). The effect of personal protective equipment on thermal stress: an experimental study on firefighters. *Work*. 67(1):141–7. doi:10.3233/WOR-203259 PMID:32955479

Gianniou N, Giannakopoulou C, Dima E, Kardara M, Katsaounou P, Tsakatikas A, et al. (2018). Acute effects of smoke exposure on airway and systemic inflammation in forest firefighters. *J Asthma Allergy*. 11:81–8. doi:10.2147/JAA.S136417 PMID:29719412

Gianniou N, Katsaounou P, Dima E, Giannakopoulou CE, Kardara M, Saltagianni V, et al. (2016). Prolonged occupational exposure leads to allergic airway sensitization and chronic airway and systemic inflammation in professional firefighters. *Respir Med*. 118:7–14. doi:10.1016/j.rmed.2016.07.006 PMID:27578465

Gilbert AC (2021). After Tesla Megapack battery burst into flames, it took 150 firefighters to put fire out. USA Today Money. 2 August 2021. Available from: https://www.usatoday.com/story/money/cars/2021/08/02/tesla-megapack-battery-ignites-fire-australia-burns-4-days/5453874001/, accessed November 2022.

Giles G, Staples M, Berry J (1993). Cancer incidence in Melbourne Metropolitan Fire Brigade members, 1980-1989. *Health Rep*. 5(1):33–8. PMID:8334236

Gill B, Jobst K, Britz-McKibbin P (2020a). Rapid screening of urinary 1-hydroxypyrene glucuronide by multi-segment injection-capillary electrophoresis-tandem mass spectrometry: A high-throughput method for biomonitoring of recent smoke exposures. *Anal Chem*. 92(19):13558–64. doi:10.1021/acs.analchem.0c03212 PMID:32901481

Gill B, Mell A, Shanmuganathan M, Jobst K, Zhang X, Kinniburgh D, et al. (2019). Urinary hydroxypyrene determination for biomonitoring of firefighters deployed at the Fort McMurray wildfire: an inter-laboratory method comparison. *Anal Bioanal Chem*. 411(7):1397–407. doi:10.1007/s00216-018-01569-1 PMID:30683964

Gill R, Hurley S, Brown R, Tarrant D, Dhaliwal J, Sarala R, et al. (2020b). Polybrominated diphenyl ether and organophosphate flame retardants in Canadian fire station dust. *Chemosphere*. 253:126669. doi:10.1016/j.chemosphere.2020.126669 PMID:32464780

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2016b). Mortality and cancer incidence at a fire training college. *Occup Med (Lond)*. 66(7):536–42. doi:10.1093/occmed/kqw079 PMID:27371948

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2017). Mortality and cancer incidence among male volunteer Australian firefighters. *Occup Environ Med*. 74(9):628–38. doi:10.1136/oemed-2016-104088 PMID:28391245

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2019). Mortality and cancer incidence among female Australian firefighters. *Occup Environ Med*. 76(4):215–21. doi:10.1136/oemed-2018-105336 PMID:30674605

Glass DC, Pircher S, Del Monaco A, Hoorn SV, Sim MR (2016a). Mortality and cancer incidence in a cohort of male paid Australian firefighters. *Occup Environ Med*. 73(11):761–71. doi:10.1136/oemed-2015-103467 PMID:27456156

Gold A, Burgess WA, Clougherty EV (1978). Exposure of firefighters to toxic air contaminants. *Am Ind Hyg Assoc J*. 39(7):534–9. doi:10.1080/0002889778507805 PMID:211840

Goldfarb DG, Putman B, Lahousse L, Zeig-Owens R, Vaeth BM, Schwartz T, et al. (2021). Lung function decline before and after treatment of World Trade Center associated obstructive airways disease with inhaled corticosteroids and long-acting beta agonists. *Am J Ind Med*. 64(10):853–60. doi:10.1002/ajim.23272 PMID:34254700

González ME, Gomez-Gonzalez S, Lara A, Garreaud R, Diaz-Hormazabal I (2018). The 2010–2015 megadrought and its influence on the fire regime in central and south-central Chile. *Ecosphere*. 9(8):e02300. doi:10.1002/ecs2.2300

Goodrich JM, Calkins MM, Caban-Martinez AJ, Stueckle T, Grant C, Calafat AM, et al. (2021). Per- and polyfluoroalkyl substances, epigenetic age and DNA methylation: a cross-sectional study of firefighters. *Epigenomics*. 13(20):1619–36. doi:10.2217/epi-2021-0225 PMID:34670402

Goodrich JM, Jung AM, Furlong MA, Beitel S, Littau S, Gulotta J, et al. (2022). Repeat measures of DNA methylation in an inception cohort of firefighters. *Occup Environ Med*. 79(10):656–63. doi:10.1136/oemed-2021-108153 PMID:35332072

Government of Canada (2021). Canadian National Fire Database (CNFDB). Natural Resources Canada. Government of Canada. Available from: https://cwfis.cfs.nrcan.gc.ca/ha/nfdb, accessed November 2022.

Government of Canada (2022). Uses of human biomonitoring data in risk assessment. Available from: https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/human-biomonitoring-data-risk-assessment.html, accessed 2 April 2022.

Government of Ontario (2022). Firefighter guidance notes: Section 6, procedures. 6–36 Limiting exposure to fire gases. Available from: https://www.ontario.ca/document/firefighter-guidance-notes/6-36-limiting-exposure-fire-gases#section-3%20https://www.irsst.qc.ca/media/documents/PubIRSST/R-572.pdf, accessed July 2022.

Government of the United Kingdom (2021). Fire and rescue workforce and pensions statistics: England, April 2020 to March 2021. Official Statistics. Updated 5 November 2021. London, England: Home Office, Government of the United Kingdom. Available from: https://www.gov.uk/government/statistics/fire-and-rescue-workforce-and-pensions-statistics-england-april-2020-to-march-2021/fire-and-rescue-workforce-and-pensions-statistics-england-april-2020-to-march-2021, accessed July 2022.

Government of the United Kingdom (2022). Operational guidance for the fire and rescue service. Available from: https://www.gov.uk/government/collections/operational-guidance-for-the-fire-and-rescue-service#generic-risk-assessments, accessed July 2022.

Graber JM, Black TM, Shah NN, Caban-Martinez AJ, Lu SE, Brancard T, et al. (2021). Prevalence and predictors of per- and polyfluoroalkyl substances (PFAS) serum levels among members of a suburban US Volunteer Fire Department. *Int J Environ Res Public Health*. 18(7):3730. doi:10.3390/ijerph18073730 PMID:33918459

Grashow R, Bessonneau V, Gerona RR, Wang A, Trowbridge J, Lin T, et al. (2020). Integrating exposure knowledge and serum suspect screening as a new approach to biomonitoring: an application in firefighters and office workers. *Environ Sci Technol*. 54(7):4344–55. doi:10.1021/acs.est.9b04579 PMID:31971370

Grenfell Tower Inquiry (2019). Grenfell Tower inquiry: phase 1 report overview. Report of the public inquiry into the fire at the Grenfell Tower on 14 June 2017. London, England: Controller of Her Majesty's Stationary Office. Available from: https://assets.grenfelltowerinquiry.org.uk/GTI%20-%20Phase%201%20report%20Executive%20Summary.pdf, accessed March 2023.

Grenier M, Gangal M, Goyer N, McGinn S, Penney J, Vergunst J (2001). Sampling for diesel particulate matter in mines. IRSST report. Diesel emissions evaluations program (DEEP). Available from: https://www.irsst.qc.ca/media/documents/PubIRSST/RF-288.pdf, accessed March 2023.

Greven FE, Krop EJ, Spithoven JJ, Burger N, Rooyackers JM, Kerstjens HA, et al. (2012). Acute respiratory effects in firefighters. *Am J Ind Med*. 55(1):54–62. doi:10.1002/ajim.21012 PMID:21959832

Greven FE, Rooyackers JM, Kerstjens HA, Heederik DJ (2011). Respiratory symptoms in firefighters. *Am J Ind Med*. 54(5):350–5. doi:10.1002/ajim.20929 PMID:21246589

Grimes G, Hirsch D, Borgeson D (1991). Risk of death among Honolulu fire fighters. *Hawaii Med J*. 50(3):82–5. PMID:2061032

Guia das Profissões (2020). [Fireman]. Available from: https://www.guiadasprofissoes.info/profissoes/bombeiro/, accessed 13 June 2022. [Portuguese]

Guidotti TL (1993). Mortality of urban firefighters in Alberta, 1927–1987. *Am J Ind Med*. 23(6):921–40. doi:10.1002/ajim.4700230608 PMID:8328477

Guidotti TL, Prezant D, de la Hoz RE, Miller A (2011). The evolving spectrum of pulmonary disease in responders to the World Trade Center tragedy. *Am J Ind Med*. 54(9):649–60. doi:10.1002/ajim.20987 PMID:23236631

Gulliver SB, Zimering R, Knight J, Morissette S, Kamholz B, Meyer E, et al. (2018). Tobacco and alcohol use among firefighters during their first 3 years of service. *Psychol Addict Behav*. 32(3):255–63. doi:10.1037/adb0000366 PMID:29771556

Gündüzöz M, Birgin İritaş S, Tutkun L, Büyükşekerci M, Pinar Çetintepe S, Bal C, et al. (2018). A new potential biomarker in early diagnosis of firefighter lung function impairment: dynamic thiol/disulphide homeostasis. *Cent Eur J Public Health*. 26(3):190–4. doi:10.21101/cejph.a4972 PMID:30419620

Gurney SC, Christison KS, Williamson-Reisdorph CM, Sol JA, Quindry TS, Quindry JC, et al. (2021). Alterations in metabolic and cardiovascular risk factors during critical training in wildland firefighters. *J Occup Environ Med*. 63(7):594–9. doi:10.1097/JOM.0000000000002191 PMID:34184652

Hadden R, Switzer C (2020). Combustion related fire products: a review. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/928024/Combustion_related_fire_products_review_ISSUE.pdf, accessed November 2022.

Haddock CK, Jahnke SA, Poston WS, Jitnarin N, Kaipust CM, Tuley B, et al. (2012). Alcohol use among firefighters in the Central United States. *Occup Med (Lond)*. 62(8):661–4. doi:10.1093/occmed/kqs162 PMID:23064207

Haddock CK, Jitnarin N, Poston WS, Tuley B, Jahnke SA (2011). Tobacco use among firefighters in the Central United States. *Am J Ind Med*. 54(9):697–706. doi:10.1002/ajim.20972 PMID:21656838

Haddock CK, Poston WSC, Jahnke SA, Jitnarin N (2017). Alcohol use and problem drinking among women firefighters. *Womens Health Issues*. 27(6):632–8. doi:10.1016/j.whi.2017.07.003 PMID:28822615

Haga Y, Suzuki M, Matsumura C, Okuno T, Tsurukawa M, Fujimori K, et al. (2018). Monitoring OH-PCBs in PCB transport worker's urine as a non-invasive exposure assessment tool. *Environ Sci Pollut Res Int*. 25(17):16446–54. doi:10.1007/s11356-018-1927-0 PMID:29656357

Hall SM, Patton S, Petreas M, Zhang S, Phillips AL, Hoffman K, et al. (2020). Per- and polyfluoroalkyl substances in dust collected from residential homes and fire stations in North America. *Environ Sci Technol*. 54(22):14558–67. doi:10.1021/acs.est.0c04869 PMID:33143410

Hansen S, Vestergren R, Herzke D, Melhus M, Evenset A, Hanssen L, et al. (2016). Exposure to per- and polyfluoroalkyl substances through the consumption of fish from lakes affected by aqueous film-forming foam emissions - a combined epidemiological and exposure modeling approach. The SAMINOR 2 Clinical Study. *Environ Int*. 94:272–82. doi:10.1016/j.envint.2016.05.030 PMID:27286038

Harris MA, Kirkham TL, MacLeod JS, Tjepkema M, Peters PA, Demers PA (2018). Surveillance of cancer risks for firefighters, police, and armed forces among men in a Canadian census cohort. *Am J Ind Med*. 61(10):815–23. doi:10.1002/ajim.22891 PMID:30073696

Hartin E (2019). Fire helmets in the US - traditional vs European. Firehouse. Available from: https://www.firehouse.com/safety-health/ppe/helmets/article/21080087/traditional-vs-european-helmets, accessed November 2022.

Hasenmeier P (2008). The history of firefighter personal protective equipment. From the 2008 personal protective equipment e-Newsletter. Fire Engineering. Available from: https://www.fireengineering.com/fire-prevention-protection/the-history-of-firefighter-personal-protective-equipment/#gref.

Haynes HJG, Stein GP (2018). Canadian fire department profile, 2014–2016. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org//-/media/Files/News-and-Research/Fire-statistics-and-reports/Emergency-responders/oscanada.pdf, accessed March 2023.

HBM4EU (2022). Population distribution of internal exposure levels. European Human Biomonitoring Dashboard. Available from: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard, accessed 13 June 2022.

Heibati B, Godri Pollitt KJ, Charati JY, Ducatman A, Shokrzadeh M, Karimi A, et al. (2018). Biomonitoring-based exposure assessment of benzene, toluene, ethylbenzene and xylene among workers at petroleum distribution facilities. *Ecotoxicol Environ Saf*. 149:19–25. doi:10.1016/j.ecoenv.2017.10.070 PMID:29145162

Hejl AM, Adetona O, Diaz-Sanchez D, Carter JD, Commodore AA, Rathbun SL, et al. (2013). Inflammatory effects of woodsmoke exposure among wildland firefighters working at prescribed burns at the Savannah River Site, SC. *J Occup Environ Hyg*. 10(4):173–80. doi:10.1080/15459624.2012.760064 PMID:23363434

Hemmatjo R, Motamedzade M, Aliabadi M, Kalatpour O, Farhadian M (2018). The effect of artificial smoke compound on physiological responses, cognitive functions and work performance during firefighting activities in a smoke-diving room: an intervention study. *Int J Occup Saf Ergon*. 24(3):358–65. doi:10.1080/10803548.2017.1299995 PMID:28278005

Hena KM, Yip J, Jaber N, Goldfarb D, Fullam K, Cleven K, et al.; FDNY Sarcoidosis Clinical Research Group (2018). Clinical course of sarcoidosis in World Trade Center-exposed firefighters. *Chest*. 153(1):114–23. doi:10.1016/j.chest.2017.10.014 PMID:29066387

Hengstler JG, Fuchs J, Bolm-Audorff U, Meyer S, Oesch F (1995). Single-strand breaks in deoxyribonucleic acid in fire fighters accidentally exposed to *o*-nitroanisole and other chemicals. *Scand J Work Environ Health*. 21(1):36–42. doi:10.5271/sjweh.6 PMID:7784863

Henn SA, Butler C, Li J, Sussell A, Hale C, Broyles G, et al. (2019). Carbon monoxide exposures among US wildland firefighters by work, fire, and environmental characteristics and conditions. *J Occup Environ Hyg*. 16(12):793–803. doi:10.1080/15459624.2019.1670833 PMID:31658425

Hess-Kosa K (2016). Building materials. Product emission and combustion health hazards. 1st ed. Boca Raton (FL), USA: CRC Press.

Hewitt F, Christou A, Dickens K, Walker R, Stec AA (2017). Release of volatile and semi-volatile toxicants during house fires. *Chemosphere*. 173:580–93. doi:10.1016/j.chemosphere.2016.12.079 PMID:28157555

Hill TA, Siedle AR, Perry R (1972). Chemical hazards of a fire-fighting training environment. *Am Ind Hyg Assoc J*. 33(6):423–30. doi:10.1080/0002889728506675 PMID:4651528

HomChaudhuri B, Kumar M, Cohen K (2010). Optimal fireline generation for wildfire fighting in uncertain and heterogeneous environment. Proceedings of the 2010 American Control Conference, 30 June–2 July 2010, Baltimore (MD), USA; pp. 5638–5643. doi:10.1109/ACC.2010.5531049

Homeland Security (2014). Wildland firefighter personal protective equipment (PPE) selection guide. System Assessment and Validation for Emergency Responders (SAVER). United States Department of Homeland Security. Science and Technology. Available from: https://www.dhs.gov/sites/default/files/publications/Wild-FF-PPE-SG_0614-508.pdf, accessed November 2022.

Hong O, Samo DG (2007). Hazardous decibels: hearing health of firefighters. *AAOHN J*. 55(8):313–9. doi:10.1177/216507990705500803 PMID:17847625

Hoppe-Jones C, Beitel S, Burgess JL, Snyder S, Flahr L, Griffin S, et al. (2018). 515 use of urinary biomarkers and bioassays to evaluate chemical exposure and activation of cancer pathways in firefighters. *Occup Environ Med*. 75:A412. doi:10.1136/oemed-2018-ICOHabstracts.1178

Hoppe-Jones C, Griffin SC, Gulotta JJ, Wallentine DD, Moore PK, Beitel SC, et al. (2021). Evaluation of fireground exposures using urinary PAH metabolites. *J Expo Sci Environ Epidemiol*. 31(5):913–22. doi:10.1038/s41370-021-00311-x PMID:33654270

Horn GP, Kerber S, Andrews J, Kesler RM, Newman H, Stewart JW, et al. (2021). Impact of repeated exposure and cleaning on protective properties of structural firefighting turnout gear. *Fire Technol*. 57(2):791–813. doi:10.1007/s10694-020-01021-w PMID:35673328

Horn GP, Kesler RM, Kerber S, Fent KW, Schroeder TJ, Scott WS, et al. (2018). Thermal response to firefighting activities in residential structure fires: impact of job assignment and suppression tactic. *Ergonomics*. 61(3):404–19. doi:10.1080/00140139.2017.1355072 PMID:28737481

Horn GP, Madrzykowski D, Neumann DL, Mayer AC, Fent KW (2022). Airborne contamination during post-fire investigations: hot, warm and cold scenes. *J Occup Environ Hyg*. 19(1):35–49. doi:10.1080/15459624.2021.2002343 PMID:34762010

Hoskins JA, Brown RC (1994). Contamination of the air with mineral fibers following the explosive destruction of buildings and fire. *Drug Metab Rev*. 26(4):663–73. doi:10.3109/03602539408998321 PMID:7875060

Hostynek JJ (2003). Factors determining percutaneous metal absorption. *Food Chem Toxicol*. 41(3):327–45. doi:10.1016/S0278-6915(02)00257-0 PMID:12504165

Hou R, Xu Y, Wang Z (2016). Review of OPFRs in animals and humans: absorption, bioaccumulation, metabolism, and internal exposure research. *Chemosphere*. 153:78–90. doi:10.1016/j.chemosphere.2016.03.003 PMID:27010170

Hsu JF, Guo HR, Wang HW, Liao CK, Liao PC (2011). An occupational exposure assessment of polychlorinated dibenzo-*p*-dioxin and dibenzofurans in firefighters. *Chemosphere*. 83(10):1353–9. doi:10.1016/j.chemosphere.2011.02.079 PMID:21458022

Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaider LA, Grandjean P, et al. (2016). Detection of poly- and perfluoroalkyl substances (PFASs) in US drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. *Environ Sci Technol Lett*. 3(10):344–50. doi:10.1021/acs.estlett.6b00260 PMID:27752509

Hu Y, Fernandez-Anez N, Smith TEL, Rein G (2018). Review of emissions from smouldering peat fires and their contribution to regional haze episodes. *Int J Wildland Fire*. 27(5):293–312. doi:10.1071/WF17084

Huang C-J, Acevedo EOJAJLM (2011). Occupational stress: the influence of obesity and physical activity/fitness on immune function. *Am J Lifestyle Med*. 5(6):486–93. doi:10.1177/1559827611418168

Huang CJ, Webb HE, Garten RS, Kamimori GH, Acevedo EO (2010a). Psychological stress during exercise: lymphocyte subset redistribution in firefighters. *Physiol Behav*. 101(3):320–6. doi:10.1016/j.physbeh.2010.05.018 PMID:20570686

Huang C-J, Webb HE, Garten RS, Kamimori GH, Evans RK, Acevedo EO (2010b). Stress hormones and immunological responses to a dual challenge in professional firefighters. *Int J Psychophysiol*. 75(3):312–8. doi:10.1016/j.ijpsycho.2009.12.013 PMID:20079388

Huizink AC, Slottje P, Witteveen AB, Bijlsma JA, Twisk JWR, Smidt N, et al. (2006). Long term health complaints following the Amsterdam Air Disaster in police officers and fire-fighters. *Occup Environ Med*. 63(10):657–62. doi:10.1136/oem.2005.024687 PMID:16644894

Hutzinger O, Choudhry GG, Chittim BG, Johnston LE (1985). Formation of polychlorinated dibenzofurans and dioxins during combustion, electrical equipment fires and PCB incineration. *Environ Health Perspect*. 60:3–9. doi:10.1289/ehp.85603 PMID:3928357

Hwang J, Taylor R, Cann C, Norris P, Golla V (2019b). Evaluation of accumulated polycyclic aromatic hydrocarbons and asbestiform fibers on firefighter vehicles: pilot study. *Fire Technol*. 55(6):2195–213. doi:10.1007/s10694-019-00851-7

Hwang J, Taylor R, Macy G, Cann C, Golla VJJoEH (2019a). Comparison of use, storage, and cleaning practices for personal protective equipment between career and volunteer firefighters in northwestern Kentucky in the United States. *J Environ Health*. 82(5):8–14.

IAAI (2018). Standard for professional qualifications for fire investigator. *Fire&Arson Investigator*. January 2018. International Association of Arson Investigators Fire Investigation Standards Committee. Available from: https://www.firearson.com/Download.aspx?DownloadId=51af7ce9-ae2d-447b-9e28-c49f3842b9e5, accessed November 2022.

IAAI (2020). Fire investigator health and safety best practices. Second edition. 4 May 2020. Health & Safety Committee, International Association of Arson Investigators, Inc. Available from: https://www.firearson.com/uploads/FireInvestigatorHealthSafetyBestPracticesSecond.pdf, accessed November 2022.

IARC (2002). Man-made vitreous fibres. *IARC Monogr Eval Carcinog Risks Hum*. 81:1–418. Available from: https://publications.iarc.fr/99 PMID:12458547

IARC (2010). Painting, firefighting, and shiftwork. *IARC Monogr Eval Carcinog Risks Hum*. 98:1–804. Available from: https://publications.iarc.fr/116 PMID:21381544

IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*. 105:1–703. Available from: https://publications.iarc.fr/129 PMID:26442290

IARC (2020). Night shift work. *IARC Monogr Identif Carcinog Hazard Hum*. 124:1–371. Available from: https://publications.iarc.fr/593 PMID:33656825

Ide CW (1998). Failing firefighters: a survey of causes of death and ill-health retirement in serving firefighters in Strathclyde, Scotland from 1985–94. *Occup Med (Lond)*. 48(6):381–8. doi:10.1093/occmed/48.6.381 PMID:10024734

IFA (2022). GESTIS International Limit Values database. Germany: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance). Available from: https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp.

IFSTA (2022). Chapter 6. Classroom instruction. In: Fire and emergency services instructor. Ninth edition. International Fire Service Training Association. Available from: https://www.ifsta.org/sites/default/files/Fire%20and%20Emergency%20Services%20Instructor%209th%20Edition%20-%20Manual%20Chapter%206%20%28PDF%29.pdf, accessed November 2022.

ITRC (2020). History and use of per- and polyfluoroalkyl substances (PFAS) found in the environment. Washington (DC), USA: Interstate Technology Regulatory Council. Available from: https://pfas-1.itrcweb.org/wp-content/uploads/2020/10/history_and_use_508_2020Aug_Final.pdf, accessed 30 August 2022.

Jackson R, Logue BA (2017). A review of rapid and field-portable analytical techniques for the diagnosis of cyanide exposure. *Anal Chim Acta*. 960:18–39. doi:10.1016/j.aca.2016.12.039 PMID:28193360

Jahnke SA, Kaipust C, Jitnarin N, Hollerbach BS, Koeppel MDH, Haddock CK, et al. (2022). Prevalence and predictors of obesity among women in the fire service. *Occup Environ Med*. 79(5):289–94. doi:10.1136/oemed-2021-107590 PMID:34697223

Jakobsen J, Babigumira R, Danielsen M, Grimsrud TK, Olsen R, Rosting C, et al. (2020). Work conditions and practices in Norwegian fire departments from 1950 until today: a survey on factors potentially influencing carcinogen exposure. *Saf Health Work*. 11(4):509–16. doi:10.1016/j.shaw.2020.07.004 PMID:33329918

Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, et al. (2018). Current cigarette smoking among adults – United States, 2016. *MMWR Morb Mortal Wkly Rep*. 67(2):53–9. doi:10.15585/mmwr.mm6702a1

Jang TW, Jeong KS, Ahn YS, Choi KS (2020). The relationship between the pattern of shift work and sleep disturbances in Korean firefighters. *Int Arch Occup Environ Health*. 93(3):391–8. doi:10.1007/s00420-019-01496-3 PMID:31768636

Jankovic J, Jones W, Burkhart J, Noonan G (1991). Environmental study of firefighters. *Ann Occup Hyg*. 35(6):581–602. doi:10.1093/annhyg/35.6.581 PMID:1768008

Jankovic J, Jones W, Castranova V, Dalal N (1993). Measurement of short-lived reactive species and long-lived free radicals in air samples from structural fires. *Appl Occup Environ Hyg*. 8(7):650–4. doi:10.1080/1047322X.1993.10388174

Jarvis MJ, Belcher M, Vesey C, Hutchison DC (1986). Low cost carbon monoxide monitors in smoking assessment. *Thorax*. 41(11):886–7. doi:10.1136/thx.41.11.886 PMID:3824275

Jayatilaka NK, Restrepo P, Davis Z, Vidal M, Calafat AM, Ospina M (2019). Quantification of 16 urinary biomarkers of exposure to flame retardants, plasticizers, and organophosphate insecticides for biomonitoring studies. *Chemosphere*. 235:481–91. doi:10.1016/j.chemosphere.2019.06.181 PMID:31272008

Jayatilaka NK, Restrepo P, Williams L, Ospina M, Valentin-Blasini L, Calafat AM (2017). Quantification of three chlorinated dialkyl phosphates, diphenyl phosphate, 2,3,4,5-tetrabromobenzoic acid, and four other organophosphates in human urine by solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. *Anal Bioanal Chem*. 409(5):1323–32. doi:10.1007/s00216-016-0061-4 PMID:27838756

Jeong KS, Ahn YS, Jang TW, Lim G, Kim HD, Cho SW, et al. (2019). Sleep assessment during shift work in Korean firefighters: a cross-sectional study. *Saf Health*

Work. 10(3):254–9. doi:10.1016/j.shaw.2019.05.003 PMID:31497322

Jeong KS, Zhou J, Griffin SC, Jacobs ET, Dearmon-Moore D, Zhai J, et al. (2018). MicroRNA changes in firefighters. *J Occup Environ Med*. 60(5):469–74. doi:10.1097/JOM.0000000000001307 PMID:29465512

Jeyaratnam M, West NG (1994). A study of heat-degraded chrysotile, amosite and crocidolite by X-ray diffraction. *Ann Occup Hyg*. 38(2):137–48. doi:10.1093/annhyg/38.2.137

Jin C, Sun Y, Islam A, Qian Y, Ducatman A (2011). Perfluoroalkyl acids including perfluorooctane sulfonate and perfluorohexane sulfonate in firefighters. *J Occup Environ Med*. 53(3):324–8. doi:10.1097/JOM.0b013e31820d1314 PMID:21346631

Jitnarin N, Poston WSC, Haddock CK, Jahnke SA (2019). Tobacco use among women firefighters. *Womens Health Issues*. 29(5):432–9. doi:10.1016/j.whi.2019.05.006 PMID:31229361

Jitnarin N, Poston WSC, Haddock CK, Jahnke SA, Day RS, Severson HH (2017). Prevalence and correlates of late initiation of smokeless tobacco in US firefighters. *Nicotine Tob Res*. 20(1):130–4. PMID:27940900

Jo J, Sokolowski S, McQuerry M, Griffin L, Park H (2022). Firefighters' feet: differences by sex and weight-bearing. *Appl Ergon*. 102:103753. doi:10.1016/j.apergo.2022.103753 PMID:35344794

Johnson CH, Patterson AD, Idle JR, Gonzalez FJ (2012). Xenobiotic metabolomics: major impact on the metabolome. *Annu Rev Pharmacol Toxicol*. 52(1):37–56. doi:10.1146/annurev-pharmtox-010611-134748 PMID:21819238

Jones N, Peck G, McKenna ST, Glockling JLD, Harbottle J, Stec AA, et al. (2021). Burning behaviour of rainscreen façades. *J Hazard Mater*. 403:123894. doi:10.1016/j.jhazmat.2020.123894 PMID:33264958

Jongeneelen FJ, Anzion RBM, Henderson PT (1987). Determination of hydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. *J Chromatogr A*. 413:227–32. doi:10.1016/0378-4347(87)80230-X PMID:3558672

Josyula AB, Kurzius-Spencer M, Littau SR, Yucesoy B, Fleming J, Burgess JL (2007). Cytokine genotype and phenotype effects on lung function decline in firefighters. *J Occup Environ Med*. 49(3):282–8. doi:10.1097/JOM.0b013e3180322584 PMID:17351514

Jung AM, Jahnke SA, Dennis LK, Bell ML, Burgess JL, Jitnarin N, et al. (2021a). Occupational factors and miscarriages in the US fire service: a cross-sectional analysis of women firefighters. *Environ Health*. 20(1):116. doi:10.1186/s12940-021-00800-4 PMID:34749749

Jung AM, Zhou J, Beitel SC, Littau SR, Gulotta JJ, Wallentine DD, et al. (2021b). Longitudinal evaluation of whole blood miRNA expression in firefighters. *J Expo Sci Environ Epidemiol*. 31(5):900–12. doi:10.1038/s41370-021-00306-8 PMID:33603099

Junk AK, Egner P, Gottloeber P, Peter RU, Stefani FH, Kellerer AM (1999). [Long-term radiation damage to the skin and eye after combined beta- and gamma-radiation exposure during the reactor accident in Chernobyl]. *Klin Monatsbl Augenheilkd*. 215(6):355–60. [German] doi:10.1055/s-2008-1034732 PMID:10637800

Kales SN, Pentiuc F, Christiani DC (1994). Pseudoelevation of carboxyhemoglobin levels in firefighters. *J Occup Med*. 36(7):752–6. PMID:7931741

Kales SN, Soteriades ES, Christophi CA, Christiani DC (2007). Emergency duties and deaths from heart disease among firefighters in the United States. *N Engl J Med*. 356(12):1207–15. doi:10.1056/NEJMoa060357 PMID:17377158

Kang D, Davis LK, Hunt P, Kriebel D (2008). Cancer incidence among male Massachusetts firefighters, 1987–2003. *Am J Ind Med*. 51(5):329–35. doi:10.1002/ajim.20549 PMID:18306327

Kanny D, Liu Y, Brewer RD, Lu H; Centers for Disease Control and Prevention (CDC) (2013). Binge drinking - United States, 2011. *MMWR Suppl*. 62(3):77–80. PMID:24264494

Katami T, Yasuhara A, Okuda T, Shibamoto T (2002). Formation of PCDDs, PCDFs, and coplanar PCBs from polyvinyl chloride during combustion in an incinerator. *Environ Sci Technol*. 36(6):1320–4. doi:10.1021/es0109904 PMID:11944687

Kazemi R, Zare S, Hemmatjo R (2018). Comparison of melatonin profile and alertness of firefighters with different work schedules. *J Circadian Rhythms*. 16(1):1. doi:10.5334/jcr.155 PMID:30210561

Keeley JE, Syphard AD (2021). Large California wildfires: 2020 fires in historical context. *Fire Ecol*. 17(1):22. doi:10.1186/s42408-021-00110-7

Keir JLA, Akhtar US, Matschke DMJ, Kirkham TL, Chan HM, Ayotte P, et al. (2017). Elevated exposures to polycyclic aromatic hydrocarbons and other organic mutagens in Ottawa firefighters participating in emergency, on-shift fire suppression. *Environ Sci Technol*. 51(21):12745–55. doi:10.1021/acs.est.7b02850 PMID:29043785

Keir JLA, Akhtar US, Matschke DMJ, White PA, Kirkham TL, Chan HM, et al. (2020). Polycyclic aromatic hydrocarbon (PAH) and metal contamination of air and surfaces exposed to combustion emissions during emergency fire suppression: Implications for firefighters' exposures. *Sci Total Environ*. 698:134211. doi:10.1016/j.scitotenv.2019.134211 PMID:31514022

Keir JLA, Cakmak S, Blais JM, White PA (2021). The influence of demographic and lifestyle factors on urinary levels of PAH metabolites-empirical analyses of Cycle 2 (2009-2011) CHMS data. *J Expo Sci Environ Epidemiol*. 31(2):386–97. doi:10.1038/s41370-020-0208-4 PMID:32066882

Kelly KJ, Connelly E, Reinhold GA, Byrne M, Prezant DJ (2002). Assessment of health effects in New York City firefighters after exposure to polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs): the Staten Island Transformer Fire Health Surveillance Project. *Arch Environ Health*. 57(4):282–93. doi:10.1080/00039890209601411 PMID:12530594

Kerber S (2012). Analysis of changing residential fire dynamics and its implications on firefighter operational timeframes. *Fire Technol*. 48(4):865–91. doi:10.1007/s10694-011-0249-2

Kern DG, Neill MA, Schachter J (1993). A seroepidemiologic study of Chlamydia pneumoniae in Rhode Island. Evidence of serologic cross-reactivity. *Chest*. 104(1):208–13. doi:10.1378/chest.104.1.208 PMID:8325072

Kesler RM, Mayer A, Fent KW, Chen IC, Deaton AS, Ormond RB, et al. (2021). Effects of firefighting hood design, laundering and doffing on smoke protection, heat stress and wearability. *Ergonomics*. 64(6):755–67. doi:10.1080/00140139.2020.1867241 PMID:33393449

Kganyago M, Shikwambana L (2020). Assessment of the characteristics of recent major wildfires in the USA, Australia and Brazil in 2018–2019 using multi-source satellite products. *Remote Sens (Basel)*. 12(11):1803. doi:10.3390/rs12111803

Khalil N, Ducatman AM, Sinari S, Billheimer D, Hu C, Littau S, et al. (2020). Per- and polyfluoroalkyl substance and cardio metabolic markers in firefighters. *J Occup Environ Med*. 62(12):1076–81. doi:10.1097/JOM.0000000000002062 PMID:33105404

Kim D-H, Kim S, Lee JY (2022). An empirical investigation of firefighting personal protective equipment and burn injuries in Korea. *Ind Health*. 60(1):2–15. doi:10.2486/indhealth.2021-0068 PMID:34615835

Kim H-S, Jeong KS, Ahn Y-S, Song JH, Kim K-Y (2021). Biological monitoring for exposure assessment of volatile organic compounds by Korean firefighters at the fire site. *Ind Health*. 60(5):2021-0108. doi:10.2486/indhealth.2021-0108 PMID:34719580

Kim SC, Lee HJ, Shin DM, Ku BS, Oh JH, Cho BJ, et al. (2018). Cardiovascular risk in fire academy instructors during live-fire simulation activity. *Ann Burns Fire Disasters*. 31(4):313–21. PMID:30983932

Kim YC, Zhang YL, Park WJ, Cha GW, Hong WH (2020a). Quantifying asbestos fibers in post-disaster situations: preventive strategies for damage control. *Int J Disaster Risk Reduct*. 2020:48. doi:10.1016/j.ijdrr.2020.101563

Kim YT, Kim WJ, Choi JE, Bae MJ, Jang H, Lee CJ, et al. (2020b). Cohort profile: firefighter research on the enhancement of safety and health (fresh), a prospective cohort study on Korean firefighters. *Yonsei Med J*. 61(1):103–9. doi:10.3349/ymj.2020.61.1.103 PMID:31887807

Kimbrel NA, Steffen LE, Meyer EC, Kruse MI, Knight JA, Zimering RT, et al. (2011). A revised measure of occupational stress for firefighters: psychometric properties and relationship to posttraumatic stress disorder, depression, and substance abuse. *Psychol Serv*. 8(4):294–306. doi:10.1037/a0025845

Kinsey K, Ahrens M (2016). NFIRS incident types. Why aren't they telling a clearer story? January 2016. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/-/media/Files/News-and-Research/Fire-statistics-and-reports/Emergency-responders/osNFIRSIncidentType.ashx?la=en, accessed November 2022.

Kirk KM, Logan MB (2015a). Firefighting instructors' exposures to polycyclic aromatic hydrocarbons during live fire training scenarios. *J Occup Environ Hyg*. 12(4):227–34. doi:10.1080/15459624.2014.955184 PMID:25679824

Kirk KM, Logan MB (2015b). Structural fire fighting ensembles: accumulation and off-gassing of combustion products. *J Occup Environ Hyg*. 12(6):376–83. doi:10.1080/15459624.2015.1006638 PMID:25626009

Kirk KM, Logan MB (2019). Exposures to air contaminants in compartment fire behavior training (CFBT) using particleboard fuel. *J Occup Environ Hyg*. 16(7):432–9. doi:10.1080/15459624.2019.1603388 PMID:31021707

Kirk KM, Ridgway M, Splawinski Z, Logan MB, editors (2011). Firefighter exposures to airborne contaminants during extinguishment of simulated residential room fires. Research Report. Queensland, Australia: Queensland Fire and Rescue Service Scientific Branch. Available from: https://docplayer.net/208351306-Research-report.html, accessed November 2022.

Kirkham TL, Koehoorn MW, Davies H, Demers PA (2011). Characterization of noise and carbon monoxide exposures among professional firefighters in British Columbia. *Ann Occup Hyg*. 55(7):764–74.doi:10.1093/annhyg/mer038 PMID:21765005

Kitt LR (2009). Breaking the silence: insights into the impact of being a firefighter on men's mental health [dissertation]. Vancouver (BC), Canada: University of British Columbia. Available from: https://open.library.ubc.ca/soa/cIRcle/collections/ubctheses/24/items/1.0053826, accessed March 2023.

Klein WM, Bloch M, Hesse BW, McDonald PG, Nebeling L, O'Connell ME, et al. (2014). Behavioral research in cancer prevention and control: a look to the future. *Am J Prev Med*. 46(3):303–11. doi:10.1016/j.amepre.2013.10.004 PMID:24512871

Kleinman LI, Sedlacek AJ 3rd, Adachi K, Buseck PR, Collier S, Dubey MK, et al. (2020). Rapid evolution of aerosol particles and their optical properties downwind of wildfires in the western US. *Atmos Chem Phys*. 20(21):13319–41. doi:10.5194/acp-20-13319-2020

Kling H, Santiago K, Benitez L, Schaefer Solle N, Caban-Martinez AJ (2020). Characterizing objective and self-reported levels of physical activity among Florida firefighters across weight status category: a cross-sectional pilot study. *Workplace Health Saf.*

68(11):513–8. doi:10.1177/2165079920925505 PMID: 32610031

Klitzman S, Freudenberg N (2003). Implications of the World Trade Center attack for the public health and health care infrastructures. *Am J Public Health*. 93(3):400–6. doi:10.2105/AJPH.93.3.400 PMID:12604481

Koopmans E, Cornish K, Fyfe TM, Bailey K, Pelletier CA (2022). Health risks and mitigation strategies from occupational exposure to wildland fire: a scoping review. *J Occup Med Toxicol*. 17(1):2. doi:10.1186/s12995-021-00328-w PMID:34983565

Krüger S, Hofmann A, Berger A, Gude N (2016). Investigation of smoke gases and temperatures during car fire – large-scale and small-scale tests and numerical investigations. *Fire Mater*. 40(6):785–99. doi:10.1002/fam.2342

Kuan PF, Mi Z, Georgopoulos P, Hashim D, Luft BJ, Boffetta P (2019). Enhanced exposure assessment and genome-wide DNA methylation in World Trade Center disaster responders. *Eur J Cancer Prev*. 28(3):225–33. doi:10.1097/CEJ.0000000000000460 PMID:30001286

Kudaeva IV, Budarina LA (2005). [Features of biochemical parameters in firemen]. *Med Tr Prom Ekol*. (12):32–7. [Russian] PMID:16430120

Kudaeva IV, Budarina LA (2007). [Biochemical criteria of occupationally related diseases formation in firemen]. *Med Tr Prom Ekol*. (6):12–8. [Russian] PMID:17695263

Kullberg C, Andersson T, Gustavsson P, Selander J, Tornling G, Gustavsson A, et al. (2018). Cancer incidence in Stockholm firefighters 1958–2012: an updated cohort study. *Int Arch Occup Environ Health*. 91(3):285–91. doi:10.1007/s00420-017-1276-1 PMID:29164319

Kwak K, Kim BK, Jang TW, Sim CS, Ahn YS, Choi KS, et al. (2020). Association between shift work and neurocognitive function among firefighters in South Korea: a prospective before-after study. *Int J Environ Res Public Health*. 17(13):4647. doi:10.3390/ijerph17134647 PMID:32605225

Lachocki TM, Church DF, Pryor WA (1988). Persistent free radicals in the smoke of common household materials: biological and clinical implications. *Environ Res*. 45(1):127–39. doi:10.1016/S0013-9351(88)80015-X PMID:3338431

Laitinen J, Mäkelä M, Mikkola J, Huttu I (2010). Fire fighting trainers' exposure to carcinogenic agents in smoke diving simulators. *Toxicol Lett*. 192(1):61–5. doi:10.1016/j.toxlet.2009.06.864 PMID:19576276

Laitinen J, Mäkelä M, Mikkola J, Huttu I (2012). Firefighters' multiple exposure assessments in practice. *Toxicol Lett*. 213(1):129–33. doi:10.1016/j.toxlet.2012.06.005 PMID:22710199

Laitinen JA, Koponen J, Koikkalainen J, Kiviranta H (2014). Firefighters' exposure to perfluoroalkyl acids and 2-butoxyethanol present in firefighting foams. *Toxicol Lett*. 231(2):227–32. doi:10.1016/j.toxlet.2014.09.007 PMID:25447453

Lam D (2009). [Female firefighters are "equal to men"]. 1 June 2009. *Diario de Noticias*. Available from: https://www.dn.pt/portugal/sul/bombeiras-sao-iguais-aos-homens-1250127.html, accessed 13 June 2022. [Spanish]

Lam R, Haider SH, Crowley G, Caraher EJ, Ostrofsky DF, Talusan A, et al. (2020). Synergistic effect of WTC-particulate matter and lysophosphatidic acid exposure and the role of RAGE: in-vitro and translational assessment. *Int J Environ Res Public Health*. 17(12):E4318. doi:10.3390/ijerph17124318 PMID:32560330

Landgren O, Zeig-Owens R, Giricz O, Goldfarb D, Murata K, Thoren K, et al. (2018). Multiple myeloma and its precursor disease among firefighters exposed to the World Trade Center disaster. *JAMA Oncol*. 4(6):821–7. doi:10.1001/jamaoncol.2018.0509 PMID:29710195

Landrigan PJ (2001). Health consequences of the 11 September 2001 attacks. *Environ Health Perspect*. 109(11):A514–5. doi:10.1289/ehp.109-a514 PMID:11713006

Landrigan PJ, Lioy PJ, Thurston G, Berkowitz G, Chen LC, Chillrud SN, et al.; NIEHS World Trade Center Working Group (2004). Health and environmental consequences of the World Trade Center disaster. *Environ Health Perspect*. 112(6):731–9. doi:10.1289/ehp.6702 PMID:15121517

Langevin SM, Eliot M, Butler RA, McClean M, Kelsey KT (2020). Firefighter occupation is associated with increased risk for laryngeal and hypopharyngeal squamous cell carcinoma among men from the Greater Boston area. *Occup Environ Med*. 77(6):381–5. doi:10.1136/oemed-2019-106271 PMID:32107319

Larsson F, Andersson P, Blomqvist P, Lorén A, Mellander B-E (2014). Characteristics of lithium-ion batteries during fire tests. *J Power Sources*. 271:414–20. doi:10.1016/j.jpowsour.2014.08.027

Larsson F, Andersson P, Blomqvist P, Mellander BE (2017). Toxic fluoride gas emissions from lithium-ion battery fires. *Sci Rep*. 7(1):10018. doi:10.1038/s41598-017-09784-z PMID:28855553

Lavric ED, Konnov AA, Ruyck JD (2004). Dioxin levels in wood combustion – a review. *Biomass Bioenergy*. 26(2):115–45. doi:10.1016/S0961-9534(03)00104-1

Leary DB, Takazawa M, Kannan K, Khalil N (2020). Perfluoroalkyl substances and metabolic syndrome in firefighters: a pilot study. *J Occup Environ Med*. 62(1):52–7. doi:10.1097/JOM.0000000000001756 PMID:31658221

Lebeaut A, Tran JK, Vujanovic AAJAB (2020). Posttraumatic stress, alcohol use severity, and alcohol use motives among firefighters: the role of anxiety sensitivity. *Addict Behav*. 106:106353. doi:10.1016/j.addbeh.2020.106353 PMID:32087474

Lee DJ, Koru-Sengul T, Hernandez MN, Caban-Martinez AJ, McClure LA, Mackinnon JA, et al. (2020). Cancer risk among career male and female Florida firefighters: evidence from the Florida Firefighter Cancer Registry (1981–2014). *Am J Ind Med*. 63(4):285–99. doi:10.1002/ajim.23086 PMID:31930542

Lee JY, Yamamoto Y, Oe R, Son SY, Wakabayashi H, Tochihara Y (2014). The European, Japanese and US protective helmet, gloves and boots for firefighters: thermoregulatory and psychological evaluations. *Ergonomics*. 57(8):1213–21. doi:10.1080/00140139.2014.914578 PMID:24798188

Lee SC, Sverko E, Harner T, Pozo K, Barresi E, Schachtschneider J, et al. (2016). Retrospective analysis of "new" flame retardants in the global atmosphere under the GAPS Network. *Environ Pollut*. 217:62–9. doi:10.1016/j.envpol.2016.01.080 PMID:26857525

Leon LR (2008). Thermoregulatory responses to environmental toxicants: the interaction of thermal stress and toxicant exposure. *Toxicol Appl Pharmacol*. 233(1):146–61. doi:10.1016/j.taap.2008.01.012 PMID:18313713

Leonard SS, Castranova V, Chen BT, Schwegler-Berry D, Hoover M, Piacitelli C, et al. (2007). Particle size-dependent radical generation from wildland fire smoke. *Toxicology*. 236(1–2):103–13. doi:10.1016/j.tox.2007.04.008 PMID:17482744

Leonard SS, Wang S, Shi X, Jordan BS, Castranova V, Dubick MA (2000). Wood smoke particles generate free radicals and cause lipid peroxidation, DNA damage, NFkappaB activation and TNF-α release in macrophages. *Toxicology*. 150(1–3):147–57. doi:10.1016/S0300-483X(00)00256-0 PMID:10996671

Levasseur JL, Hoffman K, Herkert NJ, Cooper E, Hay D, Stapleton HM (2022). Characterizing firefighter's exposure to over 130 SVOCs using silicone wristbands: a pilot study comparing on-duty and off-duty exposures. *Sci Total Environ*. 834:155237. doi:10.1016/j.scitotenv.2022.155237 PMID:35447169

Levine MS, Radford EP (1978). Occupational exposures to cyanide in Baltimore fire fighters. *J Occup Med*. 20(1):53–6. doi:10.1097/00043764-197801000-00011 PMID:202686

Levy AL, Lum G, Abeles FJ (1976). Carbon monoxide in firemen before and after exposure to smoke. *Ann Clin Lab Sci*. 6(5):455–8. PMID:970930

Lewalter J, Biedermann P, Angerer J, Muller G, Schaller KH, Riffelmann M (1994). Aromatic Amines. In: Angerer J, Schaller KH, Greim H, editors. Analyses of hazardous compounds in biological materials. Weinheim, Germany: Wiley-VCH.

Li Q, Hirata Y, Kawada T, Minami M (2004). Elevated frequency of sister chromatid exchanges of lymphocytes in sarin-exposed victims of the Tokyo sarin disaster 3 years after the event. *Toxicology*. 201(1–3):209–17. doi:10.1016/j.tox.2004.04.014 PMID:15297034

Li Z, Romanoff L, Bartell S, Pittman EN, Trinidad DA, McClean M, et al. (2012). Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chem Res Toxicol*. 25(7):1452–61. doi:10.1021/tx300108e PMID:22663094

Lim GY, Jang TW, Sim CS, Ahn YS, Jeong KS (2020). Comparison of cortisol level by shift cycle in Korean firefighters. *Int J Environ Res Public Health*. 17(13):17. doi:10.3390/ijerph17134760 PMID:32630691

Liou SH, Jacobson-Kram D, Poirier MC, Nguyen D, Strickland PT, Tockman MS (1989). Biological monitoring of fire fighters: sister chromatid exchange and polycyclic aromatic hydrocarbon-DNA adducts in peripheral blood cells. *Cancer Res*. 49(17):4929–35. PMID:2503247

Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenberg J, et al. (2002). Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. *Environ Health Perspect*. 110(7):703–14. doi:10.1289/ehp.02110703 PMID:12117648

Lippmann M, Cohen MD, Chen LC (2015). Health effects of World Trade Center (WTC) Dust: an unprecedented disaster's inadequate risk management. *Crit Rev Toxicol*. 45(6):492–530. doi:10.3109/10408444.2015.1044601 PMID:26058443

Lippmann M, Yeates DB, Albert RE (1980). Deposition, retention, and clearance of inhaled particles. *Br J Ind Med*. 37(4):337–62. doi:10.1136/oem.37.4.337 PMID:7004477

Litten S, McChesney DJ, Hamilton MC, Fowler B (2003). Destruction of the World Trade Center and PCBs, PBDEs, PCDD/Fs, PBDD/Fs, and chlorinated biphenylenes in water, sediment, and sewage sludge. *Environ Sci Technol*. 37(24):5502–10. doi:10.1021/es034480g PMID:14717157

Liu X, Huey G, Yokelson RJ, Selimovic V, Simpson IJ, Muller M, et al. (2017). Airborne measurements of western US wildfire emissions: comparison with prescribed burning and air quality implications. *JGR Atmospheres*. 122(11):6108–29. doi:10.1002/2016JD026315

Loflin MEJPS (1989). NFPA 1500 standard for a fire department OSH program. *Prof Saf*. 34(4):15.

Loke J, Farmer WC, Matthay RA, Virgulto JA, Bouhuys A (1976). Carboxyhemoglobin levels in fire fighters. *Lung*. 154(1):35–9. doi:10.1007/BF02713517 PMID:1018510

London Fire Brigade (2022). Breathing apparatus. The need for firefighters to enter a burning building to enable them to extinguish a fire has always been hindered by the smoke generated from the flames – so breathing apparatus is essential. London Fire Commissioner. Available from: https://www.london-fire.gov.uk/museum/history-and-stories/a-brief-history-of-our-breathing-apparatus/, accessed November 2022.

Lönnermark A, Blomqvist P (2006). Emissions from an automobile fire. *Chemosphere*. 62(7):1043–56. doi:10.1016/j.chemosphere.2005.05.002 PMID:15964054

Lorber M (2008). Exposure of Americans to polybrominated diphenyl ethers. *J Expo Sci Environ Epidemiol*. 18(1):2–19. doi:10.1038/sj.jes.7500572 PMID:17426733

Loupasakis K, Berman J, Jaber N, Zeig-Owens R, Webber MP, Glaser MS, et al. (2015). Refractory sarcoid arthritis in World Trade Center-exposed New York City firefighters: a case series. *J Clin Rheumatol*. 21(1):19–23. doi:10.1097/RHU.0000000000000185 PMID:25539429

Lourel M, Abdellaoui S, Chevaleyre S, Paltrier M, Gana KJNAJoP. (2008). Relationships between psychological job demands, job control and burnout among firefighters. *North Am J Psychol*. 10(3):489–496.

Lowden A, Moreno C, Holmbäck U, Lennernäs M, Tucker P (2010). Eating and shift work - effects on habits, metabolism and performance. *Scand J Work Environ Health*. 36(2):150–62. doi:10.5271/sjweh.2898 PMID:20143038

Lowry WT, Juarez L, Petty CS, Roberts B (1985). Studies of toxic gas production during actual structural fires in the Dallas area. *J Forensic Sci*. 30(1):59–72. doi:10.1520/JFS10965J PMID:3981122

Lui B, Cuddy JS, Hailes WS, Ruby BC (2014). Seasonal heat acclimatization in wildland firefighters. *J Therm Biol*. 45:134–40. doi:10.1016/j.jtherbio.2014.08.009 PMID:25436962

Lumley KPS (1971). Asbestos dust levels inside firefighting helmets with chrysotile asbestos covers. *Ann Occup Hyg*. 14(3):285–6. doi:10.1093/annhyg/14.3.285 PMID:5564914

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA (2006). Cancer incidence in Florida professional firefighters, 1981 to 1999. *J Occup Environ Med*. 48(9):883–8. doi:10.1097/01.jom.0000235862.12518.04 PMID:16966954

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA, Lai H, et al. (2005). Mortality in Florida professional firefighters, 1972 to 1999. *Am J Ind Med*. 47(6):509–17. doi:10.1002/ajim.20160 PMID:15898094

Ma F, Lee DJ, Fleming LE, Dosemeci M (1998). Race-specific cancer mortality in US firefighters: 1984–1993. *J Occup Environ Med*. 40(12):1134–8. PMID:9871891

Macedo RCS, Vieira A, Marin DP, Otton R (2015). Effects of chronic resveratrol supplementation in military firefighters undergo a physical fitness test–a placebo-controlled, double blind study. *Chem Biol Interact*. 227:89–95. doi:10.1016/j.cbi.2014.12.033 PMID:25572586

MacSween K, Paton-Walsh C, Roulston C, Gurette EA, Edwards G, Reisen F, et al. (2020). Cumulative firefighter exposure to multiple toxins emitted during prescribed burns in Australia. *Expo Health*. 12(4):721–33. doi:10.1007/s12403-019-00332-w

Maglio MA, Scott C, Davis AL, Allen J, Taylor JA (2016). Situational pressures that influence firefighters' decision making about personal protective equipment: a qualitative analysis. *Am J Health Behav*. 40(5):555–67. doi:10.5993/AJHB.40.5.2 PMID:27561858

Magrabi SA, Dlugogorski BZ, Jameson GJ (2002). A comparative study of drainage characteristics in AFFF and FFFP compressed-air fire-fighting foams. *Fire Saf J*. 37(1):21–52. doi:10.1016/S0379-7112(01)00024-8

Mahale P, Sturgis EM, Tweardy DJ, Ariza-Heredia EJ, Torres HA (2016). Association between hepatitis C virus and head and neck cancers. *J Natl Cancer Inst*. 108(8):djw035. doi:10.1093/jnci/djw035 PMID:27075854

Main LC, Wolkow A, Raines J, Della Gatta P, Snow R, Aisbett B (2013). The stress of firefighting: Implications for long term health outcomes. Proceedings of the 2012 AFAC & Bushfire CRC Conference Research Forum, 28–31 August 2012, Perth, Australia; pp. 160–169.

Main LC, Wolkow AP, Tait JL, Della Gatta P, Raines J, Snow R, et al. (2020). Firefighter's acute inflammatory response to wildfire suppression. *J Occup Environ Med*. 62(2):145–8. doi:10.1097/JOM.0000000000001775 PMID:31764604

Manno M, Viau C, Cocker J, Colosio C, Lowry L, Mutti A, et al. (2010). Biomonitoring for occupational health risk assessment (BOHRA). *Toxicol Lett*. 192(1):3–16. doi:10.1016/j.toxlet.2009.05.001 PMID:19446015

Marjerrison N, Jakobsen J, Grimsrud TK, Hansen J, Martinsen JI, Nordby KC, et al. (2022). Cancer incidence in sites potentially related to occupational exposures: 58 years of follow-up of firefighters in the Norwegian Fire Departments Cohort. *Scand J Work Environ Health*. 48(3):210–9. doi:10.5271/sjweh.4009 PMID:35015085

Markham RL, Tiffan NM, Kuhlwein LA, Gibbs HM (2016). The experiences of being a full-time firefighter: a qualitative study. The Research and Scholarship Symposium, 20 April 2016, Cedarville University. Cedarville (OH), USA. Available from: https://digitalcommons.cedarville.edu/research_scholarship_symposium/2016/poster_presentations/28/, accessed March 2023.

Markowitz JS, Gutterman EM, Schwartz S, Link B, Gorman SM (1989). Acute health effects among firefighters exposed to a polyvinyl chloride (PVC) fire. *Am J Epidemiol*. 129(5):1023–31. doi:10.1093/oxfordjournals.aje.a115206 PMID:2705423

Markowitz SB, Garibaldi K, Lilis R, Landrigan PJ (1991). Asbestos exposure and fire fighting. *Ann N Y Acad Sci*. 643(1):573–7. doi:10.1111/j.1749-6632.1991.tb24507.x PMID:1809170

Mastromatteo E (1959). Mortality in city firemen. II. A study of mortality in firemen of a city fire department. *AMA Arch Ind Health*. 20:227–33. PMID:14422193

Materna BL, Jones JR, Sutton PM, Rothman N, Harrison RJ (1992). Occupational exposures in California wildland fire fighting. *Am Ind Hyg Assoc J*. 53(1):69–76. doi:10.1080/15298669291359311 PMID:1317093

Matthews HB, Dedrick RL (1984). Pharmacokinetics of PCBs. *Annu Rev Pharmacol Toxicol*. 24(1):85–103. doi:10.1146/annurev.pa.24.040184.000505 PMID:6428301

Mayer AC, Fent KW, Bertke S, Horn GP, Smith DL, Kerber S, et al. (2019). Firefighter hood contamination: efficiency of laundering to remove PAHs and FRs. *J Occup Environ Hyg*. 16(2):129–40. doi:10.1080/15459624.2018.1540877 PMID:30427284

Mayer AC, Fent KW, Chen IC, Sammons D, Toennis C, Robertson S, et al. (2021). Characterizing exposures to flame retardants, dioxins, and furans among firefighters responding to controlled residential fires. *Int J Hyg Environ Health*. 236(2021):113782. doi:10.1016/j.ijheh.2021.113782 PMID:34119852

Mayer AC, Fent KW, Wilkinson A, Chen IC, Kerber S, Smith DL, et al. (2022). Characterizing exposure to benzene, toluene, and naphthalene in firefighters wearing different types of new or laundered PPE. *Int J Hyg Environ Health*. 240:113900. doi:10.1016/j.ijheh.2021.113900 PMID:34902715

Mayer AC, Horn GP, Fent KW, Bertke SJ, Kerber S, Kesler RM, et al. (2020). Impact of select PPE design elements and repeated laundering in firefighter protection from smoke exposure. *J Occup Environ Hyg*. 17(11–12):505–14. doi:10.1080/15459624.2020.1811869 PMID:32990508

McAllister MJ, Basham SA, Smith JW, Waldman HS, Krings BM, Mettler JA, et al. (2018). Effects of environmental heat and antioxidant ingestion on blood markers of oxidative stress in professional firefighters performing structural fire exercises. *J Occup Environ Med*. 60(11):e595–601. doi:10.1097/JOM.0000000000001452 PMID:30252723

McAllister MJ, Gonzalez AE, Waldman HS (2020). Impact of time restricted feeding on markers of cardiometabolic health and oxidative stress in resistance-trained firefighters. *J Strength Cond Res*. 36(9):2515–2522. doi:10.1519/JSC.0000000000003860 PMID:33136772

McAllister MJ, Gonzalez AE, Waldman HS (2021). Time restricted feeding reduces inflammation and cortisol response to a firegrounds test in professional firefighters. *J Occup Environ Med*. 63(5):441–7. doi:10.1097/JOM.0000000000002169 PMID:33928938

McCarley KD, Bunge AL (2001). Pharmacokinetic models of dermal absorption. *J Pharm Sci*. 90(11):1699–719. doi:10.1002/jps.1120 PMID:11745728

McClure LA, Koru-Sengul T, Hernandez MN, Caban-Martinez AJ, Kobetz EN, Lee DJ (2021). Comparing cancer risk estimates using occupational record linkage approaches in male Florida firefighters. *Am J Ind Med*. 64(2):78–83. doi:10.1002/ajim.23205 PMID:33283309

McCormick B, May D (2021). Bushfires and fuel reduction burning. Science, Technology, Environment and Resources Section, Parliament of Australia. Available from: https://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/rp/rp2122/FuelReductionBurning, accessed November 2022.

McGee JK, Chen LC, Cohen MD, Chee GR, Prophete CM, Haykal-Coates N, et al. (2003). Chemical analysis of World Trade Center fine particulate matter for use in toxicologic assessment. *Environ Health Perspect*. 111(7):972–80. doi:10.1289/ehp.5930 PMID:12782501

McGillis Z, Dorman SC, Robertson A, Larivière M, Leduc C, Eger T, et al. (2017). Sleep quantity and quality of Ontario wildland firefighters across a low-hazard fire season. *J Occup Environ Med*. 59(12):1188–96. doi:10.1097/JOM.0000000000001175 PMID:29216017

McKenna ST, Birtles R, Dickens K, Walker RG, Spearpoint MJ, Stec AA, et al. (2018). Flame retardants in UK furniture increase smoke toxicity more than they reduce fire growth rate. *Chemosphere*. 196:429–39. doi:10.1016/j.chemosphere.2017.12.017 PMID:29324384

McKenna ST, Jones N, Peck G, Dickens K, Pawelec W, Oradei S, et al. (2019). Fire behaviour of modern façade materials - understanding the Grenfell Tower fire. *J Hazard Mater*. 368:115–23. doi:10.1016/j.jhazmat.2018.12.077 PMID:30669035

McKinney K, Benson S, Lempert A, Singal M, Wallingford K, Snyder E; Centers for Disease Control and Prevention (CDC) (2002). Occupational exposures to air contaminants at the World Trade Center disaster site–New York, September–October, 2001. *MMWR Morb Mortal Wkly Rep*. 51(21):453–6. PMID:12054422

McMahon CK, Bush PB (1992). Forest worker exposure to airborne herbicide residues in smoke from prescribed fires in the southern United States. *Am Ind Hyg Assoc J*. 53(4):265–72. doi:10.1080/15298669291359636 PMID:1529920

McNamara ML, Semmens EO, Gaskill S, Palmer C, Noonan CW, Ward TJ (2012). Base camp personnel exposure to particulate matter during wildland fire suppression activities. *J Occup Environ Hyg*. 9(3):149–56. doi:10.1080/15459624.2011.652934 PMID:22364357

McQuerry M, Easter EJFT (2022). Wildland firefighting personal protective clothing cleaning practices in the United States. *Fire Technol*. 58(3):1667–88. doi:10.1007/s10694-021-01212-z

Mell WE, Manzello SL, Maranghides A, Butry D, Rehm RGJIJWF (2010). The wildland–urban interface fire problem–current approaches and research needs. *Int J Wildland Fire*. 19(2):238–51. doi:10.1071/WF07131

Meyer EC, Zimering R, Daly E, Knight J, Kamholz BW, Gulliver SB (2012). Predictors of posttraumatic stress disorder and other psychological symptoms in trauma-exposed firefighters. *Psychol Serv*. 9(1):1–15. doi:10.1037/a0026414 PMID:22449083

Miami Dade College (2022). Fire fighter/emergency medical technician – combined. Career technical certificate. Program overview. Miami (FL), USA: Miami Dade College. Available from: https://www.mdc.edu/firefighteremt/, accessed November 2022.

Milbrath MO, Wenger Y, Chang CW, Emond C, Garabrant D, Gillespie BW, et al. (2009). Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. *Environ Health Perspect*. 117(3):417–25. doi:10.1289/ehp.11781 PMID:19337517

Milley SA, Koch I, Fortin P, Archer J, Reynolds D, Weber KP (2018). Estimating the number of airports potentially contaminated with perfluoroalkyl and polyfluoroalkyl substances from aqueous film forming foam: a Canadian example. *J Environ Manage*. 222:122–31. doi:10.1016/j.jenvman.2018.05.028 PMID:29807261

Min J, Jang TW, Ahn YS, Sim CS, Jeong KS (2020). Association between shift work and biological factors including FGF-23, klotho, and serum 25-(OH) vitamin D3 among Korean firefighters: a cross-sectional study. *Sleep*. 43(10):zsaa075. doi:10.1093/sleep/zsaa075 PMID:32347311

Minty BD, Royston D, Jones JG, Smith DJ, Searing CS, Beeley M (1985). Changes in permeability of the alveolar-capillary barrier in firefighters. *Br J Ind Med*. 42(9):631–4. doi:10.1136/oem.42.9.631 PMID:3899161

Miranda AI, Martins V, Cascão P, Amorim JH, Valente J, Borrego C, et al. (2012). Wildland smoke exposure values and exhaled breath indicators in firefighters. *J Toxicol Environ Health A*. 75(13-15):831–43. doi:10.1080/15287394.2012.690686 PMID:22788370

Miranda AI, Martins V, Cascão P, Amorim JH, Valente J, Tavares R, et al. (2010). Monitoring of firefighters exposure to smoke during fire experiments in Portugal. *Environ Int*. 36(7):736–45. doi:10.1016/j.envint.2010.05.009 PMID:20579737

Moen BE, Øvrebø S (1997). Assessment of exposure to polycyclic aromatic hydrocarbons during firefighting by measurement of urinary 1-hydroxypyrene. *J Occup Environ Med*. 39(6):515–9. doi:10.1097/00043764-199706000-00005 PMID:9211208

Moir W, Zeig-Owens R, Daniels RD, Hall CB, Webber MP, Jaber N, et al. (2016). Post-9/11 cancer incidence in World Trade Center-exposed New York City firefighters as compared to a pooled cohort of firefighters from San Francisco, Chicago and Philadelphia (9/11/2001–2009). *Am J Ind Med*. 59(9):722–30. doi:10.1002/ajim.22635 PMID:27582474

Mokoana V, Asante J, Okonkwo J (2021). Brominated flame-retardant composition in firefighter bunker gear and its thermal performance analysis. *J Fire Sci*. 39(3):207–23. doi:10.1177/07349041211001296

Moline J, Herbert R, Nguyen N (2006). Health consequences of the September 11 World Trade Center attacks: a review. *Cancer Invest*. 24(3):294–301. doi:10.1080/07357900600633965 PMID:16809158

Molyneux S, Stec AA, Hull TR (2014). The effect of gas phase flame retardants on fire effluent toxicity. *Polym Degrad Stabil*. 106:36–46. doi:10.1016/j.polymdegradstab.2013.09.013

Monash University (2014). Final report. Australian firefighters' health study. School of Public Health & Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences. Available from: https://www.monash.edu/__data/assets/pdf_file/0005/982355/finalreport2014.pdf, accessed March 2023.

Montague BT, Wipperman MF, Hooper AT, Hamon SC, Crow R, Elemo F, et al. (2021). Anti-SARS-CoV-2 IgA identifies asymptomatic infection in first responders. *J Infect Dis*. 225(4): 578–576. PMID:34636907

Moore BA, Judkins JL, Dyal MA, Schlenk M, Meyer E, Straud CL, et al. (2022). Behavioral and occupational health in military firefighters: an understudied population. *Behav Modif*. 46(3):453–78. doi:10.1177/01454455211033515 PMID:34291696

Moraes AS, Carvalho MA, Boldt RS, Ferreira FB, Griffin L, Ashdown SP (2019a). Assessment of Portuguese firefighters' needs: preliminary results of a pilot study. Paper presented at the 10th International Conference on Applied Human Factors and Ergonomics, 24–28 July 2019, Washington (DC), USA.

Moraes ASP, Boldt R, Carvalho M, Ferreira F (2019b). Portuguese firefighters' perceptions concerning protective gloves. Proceedings of the 19th World Textile Conference-Autex 2019, Ghent, Belgium. Available from: https://openjournals.ugent.be/autex/article/id/63795/, accessed 16 June 2023.

Morgan MS (1997). The biological exposure indices: a key component in protecting workers from toxic chemicals. *Environ Health Perspect*. 105(Suppl 1):105–15. PMID:9114280

Motorykin O, Santiago-Delgado L, Rohlman D, Schrlau JE, Harper B, Harris S, et al. (2015). Metabolism and excretion rates of parent and hydroxy-PAHs in urine collected after consumption of traditionally smoked salmon for Native American volunteers. *Sci Total Environ*. 514:170–7. doi:10.1016/j.scitotenv.2015.01.083 PMID:25659315

Mottaleb MA, Petriello MC, Morris AJ (2020). High-throughput UHPLC-MS/MS measurement of per- and poly-fluorinated alkyl substances in human serum. *J Anal Toxicol*. 44(4):339–47. doi:10.1093/jat/bkz097 PMID:31776573

Muegge CM, Zollinger TW, Song Y, Wessel J, Monahan PO, Moffatt SM (2018). Excess mortality among Indiana firefighters, 1985–2013. *Am J Ind Med*. 61(12):961–7. doi:10.1002/ajim.22918 PMID:30421827

Müller M, Jeske E, Knecht U, van Sittert NJ (1997). S-phenylmercapturic acid. In: Angerer J, Schaller KH, Greim H, editors. Analyses of hazardous compounds in biological materials. Weinheim, Germany: Wiley-VCH.

Munir F, Clemes S, Houdmont J, Randall R (2012). Overweight and obesity in UK firefighters. *Occup Med (Lond)*. 62(5):362–5. doi:10.1093/occmed/kqs077 PMID:22679213

Murphy SA, Beaton RD, Pike KC, Johnson LJIJSM (1999). Occupational stressors, stress responses, and alcohol consumption among professional firefighters: a prospective, longitudinal analysis. *Int J Stress Manag*. 6(3):179–96. doi:10.1023/A:1021934725246

Muscat JE, Wynder EL (1995). Diesel exhaust, diesel fumes, and laryngeal cancer. *Otolaryngol Head Neck Surg*. 112(3):437–40. doi:10.1016/S0194-59989570280-6 PMID:7870446

Musk AW, Monson RR, Peters JM, Peters RK (1978). Mortality among Boston firefighters, 1915–1975. *Br J Ind Med*. 35(2):104–8. PMID:656333

Musk AW, Smith TJ, Peters JM, McLaughlin E (1979). Pulmonary function in firefighters: acute changes in ventilatory capacity and their correlates. *Br J Ind Med*. 36(1):29–34. doi:10.1136/oem.36.1.29 PMID:444439

Naeher LP, Achtemeier GL, Glitzenstein JS, Streng DR, Macintosh D (2006). Real-time and time-integrated $PM_{2.5}$ and CO from prescribed burns in chipped and non-chipped plots: firefighter and community exposure and health implications. *J Expo Sci Environ Epidemiol*. 16(4):351–61. doi:10.1038/sj.jes.7500497 PMID:16736059

Naeher LP, Barr DB, Adetona O, Simpson CD (2013). Urinary levoglucosan as a biomarker for woodsmoke exposure in wildland firefighters. *Int J Occup Environ Health*. 19(4):304–10. doi:10.1179/2049396713Y.0000000037 PMID:24588036

Nammari DR, Hogland W, Marques M, Nimmermark S, Moutavtchi V (2004). Emissions from a controlled fire in municipal solid waste bales. *Waste Manag*. 24(1):9–18. doi:10.1016/j.wasman.2003.08.003 PMID:14672722

National Academies of Sciences, Engineering, and Medicine (2011). Risk assessment of proposed ARFF standards. Washington (DC), USA: The National Academies Press. Available from: https://www.trb.org/Publications/Blurbs/165120.aspx, accessed November 2022.

National Air Quality Modelling & Assessment Unit (2009). Review of emission factors for incident fires. Innovation for efficiency science programme. Science report. SC060037/SR3. Bristol, UK: Environment Agency. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/291186/scho0809bqut-e-e.pdf, accessed March 2023.

National Interagency Coordination Center (2017). Wildland fire summaries and statistics annual report 2017. Boise (ID), USA: National Interagency Coordination Center. Available from: https://www.predictiveservices.nifc.gov/intelligence/2017_statssumm/annual_report_2017.pdf, accessed March 2023.

National Multi-agency Coordination Group (2002). Work/rest guidelines, length of assignment, and rest and recuperation. Email to Geographic Area Multi-agency Coordination Groups, 12 June 2002. Available from: https://gacc.nifc.gov/rmcc/administrative/mac_files/work_rest_guide.htm.

Navarro K (2020). Working in smoke: wildfire impacts on the health of firefighters and outdoor workers and mitigation strategies. *Clin Chest Med*. 41(4):763–9. doi:10.1016/j.ccm.2020.08.017 PMID:33153693

Navarro K, Vaidyanathan A (2020). Notes from the field: understanding smoke exposure in communities and fire camps affected by wildfires – California and Oregon, 2020. Weekly/December 11, 2020. 69(49):1873–1875. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6949a4.htm, accessed November 2022.

Navarro KM, Cisneros R, Noth EM, Balmes JR, Hammond SK (2017). Occupational exposure to polycyclic aromatic hydrocarbon of wildland firefighters at prescribed and wildland fires. *Environ Sci Technol*. 51(11):6461–9. doi:10.1021/acs.est.7b00950 PMID:28498656

Navarro KM, Cisneros R, Schweizer D, Chowdhary P, Noth EM, Balmes JR, et al. (2019b). Incident command post exposure to polycyclic aromatic hydrocarbons and particulate matter during a wildfire. *J Occup Environ Hyg*. 16(11):735–44. doi:10.1080/15459624.2019.1657579 PMID:31545144

Navarro KM, Kleinman MT, Mackay CE, Reinhardt TE, Balmes JR, Broyles GA, et al. (2019a). Wildland firefighter smoke exposure and risk of lung cancer and cardiovascular disease mortality. *Environ Res*. 173:462–8. doi:10.1016/j.envres.2019.03.060 PMID:30981117

Navarro KM, West MR, O'Dell K, Sen P, Chen IC, Fischer EV, et al. (2021). Exposure to particulate matter and estimation of volatile organic compounds across wildland firefighter job tasks. *Environ Sci Technol*. 55(17):11795–804. doi:10.1021/acs.est.1c00847 PMID:34488352

Nawaz N, Troynikov O (2018). Firefighters' protective jackets: fit to female form and its effects on attributes relevant to thermal comfort. *J Occup Environ Hyg*. 15(11):792–802. doi:10.1080/15459624.2018.1506587 PMID:30111264

Neitzel R, Hong O, Quinlan P, Hulea R (2013). Pilot task-based assessment of noise levels among firefighters. *Int J Ind Ergon*. 43(6):479–86. doi:10.1016/j.ergon.2012.05.004 PMID:24443622

Neitzel R, Naeher LP, Paulsen M, Dunn K, Stock A, Simpson CD (2009). Biological monitoring of smoke exposure among wildland firefighters: a pilot study comparing urinary methoxyphenols with personal exposures to carbon monoxide, particular matter, and levoglucosan. *J Expo Sci Environ Epidemiol*. 19(4):349–58. doi:10.1038/jes.2008.21 PMID:18446186

Nelson J, Chalbot M-CG, Tsiodra I, Mihalopoulos N, Kavouras IG (2021). Physicochemical characterization of personal exposures to smoke aerosol and PAHs of wildland firefighters in prescribed fires. *Expo Health*. 13(1):105–88. doi:10.1007/s12403-020-00366-5

NFPA (2001). NFPA 1951, Standard on protective ensemble for USAR operations. Quincy (MA), USA: National Fire Protection Association.

NFPA (2002). NFPA 1975, Standard for station/work uniforms for fire and emergency service. Quincy (MA), USA: National Fire Protection Association.

NFPA (2005). NFPA 1991, Standard on vapor-protective ensembles for hazardous materials emergencies. Quincy (MA), USA: National Fire Protection Association.

NFPA (2012). NFPA 1992, Standard on liquid splash-protective ensembles and clothing for hazardous materials emergencies. Quincy (MA), USA: National Fire Protection Association.

NFPA (2015). NFPA 1977, Standard on protective clothing and equipment for wildland fire fighting. Quincy (MA), USA: National Fire Protection Association.

NFPA (2018). NFPA 1971, Standard on protective ensembles for structural fire fighting and proximity fire fighting. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/codes-and-standards/all-codes-and-standards/list-of-codes-and-standards/detail?code=1971, accessed November 2022.

NFPA (2020a). NFPA 1851. Standard on selection, care, and maintenance of protective ensembles for structural fire fighting and proximity fire fighting. Available from: https://www.nfpa.org/codes-and-standards/all-codes-and-standards/list-of-codes-and-standards/detail?code=1851, accessed November 2022.

NFPA (2020b). Vehicle fires. NFPA Research; pp. 1–6. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/-/media/Files/News-and-Research/Fire-statistics-and-reports/US-Fire-Problem/osvehiclefires.pdf, accessed November 2022.

NFPA (2021a). Fireground exposure of firefighters: a literature review. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/News-and-Research/Data-research-and-tools/Emergency-Responders/Fireground-Exposure-of-Firefighters-A-Literature-Review, accessed November 2022.

NFPA (2021b). Fire loss in the United States. Quincy (MA), USA: National Fire Protection Association. Available from https://www.nfpa.org//-/media/Files/News-and-Research/Fire-statistics-and-reports/US-Fire-Problem/osFireLoss.pdf, accessed November 2022.

NFPA (2021c). Guide for fire and explosion investigations. NFPA 921. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/codes-and-standards/all-codes-and-standards/list-of-codes-and-standards/detail?code=921, accessed November 2022.

NFPA (2022). Needs assessment of US Fire Service. Quincy (MA), USA: National Fire Protection Association. Available from: https://www.nfpa.org/News-and-Research/Data-research-and-tools/Emergency-Responders/Needs-assessment, accessed November 2022.

NIFC (2022a). Fire information statistics. Boise (ID), USA: National Interagency Fire Center. Available from: https://www.nifc.gov/fire-information/statistics, accessed November 2022.

NIFC (2022b). Safety and risk management, Chapter 7. Boise (ID), USA: National Interagency Fire Center. Available from: https://www.nifc.gov/sites/default/files/redbook-files/Chapter07.pdf, accessed November 2022.

NIOSH (1977). Shift work practices in the United States. Prepared by Tasto D, Colligan M. NIOSH Technical Information. DHEW (NIOSH) Publication No. 77-148. Washington (DC), USA: National Institute for Occupational Safety and Health.

NIOSH (1991). Firefighter's exposure to smoke during fire suppression activities at wildland fires. Health Hazard Evaluation Report No. HETA 91-312-2185. Prepared by Kelly J. Gallatin National Forest, Montana. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/hhe/reports/pdfs/1991-0312-2185.pdf, accessed March 2023.

NIOSH (1992a). Health Hazard Evaluation Report No. HETA 91-312-2185. Prepared by Kelly J. Cincinnati (OH), USA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and National Institute for Occupational Safety and Health.

NIOSH (1992b). Health Hazard Evaluation Report No. HETA 92-045-2260. Characterization of fire fighters' exposures to chemical contaminants during fire suppression operations. Prepared by Kelly J. New River Gorge National River, West Virginia. Cincinnati (OH), USA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and National Institute for Occupational Safety and

Health. Available from: http://www.cdc.gov/niosh/hhe/reports/pdfs/1992-0045-2260.pdf.

NIOSH (1992c). Health Hazard Evaluation Report No. HETA 88-320-2176. Prepared by Reh C, Deitchman S. United States Department of the Interior, National Park Service. Yosemite National Park, California. Cincinnati (OH), USA: National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/hhe/reports/pdfs/1988-0320-2176.pdf.

NIOSH (1994a). Health Hazard Evaluation Report No. HETA 90-0365-2415. Prepared by Reh CM, Letts D, Deitchman S. United States Department of Interior, National Park Service, Yosemite National Park, California. Cincinnati (OH), USA: United States Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH (1994b). Nitric oxide and nitrogen dioxide. Method 6014, Issue 1. 15 August 1994. NIOSH manual of analytical methods, Fourth edition. Dated 15 August 1994. Cincinnati (OH), USA: National Institute for Occupational Safety and Health. Available from: http://niosh.dnacih.com/nioshdbs/nmam/pdfs/6014-1.pdf.

NIOSH (1998a). Health Hazard Evaluation Report No. HETA 96-0171-2692. Prepared by Kinnes G, Hine G. Bureau of Alcohol, Tobacco, and Firearms. Cincinnati (OH), USA: National Institute for Occupational Safety and Health.

NIOSH (1998b). Health Hazard Evaluation Report No. 98-0152-2729. Prepared by Sylvain D, Echt A. Wolfeboro public safety building, Wolfeboro, New Hampshire. Cincinnati (OH), USA: National Institute for Occupational Safety and Health.

NIOSH (2001). Health Hazard Evaluation Report No. HETA 99-0266-2850. Costa Mesa Fire Department, Costa Mesa, California, Prepared by Roegner KC, Sieber K, Echt A. Cincinnati (OH), USA: National Institute for Occupational Safety and Health.

NIOSH (2010). Evaluation of chemical and particle exposures during vehicle fire suppression training. Health Hazard Evaluation Report No. HETA 2008-0241-3113. Prepared by Fent KW, Evans DE, Couch J. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH (2013a). Evaluation of dermal exposure to polycyclic aromatic hydrocarbons in fire fighters. Health Hazard Evaluation Report No. 2010-0156-3196. Prepared by Fent KW, Eisenberg J, Evans D, Sammons D, Robertson S, Striley C, et al. Cincinnati (OH), USA: United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH (2013b). Evaluation of chemical exposures during fire fighter training exercises involving smoke simulant. Health Hazard Evaluation Report No. HETA 2012-0028-3190. Prepared by Fent KW, Musolin K, Methner M. Cincinnati (OH), USA: United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH (2015). Hierarchy of controls. Cincinnati (OH), USA: National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/topics/hierarchy/default.html, accessed November 2022.

NIOSH (2016a). Manual of analytical methods, diesel particulate matter (as elemental carbon). Method 5040, Issue 4, 2016. Available from: https://www.cdc.gov/niosh/docs/2014-151/pdfs/methods/5040.pdf, accessed November 2022.

NIOSH (2016b). Evaluation of diesel exhaust exposures at multiple fire stations in a city fire department. Health Hazard Evaluation Report No. 201-0159-3265. Prepared by Couch J, Broadwater K, de Perio MA. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/hhe/reports/pdfs/2015-0159-3265.pdf, accessed 30 August 2022.

NIOSH (2016c). NMAM Method 8321, Issue 1. *o*-Cresol in urine. *RTECS*. GO6300000:1–6. Washington (DC), USA: National Institute for Occupational Safety and Health.

NIOSH (2019). Evaluation of wildland fire fighters' exposures to asbestos during a prescribed burn. Health Hazard Evaluation Report No. 2017-0076-3352. Prepared by Grant MP. Cincinnati (OH), USA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/hhe/reports/pdfs/2017-0076-3352.pdf, accessed 26 August 2022.

Nordgren MD, Goldstein EA, Izeman MA (2002). The environmental impacts of the World Trade Center attacks. A preliminary assessment. February 2002. New York (NY), USA: Natural Resources Defense Council. Available from: https://www.nrdc.org/sites/default/files/wtc.pdf, accessed 2 September 2022.

Nordic Council of Ministers (2019). The cost of inaction. A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS. TemaNord 516. Copenhagen, Denmark: Nordic Council of Ministers.

NSW Rural Fire Service (2022). Service Standard 5.1.9. Respiratory protective equipment. V2.2. 20 January 2022. Sydney (NSW), Australia: NSW Rural Fire Service, New South Wales Government. Available from: https://www.rfs.nsw.gov.au/__data/assets/

pdf_file/0010/8992/5.1.9-Breathing-Apparatus.pdf, accessed November 2022.

NVFC (2010). Critical health and safety issues in the volunteer fire service. Washington (DC), USA: National Volunteer Fire Council. https://www.nvfc.org/wp-content/uploads/2015/09/CriticalHealthSafetyIssues_10_Final.pdf, accessed November 2022.

NWCG (2004). 2004 Work/rest and length of assignment standards. 6 February 2004. Boise (ID), USA: National Wildfire Coordinating Group. Available from: https://www.fs.usda.gov/Internet/FSE_DOCUMENTS/stelprdb5104541.pdf, accessed November 2022.

O'Keefe PW, Silkworth JB, Gierthy JF, Smith RM, DeCaprio AP, Turner JN, et al. (1985). Chemical and biological investigations of a transformer accident at Binghamton, NY. *Environ Health Perspect*. 60:201–9. doi:10.1289/ehp.8560201 PMID:2411536

OECD (2022). Occupational biomonitoring guidance. Paris, France: Organisation for Economic Co-operation and Development. Available from: https://issuu.com/oecd.publishing/docs/occupational-biomonitoring-guidance-document, accessed November 2022.

Offenberg JH, Eisenreich SJ, Chen LC, Cohen MD, Chee G, Prophete C, et al. (2003). Persistent organic pollutants in the dusts that settled across lower Manhattan after September 11, 2001. *Environ Sci Technol*. 37(3):502–8. doi:10.1021/es025730g PMID:12630465

Oliveira M, Costa S, Vaz J, Fernandes A, Slezakova K, Delerue-Matos C, et al. (2020b). Firefighters exposure to fire emissions: impact on levels of biomarkers of exposure to polycyclic aromatic hydrocarbons and genotoxic/oxidative-effects. *J Hazard Mater*. 383:121179. doi:10.1016/j.jhazmat.2019.121179 PMID:31522064

Oliveira M, Delerue-Matos C, Pereira MC, Morais S (2020a). Environmental particulate matter levels during 2017 large forest fires and megafires in the center region of Portugal: a public health concern? *Int J Environ Res Public Health*. 17(3):1032. doi:10.3390/ijerph17031032 PMID:32041266

Oliveira M, Slezakova K, Alves MJ, Fernandes A, Teixeira JP, Delerue-Matos C, et al. (2016). Firefighters' exposure biomonitoring: impact of firefighting activities on levels of urinary monohydroxyl metabolites. *Int J Hyg Environ Health*. 219(8):857–66. doi:10.1016/j.ijheh.2016.07.011 PMID:27449739

Oliveira M, Slezakova K, Alves MJ, Fernandes A, Teixeira JP, Delerue-Matos C, et al. (2017b). Polycyclic aromatic hydrocarbons at fire stations: firefighters' exposure monitoring and biomonitoring, and assessment of the contribution to total internal dose. *J Hazard Mater*. 323(Pt A):184–94. doi:10.1016/j.jhazmat.2016.03.012 PMID:26997333

Oliveira M, Slezakova K, Fernandes A, Teixeira JP, Delerue-Matos C, Pereira MDC, et al. (2017a). Occupational exposure of firefighters to polycyclic aromatic hydrocarbons in non-fire work environments. *Sci Total Environ*. 592:277–87. doi:10.1016/j.scitotenv.2017.03.081 PMID:28319714

Oliveira M, Slezakova K, Magalhães CP, Fernandes A, Teixeira JP, Delerue-Matos C, et al. (2017c). Individual and cumulative impacts of fire emissions and tobacco consumption on wildland firefighters' total exposure to polycyclic aromatic hydrocarbons. *J Hazard Mater*. 334:10–20. doi:10.1016/j.jhazmat.2017.03.057 PMID:28380396

Ontario Association of Fire Chiefs (2022). Firefighters' 24-hour shifts get close look. Ontario Association of Fire Chiefs. Available from: https://www.oafc.on.ca/article/firefighters-24-hour-shifts-get-close-look, accessed November 2022.

Organtini KL, Myers AL, Jobst KJ, Cochran J, Ross B, McCarry B, et al. (2014). Comprehensive characterization of the halogenated dibenzo-p-dioxin and dibenzofuran contents of residential fire debris using comprehensive two-dimensional gas chromatography coupled to time of flight mass spectrometry. *J Chromatogr A*. 1369:138–46. doi:10.1016/j.chroma.2014.09.088 PMID:25441081

Organtini KL, Myers AL, Jobst KJ, Reiner EJ, Ross B, Ladak A, et al. (2015). Quantitative analysis of mixed halogen dioxins and furans in fire debris utilizing atmospheric pressure ionization gas chromatography-triple quadrupole mass spectrometry. *Anal Chem*. 87(20):10368–77. doi:10.1021/acs.analchem.5b02463 PMID:26412694

Ormond RB, Kwon CH, Mathews MC (2019). Performance evaluation of newly developed smoke and particulate resistant structural turnout ensemble. In: Mattson PJ, Marshall J, editors. Homeland security and public safety: research, applications and standards; pp. 286–305. doi:10.1520/STP161420180049

Orris P, Worobec S, Kahn G, Hryhorczuk D, Hessl S (1986). Chloracne in firefighters. *Lancet*. 1(8474):210–1. doi:10.1016/S0140-6736(86)90683-5 PMID:2868232

Ortuño N, Moltó J, Conesa JA, Font R (2014). Formation of brominated pollutants during the pyrolysis and combustion of tetrabromobisphenol A at different temperatures. *Environ Pollut*. 191:31–7. doi:10.1016/j.envpol.2014.04.006 PMID:24792882

Ory C, Leboulleux S, Salvatore D, Le Guen B, De Vathaire F, Chevillard S, et al. (2021). Consequences of atmospheric contamination by radioiodine: the Chernobyl and Fukushima accidents. *Endocrine*. 71(2):298–309. doi:10.1007/s12020-020-02498-9 PMID:33025561

OSHA (2009). Assigned protection factors for the revised respiratory protection standard. OSHA 3352-02. Washington (DC), USA: Occupational Safety and Health Administration, United States Department of Labor. Available from: https://www.osha.gov/sites/default/files/publications/3352-APF-respirators.pdf.

Ouyang B, Baxter CS, Lam HM, Yeramaneni S, Levin L, Haynes E, et al. (2012). Hypomethylation of dual specificity phosphatase 22 promoter correlates with duration of service in firefighters and is inducible by low-dose benzo[*a*]pyrene. *J Occup Environ Med*. 54(7):774–80. doi:10.1097/JOM.0b013e31825296bc PMID:22796920

Pambianchi E, Pecorelli A, Valacchi G (2021). Gastrointestinal tissue as a "new" target of pollution exposure. *IUBMB Life*. 2021:1–12.doi:10.1002/iub.2530 PMID:34289226

Parikh J, Channiwala SA, Ghosal GK (2007). A correlation for calculating elemental composition from proximate analysis of biomass materials. *Fuel*. 86(12–13):1710–9. doi:10.1016/j.fuel.2006.12.029

Park E, Lee YJ, Lee SW, Bang CH, Lee G, Lee JK, et al. (2016). Changes of oxidative/antioxidative parameters and DNA damage in firefighters wearing personal protective equipment during treadmill walking training. *J Phys Ther Sci*. 28(11):3173–7. doi:10.1589/jpts.28.3173 PMID:27942144

Park HS, Ham S, Jeong JH, Kim SJ, Woo H (2022). Examination of factors influencing SCBA washing behavior among firefighters in metropolitan. *Int J Environ Res Public Health*. 19(4):2240. doi:10.3390/ijerph19042240 PMID:35206426

Park JS, Voss RW, McNeel S, Wu N, Guo T, Wang Y, et al. (2015). High exposure of California firefighters to polybrominated diphenyl ethers. *Environ Sci Technol*. 49(5):2948–58. doi:10.1021/es5055918 PMID:25643236

Parliament of Australia (2020). 2019–20 Australian bushfires – frequently asked questions: a quick guide. Research Paper Series, 2019–20. 12 March 2020. Department of Parliamentary Services, Parliament of Australia. Available from: https://parlinfo.aph.gov.au/parlInfo/download/library/prspub/7234762/upload_binary/7234762.pdf, accessed November 2022.

Peaslee GH, Wilkinson JT, McGuinness SR, Tighe M, Caterisano N, Lee S, et al. (2020). Another pathway for firefighter exposure to per- and polyfluoroalkyl substances: firefighter textiles. *Environ Sci Technol Lett*. 7(8):594–9. doi:10.1021/acs.estlett.0c00410

Peck G, Jones N, McKenna ST, Glockling JLD, Harbottle J, Stec AA, et al. (2021). Smoke toxicity of rainscreen façades. *J Hazard Mater*. 403:123694. doi:10.1016/j.jhazmat.2020.123694 PMID:32835994

Pedersen J, Ugelvig Petersen K, Hansen J (2020). Full employment history of Danish firefighters potentially involving additional exposures, 1964-2015. *Am J Ind Med*. 63(4):328–36. doi:10.1002/ajim.23089 PMID:31953961

Pedersen JE, Petersen KU, Hansen J (2019). Historical changes in chemical exposures encountered by Danish firefighters. *Scand J Work Environ Health*. 45(3):248–55. doi:10.5271/sjweh.3784 PMID:30614505

Pepłońska B, Burdelak W, Krysicka J, Bukowska A, Marcinkiewicz A, Sobala W, et al. (2014). Night shift work and modifiable lifestyle factors. *Int J Occup Med Environ Health*. 27(5):693–706. doi:10.2478/s13382-014-0298-0 PMID:25218108

Persson B, Simonson M (1998). Fire emissions into the atmosphere. *Fire Technol*. 34(3):266–79. doi:10.1023/A:1015350024118

Peters B, Ballmann C, Quindry T, Zehner EG, McCroskey J, Ferguson M, et al. (2018). Experimental woodsmoke exposure during exercise and blood oxidative stress. *J Occup Environ Med*. 60(12):1073–81. doi:10.1097/JOM.0000000000001437 PMID:30188494

Peters CE, Nicol AM, Demers PA (2012). Prevalence of exposure to solar ultraviolet radiation (UVR) on the job in Canada. *Can J Public Health*. 103(3):223–6. doi:10.1007/BF03403817 PMID:22905643

Petersen K, Pedersen JE, Bonde JP, Ebbehoej NE, Hansen J (2018a). Long-term follow-up for cancer incidence in a cohort of Danish firefighters. *Occup Environ Med*. 75(4):263–9. doi:10.1136/oemed-2017-104660 PMID:29055884

Petersen KU, Pedersen JE, Bonde JP, Ebbehøj NE, Hansen J (2018b). Mortality in a cohort of Danish firefighters; 1970–2014. *Int Arch Occup Environ Health*. 91(6):759–66. doi:10.1007/s00420-018-1323-6 PMID:29808435

Phan L, McNeel TS, Jewett B, Moose K, Choi K (2022). Trends of cigarette smoking and smokeless tobacco use among US firefighters and law enforcement personnel, 1992–2019. *Am J Ind Med*. 65(1):72–7. doi:10.1002/ajim.23311 PMID:34766643

Phillips KA, Yau A, Favela KA, Isaacs KK, McEachran A, Grulke C, et al. (2018). Suspect screening analysis of chemicals in consumer products. *Environ Sci Technol*. 52(5):3125–35. doi:10.1021/acs.est.7b04781 PMID:29405058

Pierrard H (2016). Interest of the determination of urinary hydroxypyrene among firefighters. *Arch Mal Prof Environ*. 77:636–9. doi:10.1016/j.admp.2015.11.007

Pinas V, Van Dijk C, Weber R (2020). Inventory and action plan for PFOS and related substances in Suriname as basis for Stockholm Convention implementation. *Emerg Contam*. 6:421–31. doi:10.1016/j.emcon.2020.10.002

Pinkerton L, Bertke SJ, Yiin J, Dahm M, Kubale T, Hales T, et al. (2020). Mortality in a cohort of US firefighters from San Francisco, Chicago and Philadelphia: an update. *Occup Environ Med*. 77(2):84–93. doi:10.1136/oemed-2019-105962 PMID:31896615

Pivnenko K, Granby K, Eriksson E, Astrup TF (2017). Recycling of plastic waste: screening for brominated flame retardants (BFRs). *Waste Manag*. 69:101–9. doi:10.1016/j.wasman.2017.08.038 PMID:28869101

Pizzurro DM, Seeley M, Kerper LE, Beck BD (2019). Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based

criteria. *Regul Toxicol Pharmacol*. 106:239–50. doi:10.1016/j.yrtph.2019.05.008 PMID:31078680

Pleil JD, Stiegel MA, Fent KW (2014). Exploratory breath analyses for assessing toxic dermal exposures of firefighters during suppression of structural burns. *J Breath Res*. 8(3):037107. doi:10.1088/1752-7155/8/3/037107 PMID:25190461

Pośniak M (2000). [Chemical hazards in fire-fighting environments]. *Med Pr*. 51(4):335–44. [Polish] PMID:11059406

Poston WS, Haddock CK, Jahnke SA, Jitnarin N, Tuley BC, Kales SN (2011). The prevalence of overweight, obesity, and substandard fitness in a population-based firefighter cohort. *J Occup Environ Med*. 53(3):266–73. doi:10.1097/JOM.0b013e31820af362 PMID:21386691

Poutasse CM, Poston WSC, Jahnke SA, Haddock CK, Tidwell LG, Hoffman PD, et al. (2020). Discovery of firefighter chemical exposures using military-style silicone dog tags. *Environ Int*. 142:105818. doi:10.1016/j.envint.2020.105818 PMID:32521346

Pravaler (2020). [Firefighters – learn all about the profession]. Pinheiros, Portugal: Pravaler. Available from: https://www.pravaler.com.br/bombeiros-saiba-tudo-sobre-a-profissao/, accessed 13 June 2022. [Portuguese]

Prezant DJ, Barker RL, Stull JO, King SJ, Rotanz RA, Malley KS, et al. (2001). The impact of protective hoods and their water content on the prevention of head burns in New York City firefighters: laboratory tests and field results. *J Burn Care Rehabil*. 22(2):165–78, discussion 163–4. doi:10.1097/00004630-200103000-00015 PMID:11302606

Pronk A, Coble J, Stewart PA (2009). Occupational exposure to diesel engine exhaust: a literature review. *J Expo Sci Environ Epidemiol*. 19(5):443–57. doi:10.1038/jes.2009.21 PMID:19277070

Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggvadottir L, et al. (2014). Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med*. 71(6):398–404. doi:10.1136/oemed-2013-101803 PMID:24510539

Purser DA, Maynard RL (2015). Overview of combustion toxicology. Chapter 1. In: Purser DA, Maynard RL, Wakefield JC, editors. Toxicology, survival and health hazards of combustion products. Washington (DC), USA: Royal Society of Chemistry. doi:10.1039/9781849737487-00001

Purser DA, Stec AA, Hull TR (2010). Fire scenarios and combustion conditions. *Fire Toxicity*. 26–50. doi:10.1533/9781845698072.1.26

Rabajczyk A, Zielecka M, Małozięć D (2020). Hazards resulting from the burning wood impregnated with selected chemical compounds. *Appl Sci (Basel)*. 10(17):6093. doi:10.3390/app10176093

Radeloff VC, Helmers DP, Kramer HA, Mockrin MH, Alexandre PM, Bar-Massada A, et al. (2018). Rapid growth of the US wildland-urban interface raises wildfire risk. *Proc Natl Acad Sci USA*. 115(13):3314–9. doi:10.1073/pnas.1718850115 PMID:29531054

Radford EP, Levine MS (1976). Occupational exposures to carbon monoxide in Baltimore firefighters. *J Occup Med*. 18(9):628–32. PMID:966096

Ramesh A, Walker SA, Hood DB, Guillén MD, Schneider K, Weyand EH (2004). Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *Int J Toxicol*. 23(5):301–33. doi:10.1080/10915810490517063 PMID:15513831

Ramsden R, Smith J, Turcotte K, Garis L, Kunz K, Maxim P, et al. (2018). Determinants of injury and death in Canadian firefighters: a case for a national firefighter wellness surveillance system. A report by the BC Injury Research and Prevention Unit, for the University of the Fraser Valley. Abbortsford (BC), Canada: British Columbia Injury Research and Prevention Unit.

Ranadive SM, Lofrano-Porto A, Soares EMKVK, Eagan L, Porto LGG, Smith DL (2021). Low testosterone and cardiometabolic risks in a real-world study of US male firefighters. *Sci Rep*. 11(1):14189. doi:10.1038/s41598-021-93603-z PMID:34244582

Rauma M, Boman A, Johanson G (2013). Predicting the absorption of chemical vapours. *Adv Drug Deliv Rev*. 65(2):306–14. doi:10.1016/j.addr.2012.03.012 PMID:22465561

Ray MR, Basu C, Mukherjee S, Roychowdhury S, Lahiri T (2005). Micronucleus frequencies and nuclear anomalies in exfoliated buccal epithelial cells of firefighters. *Int J Hum Genet*. 05(01):45–8. doi:10.1080/09723757.2005.11885915

Rebmann T, Charney RL, Loux TM, Turner JA, Nguyen D (2019). Firefighters' and emergency medical service personnel's knowledge and training on radiation exposures and safety: results from a survey. *Health Secur*. 17(5):393–402. doi:10.1089/hs.2019.0086 PMID:31593509

Reeder FF, Joos AE (2019). Fire and emergency services instructor: principles and practice: principles and practice. Jones & Bartlett Learning.

Reinhardt T, Ottmar R (2000). Smoke exposure at western wildfires. Portland (OR), USA: United States Department of Agriculture, Pacific Northwest Research Station. doi:10.2737/PNW-RP-525

Reinhardt T, Ottmar R, Hanneman A (2000). Smoke exposure among firefighters at prescribed burns in the Pacific Northwest. Research Paper PNW-RP-526. Portland (OR), USA: Department of Agriculture, Forest Service, Pacific Northwest Research Station. doi:10.2737/PNW-RP-526

Reinhardt TE, Broyles G (2019). Factors affecting smoke and crystalline silica exposure among wildland firefighters. *J Occup Environ Hyg*. 16(2):151–64. doi:10.1080/15459624.2018.1540873 PMID:30407130

Reinhardt TE, Ottmar RD (2004). Baseline measurements of smoke exposure among wildland firefighters. *J Occup Environ Hyg.* 1(9):593–606. doi:10.1080/15459620490490101 PMID:15559331

Reisen F, Brown S, Cheng M (2006). Air toxics in bushfire smoke: firefighter's exposure during prescribed burns. *For Ecol Manage.* 234:S144. doi:10.1016/j.foreco.2006.08.191

Reisen F, Brown SK (2009). Australian firefighters' exposure to air toxics during bushfire burns of autumn 2005 and 2006. *Environ Int.* 35(2):342–52. doi:10.1016/j.envint.2008.08.011 PMID:18829114

Reisen F, Hansen D, Meyer CP (2011). Exposure to bushfire smoke during prescribed burns and wildfires: firefighters' exposure risks and options. *Environ Int.* 37(2):314–21. doi:10.1016/j.envint.2010.09.005 PMID:20956017

Ribeiro LM, Viegas DX, Almeida M, McGee TK, Pereira MG, Parente J, et al. (2020). Extreme wildfires and disasters around the world: lessons to be learned. Chapter 2. In: Tedim F, Leone V, McGee TK, editors. Extreme wildfire events and disasters. Elsevier; pp. 31–51. doi:10.1016/B978-0-12-815721-3.00002-3

Ricaud G, Lim D, Bernier J (2021). Environmental exposition to aromatic hydrocarbon receptor ligands modulates the CD4+ T lymphocyte subpopulations profile. *Expo Health.* 13(3):307–22. doi:10.1007/s12403-021-00385-w

Richter K, Peter L, Rodenbeck A, Weess HG, Riedel-Heller SG, Hillemacher T (2021). Shiftwork and alcohol consumption: a systematic review of the literature. *Eur Addict Res.* 27(1):9–15. doi:10.1159/000507573 PMID:32454482

Risak MJELLJ (2019). The position of volunteers in EU-working time law. *European Labour Law Journal.* 10(4):362–9. doi:10.1177/2031952519886150

Robinson MS, Anthony TR, Littau SR, Herckes P, Nelson X, Poplin GS, et al. (2008). Occupational PAH exposures during prescribed pile burns. *Ann Occup Hyg.* 52(6):497–508. doi:10.1093/annhyg/men027 PMID:18515848

Rodkey FL, Hill TA, Pitts LL, Robertson RF (1979). Spectrophotometric measurement of carboxyhemoglobin and methemoglobin in blood. *Clin Chem.* 25(8):1388–93. doi:10.1093/clinchem/25.8.1388 PMID:455674

Rom WN, Reibman J, Rogers L, Weiden MD, Oppenheimer B, Berger K, et al. (2010). Emerging exposures and respiratory health: World Trade Center dust. *Proc Am Thorac Soc.* 7(2):142–5. doi:10.1513/pats.200908-092RM PMID:20427588

Rom WN, Weiden M, Garcia R, Yie TA, Vathesatogkit P, Tse DB, et al. (2002). Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med.* 166(6):797–800. doi:10.1164/rccm.200206-576OC PMID:12231487

Ronnee A, O'Connor PF, editors (2020). NIOSH manual of analytical methods (NMAM). 5th Edition. Cincinnati (OH), USA: National Institute for Occupational Safety and Health. February 2020. Available from: https://www.cdc.gov/niosh/nmam/pdf/NMAM_5thEd_EBook-508-final.pdf.

Rønning L (2002). The Working Time Directive revisited: EPSU campaign to strengthen the EU directive. *Transfer.* 8(1):131–5. doi:10.1177/102425890200800121

Rossbach B, Wollschläger D, Letzel S, Gottschalk W, Muttray A (2020). Internal exposure of firefighting instructors to polycyclic aromatic hydrocarbons (PAH) during live fire training. *Toxicol Lett.* 331:102–11. doi:10.1016/j.toxlet.2020.05.024 PMID:32464238

Rosting C, Olsen R (2020). Biomonitoring of the benzene metabolite *S*-phenylmercapturic acid and the toluene metabolite *S*-benzylmercapturic acid in urine from firefighters. *Toxicol Lett.* 329:20–5. doi:10.1016/j.toxlet.2020.04.018 PMID:32380125

Rotander A, Kärrman A, Toms LM, Kay M, Mueller JF, Gómez Ramos MJ (2015a). Novel fluorinated surfactants tentatively identified in firefighters using liquid chromatography quadrupole time-of-flight tandem mass spectrometry and a case–control approach. *Environ Sci Technol.* 49(4):2434–42. doi:10.1021/es503653n PMID:25611076

Rotander A, Toms L-ML, Aylward L, Kay M, Mueller JF (2015b). Elevated levels of PFOS and PFHxS in firefighters exposed to aqueous film forming foam (AFFF). *Environ Int.* 82:28–34. doi:10.1016/j.envint.2015.05.005 PMID:26001497

Rothman N, Correa-Villaseñor A, Ford DP, Poirier MC, Haas R, Hansen JA, et al. (1993). Contribution of occupation and diet to white blood cell polycyclic aromatic hydrocarbon-DNA adducts in wildland firefighters. *Cancer Epidemiol Biomarkers Prev.* 2(4):341–7. PMID:8348057

Rothman N, Shields PG, Poirier MC, Harrington AM, Ford DP, Strickland PT (1995). The impact of glutathione s-transferase M1 and cytochrome P450 1A1 genotypes on white-blood-cell polycyclic aromatic hydrocarbon-DNA adduct levels in humans. *Mol Carcinog.* 14(1):63–8. doi:10.1002/mc.2940140111 PMID:7546226

Ruokojärvi P, Aatamila M, Ruuskanen J (2000). Toxic chlorinated and polyaromatic hydrocarbons in simulated house fires. *Chemosphere.* 41(6):825–8. doi:10.1016/S0045-6535(99)00549-4 PMID:10864154

Saghir SA (2019). Determination of ADME and bioavailability following intravenous, oral, and dermal routes of exposure. *Current Protocols in Toxicology.* PMID:22714106

Saijo Y, Ueno T, Hashimoto Y (2012). Post-traumatic stress disorder and job stress among firefighters of urban Japan. *Prehosp Disaster Med.* 27(1):59–63. doi:10.1017/S1049023X12000222 PMID:22591931

Salama KF, Bashawri LA (2017). Biochemical and hematological changes among Saudi firefighters in the eastern province. *Int J Environ Health Eng.* 6(1):2. doi:10.4103/ijehe.ijehe_12_15

Sama SR, Martin TR, Davis LK, Kriebel D (1990). Cancer incidence among Massachusetts firefighters, 1982-1986. *Am J Ind Med.* 18(1):47–54. doi:10.1002/ajim.4700180106 PMID:2378369

San-Miguel-Ayanz J, Durrant T, Boca R, Maianti P, Libertá G, Artés-Vivancos T, et al. (2022). Forest fires in Europe, Middle East and North Africa 2021. EUR 31269 EN. Luxembourg: Publications Office of the European Union. Available from: https://publications.jrc.ec.europa.eu/repository/handle/JRC130846, accessed March 2023. doi:10.2760/34094

Santos JAR, Fernandes RJ, Zacca R (2020). Multimicronutrient supplementation and immunoglobulin response in well-fed firefighters. *Sports Med Int Open.* 5(1):E1–7. doi:10.1055/a-1296-1486 PMID:33376770

Santos PM, Del Nogal Sánchez M, Pérez Pavón JL, Cordero BM, Fernández RV (2019). Liquid-liquid extraction-programmed temperature vaporizer-gas chromatography-mass spectrometry for the determination of polycyclic aromatic hydrocarbons in saliva samples. Application to the occupational exposure of firefighters. *Talanta.* 192:69–78. doi:10.1016/j.talanta.2018.09.030 PMID:30348431

Schade WJ, Swanson GM (1988). Comparison of death certificate occupation and industry data with lifetime occupational histories obtained by interview: variations in the accuracy of death certificate entries. *Am J Ind Med.* 14(2):121–36. doi:10.1002/ajim.4700140203 PMID:3207099

Schafer K, Sutter R, Gibbons S (2015). Characteristics of individuals and employment among first responders. Washington (DC), USA: Chief Evaluation Office, United States Department of Labor. Available from: https://www.hsdl.org/?view&did=803088, accessed November 2022.

Scheepers PT, Bos PM, Konings J, Janssen NA, Grievink L (2011). Application of biological monitoring for exposure assessment following chemical incidents: a procedure for decision making. *J Expo Sci Environ Epidemiol.* 21(3):247–61. doi:10.1038/jes.2010.4 PMID:20336049

Schenk L, Hansson SO, Rudén C, Gilek M (2008). Occupational exposure limits: a comparative study. *Regul Toxicol Pharmacol.* 50(2):261–70. doi:10.1016/j.yrtph.2007.12.004 PMID:18226844

Schnell T, Suhr F, Weierstall-Pust R (2020). Posttraumatic stress disorder in volunteer firefighters: influence of specific risk and protective factors. *Eur J Psychotraumatol.* 11(1):1764722. doi:10.1080/20008198.2020.1764722 PMID:33029308

Schraufnagel DE (2020). The health effects of ultrafine particles. *Exp Mol Med.* 52(3):311–7. doi:10.1038/s12276-020-0403-3 PMID:32203102

Schrey A, Halme E, Ventelä S, Laine J, Irjala H (2013). PP020: extramedullary malignant tumors in the head and neck region – a case report. *Oral Oncol.* 49:S100. doi:10.1016/j.oraloncology.2013.03.263

Sebastião R, Sorte S, Fernandes JM, Miranda AI (2021). Classification of critical levels of CO exposure of firefighters through monitored heart rate. *Sensors (Basel).* 21(5):1561. doi:10.3390/s21051561 PMID:33668116

Secretariat of the Stockholm Convention (2019a). PFAS. Overview. Industrial POPs. Geneva, Switzerland: Secretariat of the Stockholm Convention, United Nations Environment Programme. Available from: http://chm.pops.int/Implementation/IndustrialPOPs/PFOS/Overview/tabid/5221/Default.aspx, accessed November 2022.

Secretariat of the Stockholm Convention (2019b). BDEs. Overview. Industrial POPs. Geneva, Switzerland: Secretariat of the Stockholm Convention, United Nations Environment Programme. Available from: https://www.pops.int/Implementation/IndustrialPOPs/BDEs/Overview/tabid/5371/Default.aspx, accessed 25 May 2023.

Semmens EO, Domitrovich J, Conway K, Noonan CW (2016). A cross-sectional survey of occupational history as a wildland firefighter and health. *Am J Ind Med.* 59(4):330–5. doi:10.1002/ajim.22566 PMID:26792645

Sharkey M, Harrad S, Abou-Elwafa Abdallah M, Drage DS, Berresheim H (2020). Phasing-out of legacy brominated flame retardants: the UNEP Stockholm Convention and other legislative action worldwide. *Environ Int.* 144:106041. doi:10.1016/j.envint.2020.106041 PMID:32822924

Shaw SD, Berger ML, Harris JH, Yun SH, Wu Q, Liao C, et al. (2013). Persistent organic pollutants including polychlorinated and polybrominated dibenzo-*p*-dioxins and dibenzofurans in firefighters from Northern California. *Chemosphere.* 91(10):1386–94. doi:10.1016/j.chemosphere.2012.12.070 PMID:23395527

Shelley CH, Cole AR, Markley TE (2007). Industrial firefighting for municipal firefighters. Fire Engineering Books.

Shemwell BE, Levendis YA (2000). Particulates generated from combustion of polymers (plastics). *J Air Waste Manag Assoc.* 50(1):94–102. doi:10.1080/10473289.2000.10463994 PMID:10680369

Shen B, Whitehead TP, Gill R, Dhaliwal J, Brown FR, Petreas M, et al. (2018). Organophosphate flame retardants in dust collected from United States fire stations. *Environ Int.* 112:41–8. doi:10.1016/j.envint.2017.12.009 PMID:29247842

Shen B, Whitehead TP, McNeel S, Brown FR, Dhaliwal J, Das R, et al. (2015). High levels of polybrominated diphenyl ethers in vacuum cleaner dust from California fire stations. *Environ Sci Technol.* 49(8):4988–94. doi:10.1021/es505463g PMID:25798547

Shen MJ, Zipes DP (2014). Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res*. 114(6):1004–21. doi:10.1161/CIRCRESAHA.113.302549 PMID:24625726

Shepardson D (2021). US urges airports to avoid using firefighting foam with fluorine. 5 October 2021. Reuters. Available from: https://www.reuters.com/business/environment/us-urges-airports-avoid-using-firefighting-foam-with-fluorine-2021-10-04/, accessed November 2022.

Shin HS, Ahn HS, Lee BH (2007). Determination of thiazolidine-4-carboxylates in urine by chloroformate derivatization and gas chromatography-electron impact mass spectrometry. *J Mass Spectrom*. 42(9):1225–32. doi:10.1002/jms.1255 PMID:17610311

Shinde A, Ormond RB (2020). Development of a headspace sampling–gas chromatography–mass spectrometry method for the analysis of fireground contaminants on firefighter turnout materials, ACS. *J Chem Health Saf*. 27(6):352–61. doi:10.1021/acs.chas.0c00041

Singh A, Liu C, Putman B, Zeig-Owens R, Hall CB, Schwartz T, et al. (2018). Predictors of asthma/COPD overlap in FDNY firefighters with World Trade Center dust exposure: a longitudinal study. *Chest*. 154(6):1301–10. doi:10.1016/j.chest.2018.07.002 PMID:30028968

Sjöström M, Julander A, Strandberg B, Lewné M, Bigert C (2019a). Dermal PAH exposure in Swedish firefighters and police forensic investigators - preliminary results from tape stripping on wrist and collarbone. 36/OEM-EPI.23. *Occup Environ Med*. 76(Suppl 1):A1–109. Available from: https://oem.bmj.com/content/oemed/76/Suppl_1/A9.1.full.pdf.

Sjöström M, Julander A, Strandberg B, Lewné M, Bigert C (2019b). Airborne and dermal exposure to polycyclic aromatic hydrocarbons, volatile organic compounds, and particles among firefighters and police investigators. *Ann Work Expo Health*. 63(5):533–45. doi:10.1093/annweh/wxz030 PMID:31111145

Slaughter JC, Koenig JQ, Reinhardt TE (2004). Association between lung function and exposure to smoke among firefighters at prescribed burns. *J Occup Environ Hyg*. 1(1):45–9. doi:10.1080/15459620490264490 PMID:15202156

Slottje P, Bijlsma JA, Smidt N, Twisk JWR, Huizink AC, Lems WF, et al. (2005). Epidemiologic study of the autoimmune health effects of a cargo aircraft disaster. *Arch Intern Med*. 165(19):2278–85. doi:10.1001/archinte.165.19.2278 PMID:16246995

Slottje P, Smidt N, Twisk JWR, Huizink AC, Witteveen AB, van Mechelen W, et al. (2006). Attribution of physical complaints to the air disaster in Amsterdam by exposed rescue workers: an epidemiological study using historic cohorts. *BMC Public Health*. 6(1):142. doi:10.1186/1471-2458-6-142 PMID:16734887

Slottje P, Twisk JWR, Smidt N, Huizink AC, Witteveen AB, van Mechelen W, et al. (2007). Health-related quality of life of firefighters and police officers 8.5 years after the air disaster in Amsterdam. *Qual Life Res*. 16(2):239–52. doi:10.1007/s11136-006-9006-2 PMID:17091369

Slottje P, Witteveen AB, Twisk JWR, Smidt N, Huizink AC, van Mechelen W, et al. (2008). Post-disaster physical symptoms of firefighters and police officers: role of types of exposure and post-traumatic stress symptoms. *Br J Health Psychol*. 13(Pt 2):327–42. doi:10.1348/135910707X198793 PMID:17535500

Sluiter JK, Frings-Dresen MHJE (2007). What do we know about ageing at work? Evidence-based fitness for duty and health in fire fighters. *Ergonomics*. 50(11):1897–913. doi:10.1080/00140130701676005 PMID:17972208

Smith BW, Ortiz JA, Steffen LE, Tooley EM, Wiggins KT, Yeater EA, et al. (2011). Mindfulness is associated with fewer PTSD symptoms, depressive symptoms, physical symptoms, and alcohol problems in urban firefighters. *J Consult Clin Psychol*. 79(5):613–7. doi:10.1037/a0025189 PMID:21875175

Smith DL, Dyer K, Petruzzello SJ (2004). Blood chemistry and immune cell changes during 1 week of intensive firefighting training. *J Therm Biol*. 29(7–8):725–9. doi:10.1016/j.jtherbio.2004.08.046

Smith DL, Haller JM, Hultquist EM, Lefferts WK, Fehling PC (2013a). Effect of clothing layers in combination with fire fighting personal protective clothing on physiological and perceptual responses to intermittent work and on materials performance test results. *J Occup Environ Hyg*. 10(5):259–69. doi:10.1080/15459624.2013.769841 PMID:23472953

Smith DL, Horn GP, Fernhall B, Kesler RM, Fent KW, Kerber S, et al. (2019). Electrocardiographic responses following live-fire firefighting drills. *J Occup Environ Med*. 61(12):1030–5. doi:10.1097/JOM.0000000000001730 PMID:31599801

Smith DL, Manning TS, Petruzzello SJJE (2001). Effect of strenuous live-fire drills on cardiovascular and psychological responses of recruit firefighters. *Ergonomics*. 44(3):244–54. doi:10.1080/00140130121115 PMID:11219758

Smith DL, Petruzzello SJ, Chludzinski MA, Reed JJ, Woods JA (2005). Selected hormonal and immunological responses to strenuous live-fire firefighting drills. *Ergonomics*. 48(1):55–65. doi:10.1080/00140130412331303911 PMID:15764306

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*. 124(6):713–21. doi:10.1289/ehp.1509912 PMID:26600562

Smith RM, O'Keefe PW, Hilker DR, Jelus-Tyror BL, Aldous KM (1982). Analysis for 2,3,7,8-tetrachlorodibenzofuran and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in a soot sample from a transformer explosion in

Binghamton, New York. *Chemosphere*. 11(8):715–20. doi:10.1016/0045-6535(82)90100-X

Smith TD, DeJoy DM, Dyal MA (2020). Safety specific transformational leadership, safety motivation and personal protective equipment use among firefighters. *Saf Sci*. 131:104930. doi:10.1016/j.ssci.2020.104930 PMID:34611382

Smith TD, Herron R, Le A, Wilson JK, Marion J, Vicenzi DA (2018). Assessment of confined space entry and rescue training for aircraft rescue and fire fighting (ARFF) members in the United States. *J Safety Res*. 67:77–82. doi:10.1016/j.jsr.2018.09.014 PMID:30553432

Smith WR, Montopoli G, Byerly A, Montopoli M, Harlow H, Wheeler AR 3rd (2013b). Mercury toxicity in wildland firefighters. *Wilderness Environ Med*. 24(2):141–5. doi:10.1016/j.wem.2013.01.004 PMID:23453729

Sol E, Martín NR (2015). Governance of EU labour law: implementation of the EU Working Time Directive in the Netherlands. In: Barbier JC, Rogowski R, Colomb F, editors. The sustainability of the European social model. Edward Elgar Publishing. doi:10.4337/9781781951767.00018

Sparer EH, Prendergast DP, Apell JN, Bartzak MR, Wagner GR, Adamkiewicz G, et al. (2017). Assessment of ambient exposures firefighters encounter while at the fire station: an exploratory study. *J Occup Environ Med*. 59(10):1017–23. doi:10.1097/JOM.0000000000001114 PMID:28991807

Spelce D, Rehak TR, Metzler RW, Johnson JS (2018). History of US respirator approval. *J Int Soc Respir Prot*. 35(1):35–46. PMID:32476728

Sritharan J, Kirkham TL, MacLeod J, Marjerrison N, Lau A, Dakouo M, et al. (2022). Cancer risk among firefighters and police in the Ontario workforce. *Occup Environ Med*. 79(8):533–9. doi:10.1136/oemed-2021-108146 PMID:35354650

Stacey B (2019). Measurement of ultrafine particles at airports: a review. *Atmos Environ*. 198:463–77. doi:10.1016/j.atmosenv.2018.10.041

Stang A, Jöckel KH, Baumgardt-Elms C, Ahrens W (2003). Firefighting and risk of testicular cancer: results from a German population-based case-control study. *Am J Ind Med*. 43(3):291–4. doi:10.1002/ajim.10178 PMID:12594776

Staskal DF, Hakk H, Bauer D, Diliberto JJ, Birnbaum LS (2006). Toxicokinetics of polybrominated diphenyl ether congeners 47, 99, 100, and 153 in mice. *Toxicol Sci*. 94(1):28–37. doi:10.1093/toxsci/kfl091 PMID:16936226

State of California (2021). California's wildfire and forest resilience action plan. A comprehensive strategy of the Governor's forest management task force. January 2021. Forest Management Task Force. State of California. Available from: https://wildfiretaskforce.org/wp-content/uploads/2022/12/californiawildfireandforestresilienceactionplan.pdf, accessed May 2023.

Statistics Canada (2018). Occupation - National Occupational Classification (NOC) 2016 (693A), Class of Worker (5A), Labour Force Status (3), Age (13A) and Sex (3) for the Labour Force Aged 15 Years and Over in Private Households of Canada, Provinces and Territories, Census Metropolitan Areas and Census Agglomerations, 2016 Census - 25% Sample Data - Occupation - National Occupational Classification (NOC) 2016 (693A), Class of Worker (5A), Labour Force Status (3), Age (13A) and Sex (3) for the Labour Force Aged 15 Years and Over in Private Households of Canada, Provinces and Territories, Census Metropolitan Areas and Census Agglomerations, 2016 Census - 25% Sample Data [XML files]. Created 28 March 2018. Government of Canada. Available from https://www12.statcan.gc.ca/open-gc-ouvert/?CTLG=98-400-X2016294, accessed February 2023.

Stec A (2017). Fire toxicity - the elephant in the room? *Fire Saf J*. 91:79–90. doi:10.1016/j.firesaf.2017.05.003

Stec AA, Dickens K, Barnes JLJ, Bedford C (2019). Environmental contamination following the Grenfell Tower fire. *Chemosphere*. 226:576–86. doi:10.1016/j.chemosphere.2019.03.153 PMID:30953902

Stec AA, Dickens KE, Salden M, Hewitt FE, Watts DP, Houldsworth PE, et al. (2018). Occupational exposure to polycyclic aromatic hydrocarbons and elevated cancer incidence in firefighters. *Sci Rep*. 8(1):2476. doi:10.1038/s41598-018-20616-6 PMID:29410452

Stec AA, Hull TR (2008). *Fire toxicity*. Cambridge, England: Woodhead Publishing.

Stec AA, Hull TR (2011). Assessment of the fire toxicity of building insulation materials. *Energy Build*. 43(2–3):498–506. doi:10.1016/j.enbuild.2010.10.015

Stec AA, Hull TR, Lebek K, Purser JA, Purser DA (2007). The effect of temperature and ventilation condition on the toxic product yields from burning polymers. *Fire Mater*. 32(1):49–60. doi:10.1002/fam.955

Stec AA, Readman J, Blomqvist P, Gylestam D, Karlsson D, Wojtalewicz D, et al. (2013). Analysis of toxic effluents released from PVC carpet under different fire conditions. *Chemosphere*. 90(1):65–71. doi:10.1016/j.chemosphere.2012.07.037 PMID:22960058

Steenland K, Beaumont J (1984). The accuracy of occupation and industry data on death certificates. *J Occup Med*. 26(4):288–96. PMID:6716197

Stein SM, Menakis J, Carr M, Comas S, Stewart S, Cleveland H, et al. (2013). Wildfire, wildlands, and people: understanding and preparing for wildfire in the wildland-urban interface. A Forests on the Edge report. Gen. Tech. Rep. RMRS-GTR-299. Fort Collins (CO), USA: United States Department of Agriculture, Forest Service, Rocky Mountain Research Station. Available from: https://www.fs.usda.gov/rm/pubs/rmrs_gtr299.pdf, accessed May 2023.

Stewart RD, Stewart RS, Stamm W, Seelen RP (1976). Rapid estimation of carboxyhemoglobin level in fire fighters. *JAMA*. 235(4):390–2. doi:10.1001/jama.1976.03260300016021 PMID:946082

Strandberg B, Julander A, Sjöström M, Lewné M, Hatice KA, Bigert C (2018). An improved method for determining dermal exposure to polycyclic aromatic hydrocarbons. *Chemosphere*. 198:274–80. doi:10.1016/j.chemosphere.2018.01.104 PMID:29421739

Stull JO, Dodgen CR, Connor MB, McCarthy RT (1996). Evaluating the effectiveness of different laundering approaches for decontaminating structural fire fighting protective clothing. In: Johnson S, Mansdorf SZ, editors. Performance of protective clothing. 5th volume. American Society for Testing and Materials. doi:10.1520/STP14086S

Sturk D, Rosell L, Blomqvist P, Ahlberg Tidblad A (2019). Analysis of Li-ion battery gases vented in an inert atmosphere thermal test chamber. *Batteries*. 5(3):61. doi:10.3390/batteries5030061

Sugi MT, Fedenko AN, Menendez LR, Allison DC (2013). Clavicular eosinophilic granuloma causing adult shoulder pain. *Rare Tumors*. 5(1):e8. doi:10.4081/rt.2013.e8 PMID:23772307

Suokas K (2015). [Forest resource data and its usage]. Savonia University of Applied Sciences, Emergency Services College. Available from: https://www.theseus.fi/bitstream/handle/10024/90421/Suokas_Kim_PeO_AMKN10.pdf?sequence=1&isAllowed=y, accessed March 2023. [Finnish]

Swiston JR, Davidson W, Attridge S, Li GT, Brauer M, van Eeden SF (2008). Wood smoke exposure induces a pulmonary and systemic inflammatory response in firefighters. *Eur Respir J*. 32(1):129–38. doi:10.1183/09031936.00097707 PMID:18256060

Tak S, Bernard BP, Driscoll RJ, Dowell CH (2007). Floodwater exposure and the related health symptoms among firefighters in New Orleans, Louisiana 2005. *Am J Ind Med*. 50(5):377–82. doi:10.1002/ajim.20459 PMID:17407147

Tame NW, Dlugogorski BZ, Kennedy EM (2009). Conversion of wood pyrolysates to PCDD/F. *Proc Combust Inst*. 32(1):665–71. doi:10.1016/j.proci.2008.07.022

Tao L, Kannan K, Aldous KM, Mauer MP, Eadon GA (2008). Biomonitoring of perfluorochemicals in plasma of New York State personnel responding to the World Trade Center disaster. *Environ Sci Technol*. 42(9):3472–8. doi:10.1021/es8000079 PMID:18522136

Taveli A, Bellera CL (2018). Drug distribution. In: Taveli A, Quiroga PAM, editors. ADME processes in pharmaceutical sciences. Dosage, design, and pharmacotherapy success. Cham, Switzerland: Springer Nature Switzerland.

Tedim F, Xanthopoulos G, Leone V (2015). Forest fires in Europe: facts and challenges. Wildfire hazards, risks and disasters. Elsevier; pp. 77–99. doi:10.1016/B978-0-12-410434-1.00005-1

Than D, Echt A, Sheehy J, Blade L (1995). Case studies: exposure to diesel exhaust emissions at three fire stations: evaluation and recommended controls. *Appl Occup Environ Hyg*. 10(5):431–8. doi:10.1080/1047322X.1995.10387631

Theobald DM, Romme WHJL, Planning U (2007). Expansion of the US wildland–urban interface. *Landsc Urban Plan*. 83(4):340–54. doi:10.1016/j.landurbplan.2007.06.002

Tishi TR, Islam I (2018). Urban fire occurrences in the Dhaka Metropolitan Area. *GeoJournal*. 84(6):1417–27. doi:10.1007/s10708-018-9923-y

Tornling G, Gustavsson P, Hogstedt C (1994). Mortality and cancer incidence in Stockholm fire fighters. *Am J Ind Med*. 25(2):219–28. doi:10.1002/ajim.4700250208 PMID:8147394

Toussaint B, Magali C, Vanina P, Albert S, Eric L, Nathalie C (2010). Volatile and semi-volatile organic compounds in smoke exposure of firefighters during prescribed burning in the Mediterranean region. *Int J Wildland Fire*. 19(5):606–12. doi:10.1071/WF08121

Toyooka T, Ibuki Y (2007). DNA damage induced by coexposure to PAHs and light. *Environ Toxicol Pharmacol*. 23(2):256–63. doi:10.1016/j.etap.2006.09.002 PMID:21783767

Treitman RD, Burgess WA, Gold A (1980). Air contaminants encountered by firefighters. *Am Ind Hyg Assoc J*. 41(11):796–802. doi:10.1080/15298668091425662 PMID:7457369

Trowbridge J, Gerona R, McMaster M, Ona K, Clarity C, Bessonneau V, et al. (2022). Organophosphate and organohalogen flame-retardant exposure and thyroid hormone disruption in a cross-sectional study of female firefighters and office workers from San Francisco. *Environ Sci Technol*. 56(1):440–50. doi:10.1021/acs.est.1c05140 PMID:34902963

Trowbridge J, Gerona RR, Lin T, Rudel RA, Bessonneau V, Buren H, et al. (2020). Exposure to perfluoroalkyl substances in a cohort of women firefighters and office workers in San Francisco. *Environ Sci Technol*. 54(6):3363–74. doi:10.1021/acs.est.9b05490 PMID:32100527

Truchot B, Fouillen F, Collet S (2018). An experimental evaluation of toxic gas emissions from vehicle fires. *Fire Saf J*. 97:111–8. doi:10.1016/j.firesaf.2017.12.002

Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM, Calvert GM (2015). Risk of cancer among firefighters in California, 1988–2007. *Am J Ind Med*. 58(7):715–29. doi:10.1002/ajim.22466 PMID:25943908

Tsukiji J, Cho SJ, Echevarria GC, Kwon S, Joseph P, Schenck EJ, et al. (2014). Lysophosphatidic acid and apolipoprotein A1 predict increased risk of developing

World Trade Center-lung injury: a nested case-control study. *Biomarkers*. 19(2):159–65. doi:10.3109/1354750X.2014.891047 PMID:24548082

Tubbs RL (1995). Noise and hearing loss in firefighting. *Occup Med*. 10(4):843–56. PMID:8903753

United Kingdom Home Office (2020). Official statistics. Fire and rescue workforce and pensions statistics: England, April 2019 to March 2020. London, England: United Kingdom Home Office. Available from: https://www.gov.uk/government/statistics/fire-and-rescue-workforce-and-pensions-statistics-england-april-2019-to-march-2020/fire-and-rescue-workforce-and-pensions-statistics-england-april-2019-to-march-2020, accessed 13 June 2022.

United Kingdom Home Office (2021a). Official statistics. Fire and rescue workforce and pensions statistics: England, April 2020 to March 2021. London, England: United Kingdom Home Office. Available from: https://www.gov.uk/government/statistics/fire-and-rescue-workforce-and-pensions-statistics-england-april-2020-to-march-2021/fire-and-rescue-workforce-and-pensions-statistics-england-april-2020-to-march-2021, accessed November 2022.

United Kingdom Home Office (2021b). Fire statistics data tables. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1111464/fire-statistics-data-tables-fire1103-201022.xlsx, accessed November 2022.

United Kingdom National Careers Service (2021). Firefighter. Available from: https://nationalcareers.service.gov.uk/job-profiles/firefighter, accessed 13 June 2022.

Urbanski SP, Hao WM, Baker S (2008). Chemical composition of wildland fire emissions. *Developments in Environmental Science*. 8:79–107. doi:10.1016/S1474-8177(08)00004-1

Urrutia-Jalabert R, Gonzalez ME, Gonzalez-Reyes A, Lara A, Garreaud R (2018). Climate variability and forest fires in central and south-central Chile. *Ecosphere*. 9(4):e02171. doi:10.1002/ecs2.2171

US BLS (2021). Firefighters. Occupational outlook handbook. Washington (DC), USA: Office of Occupational Statistics and Employment Projections, United States Bureau of Labor Statistics. Available from: https://www.bls.gov/ooh/Protective-Service/Firefighters.htm, accessed 13 June 2022.

US EPA (1992). Dermal exposure assessment: principles and applications. EPA/600/8–91/011B. Washington (DC), USA: United States Environmental Protection Agency, Office of Health and Environmental Assessment.

US EPA (1998). Toxicological review of benzene (noncancer effects). NCEA-S-0455. Washington (DC), USA: United States Environmental Protection Agency.

US EPA (2011). Chapter 6 - Inhalation rates. In: Exposure factors handbook 2011 edition (final report). EPA/600/R-09/052F. Washington (DC), USA: United States Environmental Protection Agency.

US EPA (2021a). PFAS master list of PFAS substances. CompTox Chemicals Dashboard. United States Environmental Protection Agency. Available from: https://comptox.epa.gov/dashboard/chemical_lists/pfasmaster, accessed 30 August 2022.

US EPA (2021b). An analysis of lithium-ion battery fires in waste management and recycling. EPA 530-R-21-002. Washington (DC), USA: Office of Resource Conservation and Recovery, United States Environmental Protection Agency. Available from: https://www.epa.gov/system/files/documents/2021-08/lithium-ion-battery-report-update-7.01_508.pdf, accessed 7 September 2022.

US Fire Administration (2008). Emergency incident rehabilitation. Emitsburg (MD), USA: United States Fire Administration, Federal Emergency Management Agency. Available from: https://www.usfa.fema.gov/downloads/pdf/publications/fa_314.pdf, accessed November 2022.

US Fire Administration (2018). Highway vehicle fires (2014–2016). Topical Fire Report Series. Volume 19, Issue 2. Emitsburg (MD), USA: National Fire Data Center, United States Fire Administration, Federal Emergency Management Agency. Available from: https://www.usfa.fema.gov/downloads/pdf/statistics/v19i2.pdf, accessed 13 June 2022.

USDA Forest Service (2021a). People working in fire. Washington (DC), USA: Forest Service, United States Department of Agriculture. Available from: https://www.fs.usda.gov/science-technology/fire/people, accessed 13 June 2022.

USDA Forest Service (2021b). Handcrews. Wildland fire. Washington (DC), USA: Forest Service, United States Department of Agriculture. Available from: https://www.fs.usda.gov/science-technology/fire/people/handcrews, accessed November 2022.

USDA Forest Service (2021c). Engine crews. Wildland fire. Washington (DC), USA: Forest Service, United States Department of Agriculture. Available from: https://www.fs.usda.gov/science-technology/fire/engine-crews, accessed November 2022.

USDA Forest Service (2021d). Wildland fire. Washington (DC), USA: Forest Service, United States Department of Agriculture. Available from: https://www.fs.usda.gov/managing-land/fire, accessed November 2022.

Valavanidis A, Iliopoulos N, Gotsis G, Fiotakis K (2008). Persistent free radicals, heavy metals and PAHs generated in particulate soot emissions and residue ash from controlled combustion of common types of plastic. *J Hazard Mater*. 156(1–3):277–84. doi:10.1016/j.jhazmat.2007.12.019 PMID:18249066

Valdez MK, Sexton JD, Lutz EA, Reynolds KA (2015). Spread of infectious microbes during emergency medical response. *Am J Infect Control*. 43(6):606–11. doi:10.1016/j.ajic.2015.02.025 PMID:26042849

Van den Berg M, De Jongh J, Poiger H, Olson JR (1994). The toxicokinetics and metabolism of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance for toxicity. *Crit Rev Toxicol*. 24(1):1–74. doi:10.3109/10408449409017919 PMID:8172651

van den Berg M, Denison MS, Birnbaum LS, Devito MJ, Fiedler H, Falandysz J, et al. (2013). Polybrominated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls: inclusion in the toxicity equivalency factor concept for dioxin-like compounds. *Toxicol Sci*. 133(2):197–208. doi:10.1093/toxsci/kft070 PMID:23492812

VanRooij JG, De Roos JH, Bodelier-Bade MM, Jongeneelen FJ (1993). Absorption of polycyclic aromatic hydrocarbons through human skin: differences between anatomical sites and individuals. *J Toxicol Environ Health*. 38(4):355–68. doi:10.1080/15287399309531724 PMID:8478978

Vassilev SV, Baxter D, Andersen LK, Vassileva CG (2010). An overview of the chemical composition of biomass. *Fuel*. 89(5):913–33. doi:10.1016/j.fuel.2009.10.022

Vena JE, Fiedler RC (1987). Mortality of a municipal-worker cohort: IV. Fire fighters. *Am J Ind Med*. 11(6):671–84. doi:10.1002/ajim.4700110608 PMID:3605104

Viegas S, Zare Jeddi M, B Hopf N, Bessems J, Palmen N, Galea KS, et al. (2020). Biomonitoring as an underused exposure assessment tool in occupational safety and health context-challenges and way forward. *Int J Environ Res Public Health*. 17(16):5884. doi:10.3390/ijerph17165884 PMID:32823696

Vincent GE, Aisbett B, Hall SJ, Ferguson SA (2016). Fighting fire and fatigue: sleep quantity and quality during multi-day wildfire suppression. *Ergonomics*. 59(7):932–40. PMID:26452576

Vincent GE, Aisbett B, Larsen B, Ridgers ND, Snow R, Ferguson SA (2017). The impact of heat exposure and sleep restriction on firefighters' work performance and physiology during simulated wildfire suppression. *Int J Environ Res Public Health*. 14(2):180. doi:10.3390/ijerph14020180 PMID:28208688

Vincent GE, Aisbett B, Wolkow A, Jay SM, Ridgers ND, Ferguson SA (2018). Sleep in wildland firefighters: what do we know and why does it matter? *Int J Wildland Fire*. 2018(27):73–84. doi:10.1071/WF17109

Viner BJ, Jannik T, Hepworth A, Adetona O, Naeher L, Eddy T, et al. (2018). Predicted cumulative dose to firefighters and the offsite public from natural and anthropogenic radionuclides in smoke from wildland fires at the Savannah River Site, South Carolina USA. *J Environ Radioact*. 182:1–11. doi:10.1016/j.jenvrad.2017.10.017 PMID:29175006

Waldman JM, Gavin Q, Anderson M, Hoover S, Alvaran J, Ip HSS, et al. (2016). Exposures to environmental phenols in southern California firefighters and findings of elevated urinary benzophenone-3 levels. *Environ Int*. 88:281–7. doi:10.1016/j.envint.2015.11.014 PMID:26821331

Walker A, Beatty HEW, Zanetti S, Rattray B (2017). Improving body composition may reduce the immune and inflammatory responses of firefighters working in the heat. *J Occup Environ Med*. 59(4):377–83. doi:10.1097/JOM.0000000000000980 PMID:28628047

Walker A, Keene T, Argus C, Driller M, Guy JH, Rattray B (2015). Immune and inflammatory responses of Australian firefighters after repeated exposures to the heat. *Ergonomics*. 58(12):2032–9. doi:10.1080/00140139.2015.1051596 PMID:26082313

Wallace MAG, Pleil JD, Mentese S, Oliver KD, Whitaker DA, Fent KW (2017). Calibration and performance of synchronous SIM/scan mode for simultaneous targeted and discovery (non-targeted) analysis of exhaled breath samples from firefighters. *J Chromatogr A*. 1516:114–24. doi:10.1016/j.chroma.2017.07.082 PMID:28838652

Wallace MAG, Pleil JD, Oliver KD, Whitaker DA, Mentese S, Fent KW, et al. (2019a). Targeted GC-MS analysis of firefighters' exhaled breath: exploring biomarker response at the individual level. *J Occup Environ Hyg*. 16(5):355–66. doi:10.1080/15459624.2019.1588973 PMID:30932751

Wallace MAG, Pleil JD, Oliver KD, Whitaker DA, Mentese S, Fent KW, et al. (2019b). Non-targeted GC/MS analysis of exhaled breath samples: exploring human biomarkers of exogenous exposure and endogenous response from professional firefighting activity. *J Toxicol Environ Health A*. 82(4):244–60. doi:10.1080/15287394.2019.1587901 PMID:30907277

Wang D, Xu X, Zheng M, Chiu CH (2002). Effect of copper chloride on the emissions of PCDD/Fs and PAHs from PVC combustion. *Chemosphere*. 48(8):857–63. doi:10.1016/S0045-6535(02)00020-6 PMID:12222780

Wang Q, Ping P, Zhao X, Chu GS, Sun J, Chen C (2012). Thermal runaway caused fire and explosion of lithium ion battery. *J Power Sources*. 208:210–24. doi:10.1016/j.jpowsour.2012.02.038

Watkins ER, Hayes M, Watt P, Renshaw D, Richardson AJ (2021). Extreme occupational heat exposure is associated with elevated haematological and inflammatory markers in Fire Service Instructors. *Exp Physiol*. 106(1):233–43. doi:10.1113/EP088386 PMID:32462715

Watkins ER, Hayes M, Watt P, Richardson AJ (2019a). The acute effect of training fire exercises on fire service instructors. *J Occup Environ Hyg*. 16(1):27–40. doi:10.1080/15459624.2018.1531132 PMID:30277854

Watkins ER, Hayes M, Watt P, Richardson AJ (2019b). Heat tolerance of fire service instructors. *J Therm Biol*. 82:1–9. doi:10.1016/j.jtherbio.2019.03.005 PMID:31128636

Watt PW, Willmott AG, Maxwell NS, Smeeton NJ, Watt E, Richardson AJ (2016). Physiological and psychological responses in fire instructors to heat exposures. *J Therm Biol*. 58:106–14. doi:10.1016/j.jtherbio.2016.04.008 PMID:27157340

Webb HE, Garten RS, McMinn DR, Beckman JL, Kamimori GH, Acevedo EO (2011). Stress hormones and vascular function in firefighters during concurrent challenges. *Biol Psychol*. 87(1):152–60. doi:10.1016/j.biopsycho.2011.02.024 PMID:21382435

Webber MP, Singh A, Zeig-Owens R, Salako J, Skerker M, Hall CB, et al. (2021). Cancer incidence in World Trade Center-exposed and non-exposed male firefighters, as compared with the US adult male population: 2001-2016. *Occup Environ Med*. 78(10):707–14. doi:10.1136/oemed-2021-107570 PMID:34507965

Weber R, Kuch B (2003). Relevance of BFRs and thermal conditions on the formation pathways of brominated and brominated-chlorinated dibenzodioxins and dibenzofurans. *Environ Int*. 29(6):699–710. doi:10.1016/S0160-4120(03)00118-1 PMID:12850089

Weiden MD, Kwon S, Caraher E, Berger KI, Reibman J, Rom WN, et al. (2015). Biomarkers of World Trade Center particulate matter exposure: physiology of distal airway and blood biomarkers that predict FEV_1 decline. *Semin Respir Crit Care Med*. 36(3):323–33. doi:10.1055/s-0035-1547349 PMID:26024341

Weiden MD, Singh A, Goldfarb DG, Putman B, Zeig-Owens R, Schwartz T, et al. (2021). Serum Th-2 cytokines and FEV_1 decline in WTC-exposed firefighters: a 19-year longitudinal study. *Am J Ind Med*. 64(10):845–52. doi:10.1002/ajim.23276 PMID:34288008

Wester RC, Maibach HI, Bucks DA, McMaster J, Mobayen M, Sarason R, et al. (1990). Percutaneous absorption and skin decontamination of PCBs: in vitro studies with human skin and in vivo studies in the rhesus monkey. *J Toxicol Environ Health*. 31(4):235–46. doi:10.1080/15287399009531453 PMID:2254950

WHO (2006). Dermal absorption. Environmental Health Criteria 235. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/43542, accessed March 2023.

WHO (2015). Human biomonitoring: facts and figures. Copenhagen, Denmark: WHO Regional Office for Europe. Available from: https://apps.who.int/iris/handle/10665/164588, accessed March 2023.

Williams JA, Naidoo N (2020). Sleep and cellular stress. *Curr Opin Physiol*. 15:104–10. doi:10.1016/j.cophys.2019.12.011 PMID:32043041

Williamson GJ, Bowman DMJS, Price OF, Johnston FH (2016). A transdisciplinary approach to understanding the health effects of wildfire and prescribed fire smoke regimes. *Environ Res Lett*. 11(12):125009. doi:10.1088/1748-9326/11/12/125009

Wingfors H, Nyholm JR, Magnusson R, Wijkmark CH (2018). Impact of fire suit ensembles on firefighter PAH exposures as assessed by skin deposition and urinary biomarkers. *Ann Work Expo Health*. 62(2):221–31. doi:10.1093/annweh/wxx097 PMID:29236997

Witteveen AB, Bramsen I, Twisk JWR, Huizink AC, Slottje P, Smid T, et al. (2007). Psychological distress of rescue workers eight and one-half years after professional involvement in the Amsterdam air disaster. *J Nerv Ment Dis*. 195(1):31–40. doi:10.1097/01.nmd.0000252010.19753.19 PMID:17220737

Wolfe CM, Green WH, Cognetta AB Jr, Hatfield HK (2012). Heat-induced squamous cell carcinoma of the lower extremities in a wildlands firefighter. *J Am Acad Dermatol*. 67(6):e272–3. doi:10.1016/j.jaad.2012.05.020 PMID:23158634

Wolfe MI, Mott JA, Voorhees RE, Sewell CM, Paschal D, Wood CM, et al. (2004). Assessment of urinary metals following exposure to a large vegetative fire, New Mexico, 2000. *J Expo Anal Environ Epidemiol*. 14(2):120–8. doi:10.1038/sj.jea.7500299 PMID:15014542

Wolkow A, Aisbett B, Ferguson SA, Reynolds J, Main LC (2016a). Psychophysiological relationships between a multi-component self-report measure of mood, stress and behavioural signs and symptoms, and physiological stress responses during a simulated firefighting deployment. *Int J Psychophysiol*. 110:109–18. doi:10.1016/j.ijpsycho.2016.10.015 PMID:27984046

Wolkow A, Aisbett B, Jefferies S, Main LC (2017). Effect of heat exposure and simulated physical firefighting work on acute inflammatory and cortisol responses. *Ann Work Expo Health*. 61(5):600–3. doi:10.1093/annweh/wxx029 PMID:28383724

Wolkow A, Aisbett B, Reynolds J, Ferguson SA, Main LC (2015b). Relationships between inflammatory cytokine and cortisol responses in firefighters exposed to simulated wildfire suppression work and sleep restriction. *Physiol Rep*. 3(11):e12604. doi:10.14814/phy2.12604 PMID:26603450

Wolkow A, Aisbett B, Reynolds J, Ferguson SA, Main LC (2016b). Acute psychophysiological relationships between mood, inflammatory and cortisol changes in response to simulated physical firefighting work and sleep restriction. *Appl Psychophysiol Biofeedback*. 41(2):165–80. doi:10.1007/s10484-015-9329-2 PMID:26698865

Wolkow A, Ferguson SA, Vincent GE, Larsen B, Aisbett B, Main LC (2015a). The impact of sleep restriction and simulated physical firefighting work on acute inflammatory stress responses. *PLoS One*. 10(9):e0138128. doi:10.1371/journal.pone.0138128 PMID:26378783

Wright-Beatty HE, McLellan TM, Larose J, Sigal RJ, Boulay P, Kenny GP (2014). Inflammatory responses of older firefighters to intermittent exercise in the heat. *Eur J Appl Physiol*. 114(6):1163–74. doi:10.1007/s00421-014-2843-8 PMID:24563092

Wu CM, Adetona A, Song CC, Naeher L, Adetona O (2020a). Measuring acute pulmonary responses to occupational wildland fire smoke exposure using exhaled breath condensate. *Arch Environ Occup Health*. 75(2):65–9. doi:10.1080/19338244.2018.1562413 PMID:30668286

Wu CM, Song CC, Chartier R, Kremer J, Naeher L, Adetona O (2021). Characterization of occupational smoke exposure among wildland firefighters in the midwestern United States. *Environ Res*. 193:110541. doi:10.1016/j.envres.2020.110541 PMID:33249041

Wu CM, Warren SH, DeMarini DM, Song CC, Adetona O (2020b). Urinary mutagenicity and oxidative status of wildland firefighters working at prescribed burns in a Midwestern US forest. *Occup Environ Med*. 78(5):315–22. doi:10.1136/oemed-2020-106612 PMID:33139344

Xavier RF, Ramos D, Ito JT, Rodrigues FM, Bertolini GN, Macchione M, et al. (2013). Effects of cigarette smoking intensity on the mucociliary clearance of active smokers. *Respiration*. 86(6):479–85. doi:10.1159/000348398 PMID:23615315

Xu Y, Fletcher T, Pineda D, Lindh CH, Nilsson C, Glynn A, et al. (2020). Serum half-lives for short- and long-chain perfluoroalkyl acids after ceasing exposure from drinking water contaminated by firefighting foam. *Environ Health Perspect*. 128(7):77004. doi:10.1289/EHP6785 PMID:32648786

Yang H, Yan R, Chen H, Lee DH, Zheng C (2007). Characteristics of hemicellulose, cellulose and lignin pyrolysis. *Fuel*. 86(12–13):1781–8. doi:10.1016/j.fuel.2006.12.013

Yasin S, Behary N, Curti M, Rovero G (2016). Global consumption of flame retardants and related environmental concerns: a study on possible mechanical recycling of flame retardant textiles. *Fibers (Basel)*. 4(2):16. doi:10.3390/fib4020016

Yi K, Bao Y (2016). Estimates of wildfire emissions in boreal forests of China. Forests 7(8):158. Available from: https://www.mdpi.com/1999-4907/7/8/158, accessed March 2023.

Yoschenko VI, Kashparov VA, Protsak VP, Lundin SM, Levchuk SE, Kadygrib AM, et al. (2006). Resuspension and redistribution of radionuclides during grassland and forest fires in the Chernobyl exclusion zone: part I. Fire experiments. *J Environ Radioact*. 86(2):143–63. doi:10.1016/j.jenvrad.2005.08.003 PMID:16213067

Young AS, Sparer-Fine EH, Pickard HM, Sunderland EM, Peaslee GF, Allen JG (2021). Per- and polyfluoroalkyl substances (PFAS) and total fluorine in fire station dust. *J Expo Sci Environ Epidemiol*. 31(5):930–42. doi:10.1038/s41370-021-00288-7 PMID:33542478

Yucesoy B, Kurzius-Spencer M, Johnson VJ, Fluharty K, Kashon ML, Guerra S, et al. (2008). Association of cytokine gene polymorphisms with rate of decline in lung function. *J Occup Environ Med*. 50(6):642–8. doi:10.1097/JOM.0b013e31816515e1 PMID:18545091

Zeig-Owens R, Webber MP, Hall CB, Schwartz T, Jaber N, Weakley J, et al. (2011). Early assessment of cancer outcomes in New York City firefighters after the 9/11 attacks: an observational cohort study. *Lancet*. 378(9794):898–905. doi:10.1016/S0140-6736(11)60989-6 PMID:21890054

Zhang M, Buekens A, Jiang X, Li X (2015). Dioxins and polyvinylchloride in combustion and fires. *Waste Manag Res*. 33(7):630–43. doi:10.1177/0734242X15590651 PMID:26185164

Zhang M, Buekens A, Li X (2016). Brominated flame retardants and the formation of dioxins and furans in fires and combustion. *J Hazard Mater*. 304:26–39. doi:10.1016/j.jhazmat.2015.10.014 PMID:26546701

Zhao G, Erazo B, Ronda E, Brocal F, Regidor E (2020). Mortality among firefighters in Spain: 10 years of follow-up. *Ann Work Expo Health*. 64(6):614–21. doi:10.1093/annweh/wxaa036 PMID:32253442

Zhou J, Jenkins TG, Jung AM, Jeong KS, Zhai J, Jacobs ET, et al. (2019). DNA methylation among firefighters. *PLoS One*. 14(3):e0214282. doi:10.1371/journal.pone.0214282 PMID:30913233

2. CANCER IN HUMANS

Since the previous evaluation of the carcinogenicity of firefighting by the *IARC Monographs* programme in 2007, published in Volume 98 (IARC, 2010), numerous studies have been published on cancer incidence and mortality in firefighters. A systematic search was conducted of the PubMed, Web of Science, and Embase databases to identify epidemiological studies evaluating the association between the agent – occupational exposure as a firefighter – and the occurrence (reported as incidence or mortality) of cancer in humans (Clarivate, 2022; Elsevier, 2022; NLM, 2022). The search terms used and the results of the literature search are available online at: https://hawcproject.iarc.who.int/lit/assessment/666/. The search (conducted without restriction as to start date and concluded on 13 June 2022) led to the identification of 643 studies considered for inclusion in the review of evidence on cancer in humans, Section 2 of the present monograph.

A study was excluded from the review if: (i) the occurrence of cancer as an outcome was not reported (n = 444); (ii) a cross-sectional or ecological study design (n = 3) was used; (iii) it was reported as a conference abstract or was a duplicate of an existing study (n = 15); (iv) no primary estimates of association between the agent and cancer (n = 41) were presented; (v) it was a "letter to the editor" or commentary about an included study (n = 21); or (vi) it was an occupational surveillance study that did not investigate cancer in firefighters a priori (n = 37). The exclusion of such general occupational surveillance studies was carried out to reduce the potential for publication bias in the studies included for review, given that these studies tended to only highlight occupations associated with increased risk. Some studies of this type were previously included in the evaluation of firefighting by the *IARC Monographs* programme in 2007 (IARC, 2010) but were excluded from the present evaluation. One study that was published with analytical errors was considered to be uninformative and was excluded from the evaluation (Colbeth et al., 2020b; [personal communication with the authors]).

All other studies (n = 83) were considered eligible for inclusion in the evaluation of the evidence on cancer in humans. Where study populations had been updated with additional follow-up or participants, only the most recent or most informative publication was reviewed in detail. A total of 71 studies were therefore reviewed in detail. This included 41 cohort studies, 10 case–control studies, 1 mortality surveillance study, 7 meta-analyses, and 12 case reports.

Owing to the large number of studies included in the evaluation, studies were grouped according to cancer site, type of exposure assessment, and study design. Studies were grouped

into sections numbered first by cancer site (2.x) and then by type of exposure assessment (2.x.1 or 2.x.2). For the studies grouped in Section 2.x.1, "Studies reporting occupational characteristics of firefighters", the design or analysis of the study contained an assessment of the employment or exposure characteristics of firefighters, such as the number or type of emergency responses, working in a fire combat role, or duration of employment. The studies grouped in Section 2.x.2, "Studies only reporting having ever worked as a firefighter", only provided information on having ever worked in the occupation. The latter group (Section 2.x.2) was further subdivided into: (a) occupational cohort studies; and (b) population-based studies. Within each section, studies were described in order of geographical continent (Asia, Europe, North America, Oceania) then publication year, from most to least recent. To reduce repetition in study description and appraisal, studies were described in detail at first mention (primarily in Section 2.1), and in less detail in subsequent sections.

The Working Group conducted a meta-analysis of cohort studies, the results of which are described in Section 2.8.2. A synthesis of the evidence regarding cancer in humans is presented in Section 2.9.

2.1 Cancers of the lung and respiratory system, including mesothelioma

2.1.1 Studies reporting occupational characteristics of firefighters

See Table 2.1.

The Working Group identified 26 occupational and population-based cohort studies and one pooled international case–control study that had investigated the relation between occupational exposure as a firefighter and risk of cancer of the lung and respiratory system (including the larynx, lung, trachea, and bronchus) and mesothelioma (Feuer & Rosenman, 1986; Vena & Fiedler, 1987; Demers et al., 1992a, 1994; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Bates et al., 2001; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014, 2015; Ahn & Jeong, 2015; Glass et al., 2016a, b, 2017, 2019; Bigert et al., 2016; Petersen et al., 2018a, b; Kullberg et al., 2018; Bigert et al., 2020; Pinkerton et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a, b). Some studies reported results for all cancers of the respiratory system combined (defined variously by individual studies). Studies described in this section assessed employment or exposure characteristics of firefighters in the design or analysis of the study, for example, the number or type of emergency responses, working in a fire combat role, or duration of employment.

Two studies reporting on cancer incidence and cancer mortality, respectively, originated from Asia (Ahn et al., 2012; Ahn & Jeong, 2015). Of the seven European studies, all of which were carried out in Scandinavia, five investigated cancer incidence (Tornling et al., 1994; Kullberg et al., 2018; Petersen et al., 2018a; Bigert et al., 2020; Marjerrison et al., 2022a, b), whereas four examined cancer mortality (Tornling et al., 1994; Petersen et al., 2018b; Marjerrison et al., 2022a, b). Of 13 studies from the USA, 2 reported on cancer incidence (Zeig-Owens et al., 2011; Webber et al., 2021) among firefighters working at the World Trade Center (WTC) disaster site. Five of the remaining studies comprised analyses in a pooled cohort of firefighters from San Francisco, Chicago, and Philadelphia with varying follow-up periods, exposure metrics, and types of outcome data (Daniels et al., 2014, 2015; Pinkerton et al., 2020) or analyses of the individual cohorts (Beaumont et al., 1991; Baris et al., 2001), whereas four presented incidence or mortality data based on analyses of pooled or individual cohorts from Seattle and Tacoma, in Washington, and Portland, Oregon (Heyer et al., 1990; Demers et al., 1992a, b, 1994). Three of

Table 2.1 Cohort and case–control studies reporting occupational characteristics of firefighters and cancers of the lung and respiratory system, including mesothelioma

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn & Jeong (2015) Republic of Korea Enrolment, 1980–2007/follow-up, 1992–2007 Cohort	33 442 men employed as emergency responders for ≥ 1 mo between 1980 and 2007, with (29 453) and without (3989) firefighting experience and not deceased in 1991 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Lung and bronchus, mortality	Duration of firefighting employment, 1-yr lag (SMR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include municipal and rural firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: small number of cases of lung cancer; no information on personal characteristics or confounders; follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	6	0.69 (0.25–1.48)		
			10 to < 20 yr	7	0.53 (0.21–1.10)		
			≥ 20 yr	13	0.56 (0.30–0.96)		
			Total	26	0.58 (0.38–0.84)		
		Lung and bronchus, mortality	Duration of firefighting employment, 1-yr lag (RR):				
			< 10 yr (including non-firefighters)	8	1		
			10 to < 20 yr	7	0.71 (0.26–1.96)		
			≥ 20 yr	13	1.21 (0.46–3.18)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) Republic of Korea Enrolment, 1980–2007/follow-up, 1996–2007 Cohort	33 416 men employed as emergency responders for ≥ 1 mo between 1980 and 2007, with (29 438) and without (3978) firefighting experience and not deceased in 1995 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Larynx, incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include municipal and rural firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: small number of cases of lung cancer; no information on personal characteristics or confounders (except the firefighter cohort had a lower BMI and smoked less than the comparison population for the SIR analysis); follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	0	0 (NR)		
			≥ 10 yr	3	0.72 (0.15–2.11)		
			Total	3	0.57 (0.11–1.67)		
		Lung and bronchus, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	7	0.69 (0.28–1.43)		
			≥ 10 yr	29	0.81 (0.54–1.16)		
			Total	36	0.78 (0.55–1.09)		
		Lung and bronchus, incidence	SRR:				
			Non-firefighters	3	1		
			Ever employed as a firefighter	36	0.69 (0.21–2.26)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters employed (most were full-time) in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Larynx, incidence	SIR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions, may include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr), near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; low number of cases for laryngeal cancer and mesothelioma; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	12	1.77 (0.91–3.08)		
		Larynx, incidence	Year of first employment (SIR):				
			Pre-1950	6	2.34 (0.86–5.09)		
			1950–1969	5	2.02 (0.65–4.71)		
			1970 or after	1	0.57 (0.01–3.18)		
		Larynx, incidence	Time since first employment (SIR):				
			< 20 yr	0	0 (0.00–7.04)		
			20–39 yr	2	0.59 (0.07–2.14)		
			≥ 40 yr	10	3.33 (1.60–6.13)		
		Larynx, incidence	Duration of employment (SIR):				
			< 10 yr	0	0 (0.00–5.55)		
			10–19 yr	2	2.7 (0.33–9.75)		
			20–29 yr	1	0.51 (0.01–2.85)		
			≥ 30 yr	9	2.53 (1.16–4.80)		
		Lung, incidence	SIR:				
			Firefighters	81	0.98 (0.78–1.22)		
		Lung, incidence	Year of first employment (SIR):				
			Pre-1950	40	1.37 (0.98–1.87)		
			1950–1969	28	0.87 (0.58–1.26)		
			1970 or after	13	0.61 (0.33–1.04)		
		Lung, incidence	Time since first employment (SIR):				
			< 20 yr	4	1.07 (0.29–2.74)		
			20–39 yr	22	0.64 (0.40–0.98)		
			≥ 40 yr	55	1.23 (0.93–1.60)		
		Lung, incidence	Duration of employment (SIR):				
			< 10 yr	4	0.62 (0.17–1.59)		
			10–19 yr	7	0.86 (0.34–1.76)		
			20–29 yr	18	0.81 (0.48–1.29)		
			≥ 30 yr	52	1.14 (0.85–1.49)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) (cont.)		Mesothelioma, incidence	SIR:			Age, calendar year	
			Firefighters	7	2.46 (0.99–5.06)		
		Mesothelioma, incidence	Year of first employment (SIR):				
			Pre-1950	3	3.74 (0.77–10.9)		
			1950–1969	2	1.52 (0.18–5.49)		
			1970 or after	2	2.74 (0.33–9.90)		
		Mesothelioma, incidence	Time since first employment (SIR):				
			< 20 yr	0	0 (0.00–30.4)		
			20–39 yr	1	0.98 (0.02–5.46)		
			≥ 40 yr	6	3.47 (1.27–7.55)		
		Mesothelioma, incidence	Duration of employment (SIR):				
			< 10 yr	1	4.21 (0.11–23.4)		
			10–19 yr	0	0 (0.00–11.4)		
			20–29 yr	1	1.38 (0.03–7.66)		
			≥ 30 yr	5	3.09 (1.00–7.20)		
Marjerrison et al. (2022b) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters employed (most were full-time) in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Larynx, mortality	SMR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties, may include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment.
			Firefighters	< 5	1.92 (0.52–4.91)		
		Larynx, incidence	Period of follow-up (SIR):				
			1984 or before	0	0 (0.00–1.77)		
			1985–1994	5	3.57 (1.16–8.33)		
			1995 or after	7	1.89 (0.76–3.90)		
		Larynx, mortality	Period of follow-up (SMR):				
			1984 or before	0	0 (0.00–5.58)		
			1985–1994	< 5	2.37 (0.06–13.2)		
			1995 or after	< 5	2.66 (0.55–7.77)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Larynx, incidence	Age at diagnosis (SIR):			Age, calendar year	*Limitations*: probable healthy-worker effect; low number of cases for laryngeal cancer and mesothelioma; no data on potential confounders apart from age, sex, and calendar time.
			≤ 49 yr	0	0 (0.00–6.12)		
			50–69 yr	< 5	0.74 (0.15–2.16)		
			≥ 70 yr	9	3.99 (1.82–7.57)		
		Larynx, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–34.9)		
			50–69 yr	< 5	1.00 (0.03–5.56)		
			≥ 70 yr	< 5	3.00 (0.62–8.77)		
		Lung, mortality	SMR:				
			Firefighters	61	0.91 (0.69–1.16)		
		Lung, incidence	Period of follow-up (SIR):				
			1984 or before	17	1.12 (0.65–1.79)		
			1985–1994	17	1.11 (0.64–1.77)		
			1995 or after	47	0.90 (0.66–1.20)		
		Lung, mortality	Period of follow-up (SMR):				
			1984 or before	14	1.09 (0.59–1.82)		
			1985–1994	15	1.11 (0.62–1.83)		
			1995 or after	32	0.78 (0.53–1.10)		
		Lung, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	1.00 (0.27–2.56)		
			50–69 yr	29	0.68 (0.46–0.98)		
			≥ 70 yr	48	1.33 (0.98–1.77)		
		Lung, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	< 5	0.73 (0.09–2.63)		
			50–69 yr	20	0.61 (0.37–0.94)		
			≥ 70 yr	39	1.23 (0.88–1.68)		
		Mesothelioma, mortality	SMR:				
			Firefighters	< 5	2.40 (0.65–6.15)		
		Mesothelioma, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	4.23 (0.11–23.56)		
			1985–1994	0	0 (0.00–6.16)		
			1995 or after	6	2.82 (1.04–6.14)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Mesothelioma, mortality	Period of follow-up (SMR):			Age, calendar year	
			1984 or before	< 5	0 (NR)		
			1985–1994	0	0 (NR)		
			1995 or after	< 5	1.08 (0.37–5.27)		
		Mesothelioma, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	0	0 (0.00–30.5)		
			50–69 yr	< 5	2.33 (0.48–6.80)		
			≥ 70 yr	< 5	2.74 (0.75–7.01)		
		Mesothelioma, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–159)		
			50–69 yr	< 5	3.16 (0.38–11.41)		
			≥ 70 yr	< 5	1.98 (0.24–7.14)		
Bigert et al. (2020) Sweden Enrolment, 1960–1990/follow-up, 1961–2009 Cohort	8136 male firefighters identified from national censuses in 1960, 1970, 1980, and 1990 Exposure assessment method: questionnaire; ever employed and categorical duration of employment (years) as firefighter from census surveys	Larynx, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. May include full-time, part-time, municipal, and rural firefighters. *Strengths*: near complete ascertainment of cancer incidence; long length of follow-up (mean, 28 yr); analyses stratified by calendar period of employment.
			Firefighters	12	0.92 (0.48–1.61)		
		Lung, incidence	SIR:				
			Firefighters	110	0.87 (0.72–1.05)		
		Lung, incidence	Histological type (SIR):				
			Adenocarcinoma	31	1.01 (0.69–1.43)		
			Small cell	10	0.72 (0.34–1.32)		
			Squamous cell	38	0.93 (0.66–1.28)		
			Other	31	0.77 (0.52–1.09)		
		Lung, incidence	Duration of employment (SIR):				
			1–9 yr	3	1.03 (0.21–3.01)		
			10–19 yr	33	1.06 (0.73–1.48)		
			20–29 yr	34	0.85 (0.59–1.18)		
			≥ 30 yr	40	0.78 (0.56–1.06)		
			Trend-test *P* value,	0.10			

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2020) (cont.)		Lung, incidence	Time period (SIR):			Age, calendar period	*Limitations*: no data on job duties, employment type, or potential confounders (aside from age, sex, and calendar year); probable healthy-worker hire bias; potential non-differential misclassification of employment duration
			1961–1975	11	0.94 (0.47–1.68)		
			1976–1990	32	0.84 (0.58–1.19)		
			1991–2009	67	0.88 (0.68–1.12)		
		Lung (adenocarcinoma), incidence	Duration of employment (SIR):				
			1–9 yr	1	2.59 (0.07–14.4)		
			10–19 yr	8	1.32 (0.57–2.60)		
			20–29 yr	6	0.65 (0.24–1.41)		
			≥ 30 yr	16	1.06 (0.61–1.72)		
			Trend-test *P* value, 0.94				
		Lung (adenocarcinoma), incidence	Time period (SIR):				
			1961–1975	2	1.50 (0.18–5.40)		
			1976–1990	6	0.87 (0.32–1.90)		
			1991–2009	23	1.02 (0.65–1.53)		
		Mesothelioma, incidence	SIR:				
			Firefighters	7	1.11 (0.45–2.29)		
		Mesothelioma, incidence	Duration of employment (SIR):				
			1–9 yr	1	13.68 (0.35–76.2)		
			10–19 yr	0	0 (0.00–2.80)		
			20–29 yr	3	1.46 (0.30–4.28)		
			≥ 30 yr	3	1.04 (0.21–3.04)		
			Trend-test *P* value, 0.85				
		Mesothelioma, incidence	Time period (SIR):				
			1961–1975	0	0 (0.00–19.0)		
			1976–1990	2	1.29 (0.16–4.67)		
			1991–2009	5	1.10 (0.36–2.56)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1958–2012 Cohort	1080 men who worked ≥ 1 yr as a firefighter in Stockholm between 1931 and 1983 Exposure assessment method: ever employed and categorical duration of employment (years) as an urban [municipal] firefighter from annual enrolment records	Bronchus and lung, incidence	Follow-up period (SIR):			Birth year, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Municipal firefighters. *Strengths*: long follow-up period, near complete ascertainment of cancer incidence; analyses of duration and era of employment. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year), lack of exposure assessment based on job tasks or fire responses.
			Full, 1958–2012	27	0.79 (0.52–1.15)		
			Former, 1958–1986	17	0.96 (0.56–1.55)		
			Extended, 1987–2012	10	0.61 (0.29–1.12)		
		Pleura, incidence	Follow-up period (SIR):				
			Full, 1958–2012	2	2.41 (0.29–8.71)		
			Former, 1958–1986	1	5.24 (0.13–29.19)		
			Extended, 1987–2012	1	1.57 (0.04–8.73)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tornling et al. (1994) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1951–1986 (mortality), 1958–1986 (incidence) Cohort	1116 for mortality/1091 for incidence; male firefighters employed for ≥ 1 yr by the city of Stockholm between 1931 and 1983, identified from annual enrolment records Exposure assessment method: ever firefighter and duration (years) of firefighting employment from annual enrolment records; number of fires fought ascertained from exposure index developed from fire reports	Bronchus and lung, mortality Bronchus and lung, incidence	SMR: Firefighters SIR: Firefighters	 18 16	 0.90 (0.53–1.42) 0.89 (0.51–1.45)	Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Enhanced exposure assessment (but based on 10% sample of reports) to differentiate exposure based on number of fires fought accounting for job position, station, and year of exposure. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence and mortality; assessed exposure to fire responses for some outcomes. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year).

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) Denmark Enrolment 1964–2004/follow-up, 1968–2014 Cohort	9061 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born in 1928 or later, employed before age 60 yr and 31 December 2004, no cancer diagnosis before employment as a firefighter, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years), as well as employment type, job title/ function, and work history, ascertained from civil registration, pension, employer personnel, and trade union membership records	Larynx, incidence	Reference group (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up, near-complete ascertainment of cancer incidence, use of three reference groups to evaluate healthy-worker bias; analyses by proxies of exposure including job task. *Limitations*: little information on potential confounders; results for mesothelioma based on large proportion of part-time/volunteer firefighters.
			Firefighters vs general population	16	0.92 (0.56–1.50)		
			Firefighters vs sample of employees	16	0.92 (0.57–1.51)		
			Firefighters vs military	16	1.01 (0.62–1.66)		
		Lung, incidence	Reference group (SIR):				
			Firefighters vs general population	132	0.91 (0.76–1.07)		
			Firefighters vs sample of employees	132	0.95 (0.80–1.13)		
			Firefighters vs military	132	1.06 (0.90–1.26)		
		Lung, incidence	Employment type (SIR):				
			Full-time	82	0.87 (0.70–1.08)		
			Part-time or volunteer	50	0.97 (0.73–1.27)		
		Lung, incidence	Era of first employment (SIR):				
			Pre-1970	77	0.99 (0.79–1.24)		
			1970–1994	48	0.80 (0.60–1.06)		
			1995 or after	7	0.88 (0.42–1.85)		
		Lung, incidence	Job function (SIR):				
			Regular	125	0.92 (0.77–1.09)		
			Specialized	7	0.73 (0.35–1.54)		
		Lung, incidence	Age at first employment (SIR):				
			< 25 yr	70	0.95 (0.75–1.20)		
			25–34 yr	31	0.78 (0.55–1.10)		
			≥ 35 yr	31	0.97 (0.68–1.38)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Lung, incidence	Duration of employment (SIR):			Age, calendar period	
			< 1yr	50	1.13 (0.85–1.49)		
			≥ 1 yr	82	0.81 (0.65–1.00)		
			≥ 10 yr	65	0.73 (0.57–0.93)		
			≥ 20 yr	49	0.70 (0.53–0.93)		
		Mesothelioma, incidence	Reference group (SIR):				
			Firefighters vs general population	4	0.65 (0.24–1.73)		
			Firefighters vs sample of employees	4	0.68 (0.26–1.82)		
			Firefighters vs military	4	0.71 (0.27–1.89)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018b) Denmark Enrolment, 1964–2014/follow-up, 1970–2014 Cohort	11 775 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born in 1928 or later, employed before age 60 yr and 31 December 2004, and a job title/ function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years) as a firefighter ascertained from civil registration, pension, employer personnel, and trade union membership records	Larynx, trachea, and lung (ICD-10, C32–C34), mortality Larynx, trachea, and lung (ICD-10, C32–C34), mortality	Employment type (military reference group) (SMR): Full-time Part-time/ volunteer Duration of employment (military reference group) (SMR): Full-time firefighters: < 1 yr ≥ 1 yr ≥ 10 yr ≥ 20 yr	 76 42 41 35 31 24	 1.13 (0.91–1.42) 1.16 (0.86–1.57) 1.30 (0.96–1.77) 0.99 (0.71–1.37) 0.98 (0.69–1.39) 0.88 (0.59–1.31)	Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up, use of military reference group to evaluate healthy-worker bias; analyses by duration of employment. *Limitations*: little information on potential confounders.

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Webber et al. (2021) USA 2001–2016 Cohort	10 786 FDNY, 8813 CFHS male firefighters who were active on 11 September 2001; FDNY cohort included men who worked at the WTC site any time between 11 September 2001 and 25 July 2002; CFHS cohort included men who were actively employed on 11 September 2001 and assumed not to be working at the WTC site Exposure assessment method: presence at WTC site from employment records and duty rosters	Lung, incidence	Group (SIR, US reference rates)			Age, calendar year, race/ ethnicity	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. Qualitative assessment based on presence at the WTC site, exposures complex and probably unique to 9/11 disaster. Municipal firefighters. *Strengths*: ascertainment of cancer incidence, comparison of two firefighter cohorts to evaluate bias; adjustment for smoking. *Limitations*: medical surveillance bias; young age of cohort; relatively short length of follow-up.
			CFHS firefighters	83	0.71 (0.57–0.89)		
			FDNY WTC firefighters	44	0.53 (0.39–0.72)		
		Lung, incidence	SIR (2-yr adjustment for potential surveillance bias):				
			FDNY WTC firefighters	NR	0.47 (0.34–0.65)		
		Lung, incidence	Group (RR):			Age on 11 September 2001, race/ ethnicity	
			CFHS firefighters	83	1		
			FDNY WTC firefighters	44	0.87 (0.57–1.33)		
		Lung, incidence	Group RR (2-yr adjustment for potential surveillance bias):				
			CFHS firefighters	NR	1		
			FDNY WTC firefighters	NR	0.77 (0.50–1.19)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeig-Owens et al. (2011) New York City, USA Enrolment, 1996; follow-up/1996–2008 Cohort	9853 male FDNY firefighters who were employed for ≥ 18 mo, were active firefighters on 1 January 1996, with no prior cancer, and, if alive on 12 September 2001, also had known WTC exposure status Exposure assessment method: WTC exposed and unexposed firefighters from employment records and questionnaires	Lung, incidence	WTC-exposure status (SIR): Non-exposed Exposed SIR ratio (exposed vs non-exposed)	 8 9 NR	 0.52 (0.26–1.05) 0.42 (0.20–0.86) 0.80 (0.29–2.18)	Age, race, ethnic origin, calendar year	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. WTC exposure self-reported using three methods. WTC site exposures complex and probably unique to 9/11 disaster. *Strengths*: evaluation of medical surveillance bias. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
		Lung, incidence	WTC-exposure status (2-yr adjustment for potential surveillance bias) (SIR): Non-exposed Exposed SIR ratio (exposed vs non-exposed)	 8 6 NR	 0.52 (0.26–1.05) 0.28 (0.13–0.62) 0.53 (0.18–1.54)		
Pinkerton et al. (2020) San Francisco, Chicago, and Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2016 Cohort	29 992 municipal career firefighters in the CFHS cohort employed by the fire departments of San Francisco, Chicago, or Philadelphia for ≥ 1 day between 1950 and 2009; exposure–response analyses limited to 19 287 male firefighters of known race hired in 1950 or later and employed for ≥ 1 yr	Lung, mortality	Fire department (SMR): San Francisco Chicago Philadelphia Overall Heterogeneity *P* value, < 0.01	 154 638 405 1197	 0.71 (0.60–0.83) 1.2 (1.11–1.30) 1.14 (1.03–1.26) 1.08 (1.02–1.15)	Gender, race, age, calendar period	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up, exposure–response modelling for three metrics of exposure assessed using job-exposure matrices, adjustment for HWSE.

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)	Exposure assessment method: ever employed as a firefighter, and number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Lung, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	*Limitations*: healthy-worker selection bias in external comparison analyses, little information on potential confounders.
			Loglinear without HWSE adjustment	556	0.97 (0.81–1.16)		
			RCS without HWSE adjustment	556	1.01 (0.81–1.27)		
			Fully adjusted loglinear	556	1.38 (1.08–1.78)		
			Fully adjusted RCS	556	1.45 (1.06–2.01)		
		Lung, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):				
			Loglinear without HWSE adjustment	516	1.06 (0.93–1.19)		
			RCS without HWSE adjustment	516	0.95 (0.82–1.11)		
			Fully adjusted loglinear	516	1.21 (1.05–1.38)		
			Fully adjusted RCS	516	1.12 (0.95–1.33)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Lung, mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	348	1.27 (1.06–1.52)		
			RCS without HWSE adjustment	348	1.20 (0.95–1.51)		
			Fully adjusted loglinear	348	1.48 (1.21–1.80)		
			Fully adjusted RCS	348	1.46 (1.13–1.88)		
		Lung, mortality	Time since first exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Lag to < 20 yr	NR	1.53 (1.04–2.21)		
			20 to < 30 yr	NR	1.28 (0.94–1.73)		
			≥ 30 yr	NR	1.04 (0.82–1.30)		
			LRT *P* value, 0.16				
		Lung, mortality	Age at exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):				
			< 40 yr	NR	1.05 (0.83–1.31)		
			≥ 40 yr	NR	1.37 (1.11–1.69)		
			LRT *P* value, 0.13				
		Lung, mortality	Period of exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):				
			Pre-1970	NR	1.24 (0.95–1.61)		
			1970 or after	NR	1.19 (1.00–1.41)		
			LRT *P* value, 0.79				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Mesothelioma, mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	< 5	2.00 (0.54–5.12)		
			Chicago	10	2.14 (1.03–3.93)		
			Philadelphia	< 5	1.33 (0.36–3.40)		
			Overall	18	1.86 (1.10–2.94)		
			Heterogeneity *P* value, 0.71				
Daniels et al. (2015) San Francisco, Chicago, Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	19 309; all male career firefighters in the CFHS cohort of known race who were on active duty ≥ 1 day from 1950 through 2009 in the fire departments of Chicago, Philadelphia, or San Francisco with ≥ 1 yr of employment Exposure assessment method: number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Lung, incidence	Exposed-days model (HR, loglinear model, 10-yr lag):			Age, race, fire department, birth cohort	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up, exposure–response modelling for three metrics of exposure assessed using job-exposure matrices. *Limitations*: little information on potential confounders.
			8700 days vs 2500 days	382	1.05 (0.84–1.33)		
		Lung, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, loglinear model, 10-yr lag):			Age, race, fire department, birth cohort	
			8800 runs vs 2100 runs	358	1.10 (0.94–1.28)		
		Lung, incidence	Fire-hours (Chicago only) model (HR, loglinear model, 10-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	243	1.39 (1.10–1.74)		
		Lung, incidence	Time since first exposure in piecewise loglinear fire-runs (Chicago and Philadelphia only) model (HR at 4600 runs, 10-yr lag):			Age, race, fire department, birth cohort	
			10–20 yr	NR	1.06 (0.80–1.37)		
			20–30 yr	NR	1.08 (0.86–1.34)		
			> 30 yr	NR	1.08 (0.88–1.32)		
			LRT *P* value, 0.987				
		Lung, incidence	Age at exposure in piecewise loglinear fire-runs (Chicago and Philadelphia only) model (HR at 4600 runs, 10-yr lag):			Age, race, fire department, birth cohort	
			< 40 yr	NR	0.97 (0.81–1.16)		
			≥ 40 yr	NR	1.17 (0.99–1.37)		
			LRT *P* value, 0.194				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2015) (cont.)		Lung, incidence	Exposure period in piecewise loglinear fire-runs (Chicago and Philadelphia only) model (HR at 4600 runs, 10-yr lag):			Age, race, fire department, birth cohort	
			Pre-1970	NR	1.06 (0.86–1.29)		
			1970 or after	NR	1.08 (0.94–1.24)		
			LRT *P* value, 0.922				
Daniels et al. (2014) Chicago, San Francisco, and Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	29 993 (24 453 for incidence analyses) male and female career firefighters in the CFHS cohort employed for ≥ 1 day in Chicago, San Francisco, or Philadelphia fire departments between 1950 and 2009 Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Larynx, incidence	SIR:			Gender, race, age, calendar period	*Exposure assessment critique*: Satisfactory quality. Minimum exposure is 1 day of work as a municipal firefighter. *Strengths*: long period of follow-up, ascertained incidence outcomes, included female firefighters. *Limitations*: healthy-worker hire bias in external comparisons, little information on potential confounders.
			All cancers	84	1.50 (1.19–1.85)		
		Larynx, incidence	Fire department (SIR, all cancers):				
			San Francisco	10	1.02 (0.49–1.88)		
			Chicago	42	1.51 (1.08–2.03)		
			Philadelphia	32	1.73 (1.18–2.44)		
		Lung, incidence	SIR:				
			All cancers	716	1.12 (1.04–1.21)		
			First primary cancer	602	1.13 (1.04–1.22)		
		Lung, incidence	Fire department (SIR, all cancers):				
			San Francisco	81	0.70 (0.56–0.87)		
			Chicago	409	1.30 (1.17–1.43)		
			Philadelphia	226	1.09 (0.96–1.25)		
			Heterogeneity *P* value, < 0.001				
		Lung, incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men: Caucasian [White]	689	1.15 (1.07–1.24)		
			Other	24	0.67 (0.43–1.00)		
		Lung, incidence	Age (SIR, all cancers):			Gender, race, age, calendar period	
			17–64 yr	222	1.12 (0.98–1.28)		
			65 to ≥ 85 yr	494	1.13 (1.03–1.23)		
			Heterogeneity *P* value, 1.00				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Mesothelioma, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	35	2.29 (1.60–3.19)		
			First primary cancer	26	2.00 (1.31–2.93)		
		Mesothelioma, incidence	Fire department (SIR, all cancers):				
			San Francisco	6	2.05 (0.75–4.47)		
			Chicago	20	2.71 (1.65–4.18)		
			Philadelphia	9	1.82 (0.83–3.46)		
Demers et al. (1994) Seattle and Tacoma, USA Enrolment, 1944–1979/follow-up, 1974–1989 Cohort	2447 male firefighters employed for ≥ 1 yr between 1944 and 1979, alive as of 1 January 1974 and known to be a resident of one of 13 counties in the catchment area of the tumour registry for ≥ 1 mo; reference group included 1878 local male police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration of employment (years) in direct firefighting positions from employment records	Larynx, incidence	SIR (local county rates):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Duration of years involved in direct firefighting (surrogate for fire smoke) was not measured equally in the two study populations. Municipal firefighters. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders, including smoking.
			Firefighters	5	1.0 (0.3–2.3)		
		Larynx, incidence	IDR:				
			Local police	4	1		
			Firefighters	5	0.8 (0.2–3.5)		
		Lung, incidence	SIR (local county rates):				
			Firefighters	45	1.0 (0.7–1.3)		
		Lung, incidence	Histological type (SIR):				
			Adenocarcinoma	14	1.1 (NR)		
			Squamous cell	10	0.7 (NR)		
			Small cell	7	1.0 (NR)		
			Large cell	5	1.3 (NR)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		Lung, incidence	Duration of exposed employment (SIR, local county rates):			Age, calendar period	
			< 10 yr	8	1.4 (0.6–2.7)		
			10–19 yr	9	1.4 (0.7–2.7)		
			20–29 yr	26	0.9 (0.6–1.3)		
			≥ 30 yr	2	0.4 (0.1–1.5)		
		Lung, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	0	0 (0.0–2.5)		
			20–29 yr	11	1.5 (0.7–2.6)		
			≥ 30 yr	34	0.9 (0.6–1.3)		
		Lung, incidence	IDR:				
			Local police	20	1		
			Firefighters	45	1.1 (0.6–1.9)		
Demers et al. (1992a) Seattle and Tacoma, Washington; Portland, Oregon, USA Enrolment, 1944–1979/follow-up, 1945–1989 Cohort	4401 male firefighters employed for ≥ 1 yr between 1944 and 1979 in Seattle, Tacoma, or Portland, USA; reference group included 3676 local police officers Exposure assessment method: records; ever employed for ≥ 1 yr, and categorical duration (years) of exposure to fire combat from employment records	Larynx, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Duration of years involved in fire combat (surrogate for fire smoke) was not measured equally in the three municipal firefighter populations. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders.
			Firefighters	2	0.47 (0.06–1.70)		
		Lung, mortality	SMR:				
			Firefighters	95	0.96 (0.77–1.17)		
		Lung, mortality	IDR:				
			Local police	55	1		
			Firefighters	95	0.95 (0.67–1.33)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena & Fiedler (1987) Buffalo, New York, USA 1950–1979 Cohort	1867 White male career firefighters employed by the City of Buffalo for ≥ 5 yr, with ≥ 1 yr as a firefighter Exposure assessment method: ever-employment, timing, and duration of employment from employment records	Respiratory system, mortality	Years worked as a firefighter (SMR): 1–9 yr 10–19 yr 20–29 yr 30–39 yr ≥ 40 yr Total	 0 3 11 9 5 28	 0 [0.91 (0.2–2.5)] [1.20 (0.6–2.1)] [0.76 (0.4–1.4)] [1.22 (0.4–2.7)] 0.94 (0.62–1.36)	Age, calendar period	*Exposure assessment critique*: Minimal quality. Only assessed ever-employment and duration of employment as a municipal firefighter. *Strengths*: long length of follow-up. *Limitations*: healthy-worker hire bias; little information on potential confounders or exposure to firefighting activities.
Feuer & Rosenman (1986) New Jersey (NJ), USA 1974–1980 Cohort	263 deceased White male firefighters in the New Jersey Police and Firemen Retirement System (firefighters vested with ≥ 10 yr of service, or firefighters who died while on payroll regardless of employment duration); one reference group included 567 White male police deaths Exposure assessment method: ever employed, and categorical duration of employment (years), as a career firefighter from retirement system records	Respiratory system, mortality Respiratory system, mortality	Reference population (PMR): Firefighters vs US White men Firefighters vs NJ White men Firefighters vs White male NJ police Duration of employment (PMR): ≤ 20 yr 20–25 yr > 25 yr	 23 23 23 4 7 12	 [0.98 (0.64–1.45)] [0.92 (0.60–1.35)] [1.02 (0.66–1.50)] [0.72 (0.23–1.74)] [0.96 (0.42–1.90)] [0.98 (0.53–1.67)]	Age	*Exposure assessment critique*: Satisfactory quality. Assessment provides duration of employment categories. May include municipal and rural firefighters. *Strengths*: comparison with other uniformed service occupation. *Limitations*: PMR study design lacks event-free follow-up time, short observation period; little information on potential confounders.

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aronson et al. (1994) Toronto, Canada 1950–1989 Cohort	5414 male firefighters employed for ≥ 6 mo at one of six fire departments in Metropolitan Toronto any time between 1950 and 1989 Exposure assessment method: ever employed and categorical duration of employment (years) as municipal firefighter from employment records	Larynx, mortality Lung, mortality Lung, mortality Lung, mortality Lung, mortality	SMR: Any employment SMR: Any employment Years since first employment (SMR): < 20 yr 20–29 yr ≥ 30 yr Years of employment (SMR): < 15 yr 15–29 yr ≥ 30 yr Age (SMR): < 60 yr ≥ 60 yr	1 54 1 13 40 8 16 27 22 32	0.37 (0.01–2.06) 0.95 (0.71–1.24) 0.23 (0.01–1.29) 1.03 (0.55–1.76) 1.00 (0.71–1.36) 1.30 (0.56–2.57) 0.85 (0.49–1.38) 0.85 (0.56–1.24) 0.91 (0.57–1.39) 0.97 (0.66–1.37)	Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Likely municipal firefighters. *Strengths*: long period of follow-up, analysis of employment duration. *Limitations*: healthy-worker hire bias; little information on confounders or exposure; ascertained mortality outcomes only.
Guidotti (1993) Edmonton and Calgary, Canada 1927–1987 Cohort	3328; all firefighters employed between 1927 and 1987 by either of the fire departments of Edmonton or Calgary Exposure assessment method: ever employed and categorical duration of employment (years) from employment records; exposure index of years of employment weighted by time spent in proximity to fires based on job classification	Lung, mortality Lung, mortality	SMR Any employment Year of cohort entry (SMR): Pre-1920 1920–1929 1930–1939 1940–1949 1950–1959 1960–1969 1970–1979	24 6 1 0 7 6 2 1	1.42 (0.91–2.11) [2.23 (0.90–4.63)] [0.95 (0.05–4.68)] 0 [1.55 (0.68–3.06)] [1.18 (0.48–2.44)] [1.69 (0.28–5.57)] [2.61 (0.13–12.8)]	Age, calendar period	*Exposure assessment critique*: Good quality. Good approach to differentiate exposure between ranks. Municipal firefighters. *Strengths*: long length of follow-up; analyses by duration of employment and exposure index. *Limitations*: little information on potential confounders; ascertained mortality outcomes only; low number of cases for stratified analyses.

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) (cont.)		Lung, mortality	Latency (SMR):			Age, calendar period	
			< 20 yr	4	[1.92 (0.61–4.64)]		
			20–29 yr	4	[0.95 (0.30–2.29)]		
			30–39 yr	10	[1.73 (0.88–3.08)]		
			40–49 yr	3	[0.97 (0.25–2.63)]		
			≥ 50 yr	3	[1.75 (0.44–4.75)]		
		Lung, mortality	Duration of employment (SMR):				
			< 1 yr	2	[2.83 (0.47–9.35)]		
			1–9 yr	4	[1.97 (0.63–4.75)]		
			10–19 yr	3	[1.49 (0.38–4.06)]		
			20–29 yr	6	[1.31 (0.53–2.73)]		
			30–39 yr	7	[1.07 (0.47–2.12)]		
			≥ 40 yr	2	[2.02 (0.34–6.67)]		
		Lung, mortality	Exposure index (year × weight) (SMR):				
			0	2	[1.76 (0.30–5.82)]		
			> 0, < 1	1	[1.69 (0.08–8.33)]		
			1–4	1	[1.14 (0.06–5.62)]		
			5–9	4	[2.58 (0.82–6.23)]		
			10–14	2	[1.90 (0.32–6.28)]		
			15–19	2	[1.39 (0.23–4.59)]		
			20–24	1	[0.32 (0.02–1.58)]		
			25–29	4	[1.11 (0.35–2.68)]		
			30–35	3	[1.21 (0.31–3.29)]		
			> 35	4	[4.08 (1.30–9.85)]		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) Australia Enrolment, varied by agency/follow-up, 1980–2011 (mortality); 1982–2010 (incidence) Cohort	39 644 female firefighters, both paid [career] (1682) and volunteer (37 962), from nine fire agencies in Australia Exposure assessment method: ever career or volunteer firefighter, ever attended an incident, tertiles of cumulative number of incidents and type of incidents attended from personnel records	Respiratory system, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents for volunteer firefighters. Included specific incident types but early exposure extrapolated from more recent data. Volunteers mainly rural. *Strengths*: study of female firefighters, includes predominantly rural firefighters, ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up, young age at end of follow-up, probable healthy-worker bias; little information on confounders.
			All volunteer firefighters	66	0.90 (0.70–1.15)		
			Volunteers who attended incidents	34	1.23 (0.85–1.72)		
		Respiratory system, incidence	No. of incidents, all volunteers (RIR) [equivalent to rate ratios]:				
			Zero incidents	28	1		
			Tertile 1	10	1.25 (0.61–2.57)		
			Tertile 2	11	1.17 (0.58–2.35)		
			Tertile 3	13	1.60 (0.83–3.09)		
			Trend-test *P* value, 0.51				
		Respiratory system, incidence	No. of fire incidents, all volunteers (RIR):				
			Zero incidents	30	1		
			Tertile 1	10	1.27 (0.62–2.60)		
			Tertile 2	9	1.11 (0.53–2.34)		
			Tertile 3	13	1.69 (0.88–3.23)		
			Trend-test *P* value, 0.46				
		Respiratory system, incidence	No. of structure fire incidents, all volunteers (RIR):				
			Zero incidents	52	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	6	1.21 (0.52–2.82)		
			Tertile 3	4	0.84 (0.30–2.33)		
			Trend-test *P* value, 0.17				
		Respiratory system, incidence	No. of landscape fire incidents, all volunteers (RIR):				
			Zero incidents	33	1		
			Tertile 1	10	1.52 (0.75–3.09)		
			Tertile 2	5	0.64 (0.25–1.63)		
			Tertile 3	14	1.82 (0.97–3.40)		
			Trend-test *P* value, 0.56				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Respiratory system, incidence	No. of vehicle fire incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	53	1		
			Tertile 1	1	0.38 (0.05–2.59)		
			Tertile 2	3	0.90 (0.28–2.86)		
			Tertile 3	5	1.50 (0.60–3.76)		
			Trend-test *P* value, 0.18				
		Lung, incidence	SIR:				
			All volunteer firefighters	65	0.93 (0.72–1.18)		
			Volunteers who attended incidents	34	1.30 (0.90–1.82)		
		Lung, incidence	No. of incidents, all volunteers (RIR):				
			Zero incidents	27	1		
			Tertile 1	10	1.29 (0.63–2.67)		
			Tertile 2	11	1.21 (0.60–2.45)		
			Tertile 3	13	1.66 (0.86–3.22)		
			Trend-test *P* value, 0.51				
		Lung, incidence	No. of fire incidents, all volunteers (RIR):				
			Zero incidents	29	1		
			Tertile 1	10	1.31 (0.64–2.70)		
			Tertile 2	9	1.15 (0.54–2.43)		
			Tertile 3	13	1.74 (0.90–3.35)		
			Trend-test *P* value, 0.46				
		Lung, incidence	No. of structure fire incidents, all volunteers (RIR):				
			Zero incidents	51	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	6	1.23 (0.53–2.88)		
			Tertile 3	4	0.86 (0.31–2.37)		
			Trend-test *P* value, 0.17				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Lung, incidence	No. of landscape fire incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	32	1		
			Tertile 1	10	1.57 (0.78–3.19)		
			Tertile 2	5	0.66 (0.26–1.69)		
			Tertile 3	14	1.87 (1.00–3.51)		
			Trend-test *P* value, 0.56				
		Lung, incidence	No. of vehicle fire incidents, all volunteers (RIR):				
			Zero incidents	52	1		
			Tertile 1	1	0.36 (0.05–2.64)		
			Tertile 2	3	0.91 (0.29–2.93)		
			Tertile 3	5	1.53 (0.61–3.83)		
			Trend-test *P* value, 0.18				
		Mesothelioma, incidence	SIR:				
			All volunteer firefighters	3	1.47 (0.30–4.29)		
			Volunteers who attended incidents	1	1.29 (0.03–7.19)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) Australia Enrolment, date varied by agency (1998–2000)/ follow-up to 30 November 2011 (mortality) and 31 December 2010 (cancer incidence) Cohort	163 094 male volunteer firefighters from five fire agencies enrolled on or after the date on which the agency's roll was complete and who had ever held an active firefighting role Exposure assessment method: ever volunteer firefighter, categorical volunteer duration (years) and era from service records; ever volunteer firefighter who attended an incident, tertiles of cumulative emergency incidents from contemporary incident data	Respiratory system, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents. Included specific incident types but early exposure extrapolated from more recent data. Firefighters from rural or peri-urban areas. *Strengths*: includes predominantly rural firefighters, ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up, young age at end of follow-up, probable healthy-worker bias; little information on confounders.
			All volunteers	429	0.49 (0.45–0.54)		
			Volunteers who attended incidents	263	0.48 (0.42–0.54)		
		Respiratory system, incidence	Era of first service (SIR):				
			Pre-1970	118	0.41 (0.34–0.49)		
			1970–1994	163	0.50 (0.43–0.59)		
			1995 or after	148	0.58 (0.49–0.68)		
		Respiratory system, incidence	Duration of service, all volunteers (RIR) [equivalent to rate ratios]:				
			> 3 mo to < 10 yr	136	1		
			10–20 yr	101	1.18 (0.91–1.53)		
			≥ 20 yr	187	0.76 (0.61–0.96)		
			Trend-test *P* value, < 0.01				
		Respiratory system, incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	62	1		
			10–20 yr	67	1.35 (0.96–1.92)		
			≥ 20 yr	133	0.70 (0.51–0.95)		
			Trend-test *P* value, < 0.01				
		Respiratory system, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	247	1		
			Group 2	9	0.79 (0.41–1.54)		
			Group 3	7	1.27 (0.60–2.69)		
		Respiratory system, incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	246	1		
			Group 2	12	1.01 (0.57–1.81)		
			Group 3	5	1.03 (0.42–2.49)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Respiratory system, incidence	No. of structure fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	252	1		
			Group 2	7	1.01 (0.48–2.14)		
			Group 3	4	1.09 (0.41–2.93)		
		Respiratory system, incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	218	1		
			Group 2	29	0.74 (0.50–1.09)		
			Group 3	16	1.08 (0.65–1.80)		
		Respiratory system, incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	248	1		
			Group 2	9	0.76 (0.39–1.47)		
			Group 3	6	1.31 (0.58–2.95)		
		Larynx, incidence	SIR:				
			All volunteers	36	0.45 (0.31–0.62)		
			Volunteers who attended incidents	22	0.42 (0.26–0.63)		
		Lung, incidence	SIR:				
			All volunteers	371	0.48 (0.44–0.54)		
			Volunteers who attended incidents	228	0.47 (0.41–0.54)		
		Lung, incidence	Era of first service (SIR):				
			Pre-1970	109	0.42 (0.34–0.50)		
			1970–1994	141	0.50 (0.42–0.59)		
			1995 or after	121	0.55 (0.45–0.65)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Lung, incidence	Duration of service, all volunteers (RIR):			Age, calendar period	
			> 3 mo to < 10 yr	114	1		
			10–20 yr	86	1.19 (0.90–1.57)		
			≥ 20 yr	168	0.79 (0.62–1.01)		
			Trend-test *P* value, 0.03				
		Lung, incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	52	1		
			10–20 yr	57	1.36 (0.93–1.98)		
			≥ 20 yr	119	0.72 (0.51–1.00)		
			Trend-test *P* value, 0.01				
		Lung, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	214	1		
			Group 2	8	0.81 (0.40–1.65)		
			Group 3	6	1.26 (0.56–2.84)		
		Lung, incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	213	1		
			Group 2	11	1.07 (0.58–1.96)		
			Group 3	4	0.95 (0.35–2.56)		
		Lung, incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	218	1		
			Group 2	7	1.17 (0.55–2.49)		
			Group 3	3	0.95 (0.30–2.95)		
		Lung, incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	186	1		
			Group 2	27	0.81 (0.54–1.21)		
			Group 3	15	1.18 (0.70–2.00)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Lung, incidence	No. of vehicle fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	215	1		
			Group 2	9	0.88 (0.45–1.71)		
			Group 3	4	1.01 (0.38–2.73)		
		Mesothelioma, incidence	SIR:				
			All volunteers	42	0.64 (0.46–0.87)		
			Volunteers who attended incidents	22	0.54 (0.34–0.81)		
		Mesothelioma, incidence	Era of first service (SIR):				
			Pre-1970	7	0.30 (0.12–0.63)		
			1970–1994	17	0.72 (0.42–1.15)		
			1995 or after	18	0.98 (0.58–1.55)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) Australia Enrolment, 1976–2003/follow-up, 1976–2011 (mortality), 1982–2010 (incidence, except two states, 2009) Cohort	30 057 full- (17 394) or part-time (12 663) paid male firefighters employed at one of eight Australian fire agencies for ≥ 3 mo from start of personnel records (1976–2003, depending on agency) Exposure assessment method: employed as a part-time or full-time firefighter for ≥ 3 mo, categorical employment duration (years) and era from employment records; tertiles of cumulative emergency incidents and type of incident attended from contemporary incident data	Respiratory system, incidence	Firefighter status (SIR):			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents, including specific incident types. Included specific incident types but early exposure extrapolated from more recent data. Municipal firefighters. *Strengths*: internal analysis by exposure to number and type of incidents, ascertained cancer incidence. *Limitations*: healthy-worker hire bias; short length of follow-up, young age at end of follow-up; little information on potential confounders.
			Full-time	100	0.81 (0.66–0.99)		
			Part-time	17	0.41 (0.24–0.65)		
			All	117	0.71 (0.59–0.85)		
		Respiratory system, incidence	Duration of employment, full-time firefighters (RIR) [equivalent to rate ratios]:				
			> 3 mo to 10 yr	9	1		
			10–20 yr	15	1.28 (0.55–2.96)		
			≥ 20 yr	75	0.99 (0.45–2.18)		
			Trend-test *P* value, 0.75				
		Respiratory system, incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	5	1		
			10–20 yr	2	0.48 (0.08–2.72)		
			≥ 20 yr	10	1.13 (0.28–4.58)		
			Trend-test *P* value, 0.71				
		Respiratory system, incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	14	1		
			10–20 yr	17	1.15 (0.55–2.39)		
			≥ 20 yr	85	1.15 (0.59–2.27)		
			Trend-test *P* value, 0.71				
		Respiratory system, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	6	1		
			Tertile 2	4	0.72 (0.20–2.55)		
			Tertile 3	12	1.58 (0.59–4.28)		
			Trend-test *P* value, 0.31				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Respiratory system, incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	6	1		
			Tertile 2	5	0.97 (0.30–3.21)		
			Tertile 3	11	1.37 (0.50–3.76)		
			Trend-test *P* value, 0.52				
		Respiratory system, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	6	1		
			Tertile 2	6	1.19 (0.38–3.70)		
			Tertile 3	10	1.23 (0.44–3.42)		
			Trend-test *P* value, 0.70				
		Respiratory system, incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	8	1		
			Tertile 2	6	0.83 (0.29–2.40)		
			Tertile 3	8	0.79 (0.29–2.13)		
			Trend-test *P* value, 0.64				
		Respiratory system, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	5	1		
			Tertile 2	5	1.21 (0.35–4.23)		
			Tertile 3	12	1.97 (0.69–5.64)		
			Trend-test *P* value, 0.19				
		Respiratory system, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	9	1.05 (0.48–1.99)		
			10–20 yr	15	0.95 (0.53–1.56)		
			≥ 20 yr	75	0.77 (0.60–0.96)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Respiratory system, incidence	Duration of employment, part-time firefighters (SIR):			Age, calendar period	
			> 3 mo to 10 yr	5	0.57 (0.18–1.33)		
			10–20 yr	2	0.22 (0.03–0.80)		
			≥ 20 yr	10	0.42 (0.20–0.78)		
		Respiratory system, incidence	Era of first employment, full-time firefighters (SIR):			5-yr-interval age groups	
			Pre-1970	61	0.83 (0.63–1.06)		
			1970–1994	34	0.78 (0.54–1.08)		
			1995 or after	5	0.93 (0.30–2.16)		
		Respiratory system, incidence	Era of first employment, part-time firefighters (SIR):			5-yr-interval age groups	
			Pre-1970	1	0.09 (0.00–0.49)		
			1970–1994	15	0.60 (0.34–1.00)		
			1995 or after	1	0.18 (0.00–1.02)		
		Larynx, incidence	Firefighter status (SIR):			Age, calendar period	
			Full-time	11	0.86 (0.43–1.54)		
			Part-time	1	0.23 (0.01–1.26)		
			All	12	0.70 (0.36–1.22)		
		Larynx, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	1	1.05 (0.03–5.85)		
			10–20 yr	3	1.65 (0.34–4.81)		
			≥ 20 yr	7	0.71 (0.28–1.46)		
		Larynx	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	0	0 (NR)		
			10–20 yr	0	0 (NR)		
			≥ 20 yr	1	0.43 (0.01–2.38)		
		Larynx, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	5	0.72 (0.23–1.67)		
			1970–1994	5	0.97 (0.31–2.26)		
			1995 or after	1	1.71 (0.04–9.53)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Larynx, incidence	Era of first employment, part-time firefighters (SIR):			Age, calendar period	
			Pre-1970	0	0 (NR)		
			1970–1994	1	0.36 (0.01–2.00)		
			1995 or after	0	0 (NR)		
		Lung, incidence	Firefighter status (SIR):				
			Full-time	86	0.81 (0.65–1.00)		
			Part-time	15	0.42 (0.23–0.69)		
			All	101	0.71 (0.58–0.86)		
		Lung, incidence	Duration of employment, full-time firefighters (RIR):				
			> 3 mo to 10 yr	8	1		
			10–20 yr	11	1.01 (0.40–2.56)		
			≥ 20 yr	66	0.84 (0.36–1.96)		
			Trend-test *P* value, 0.60				
		Lung, incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	4	1		
			10–20 yr	2	0.70 (0.11–4.37)		
			≥ 20 yr	9	1.62 (0.33–7.90)		
			Trend-test *P* value, 0.46				
		Lung, incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	12	1		
			10–20 yr	13	0.99 (0.44–2.23)		
			≥ 20 yr	75	1.06 (0.51–2.21)		
			Trend-test *P* value, 0.84				
		Lung, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	5	1		
			Tertile 2	4	0.88 (0.24–3.31)		
			Tertile 3	7	1.07 (0.34–3.43)		
			Trend-test *P* value, 0.90				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Lung, incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	5	1		
			Tertile 2	4	0.98 (0.26–3.70)		
			Tertile 3	7	0.99 (0.31–3.18)		
			Trend-test *P* value, 0.99				
		Lung, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	5	1		
			Tertile 2	5	1.23 (0.35–4.28)		
			Tertile 3	6	0.84 (0.25–2.76)		
			Trend-test *P* value, 0.75				
		Lung, incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	7	1		
			Tertile 2	4	0.65 (0.19–2.24)		
			Tertile 3	5	0.55 (0.17–1.76)		
			Trend-test *P* value, 0.31				
		Lung, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	4	1		
			Tertile 2	4	0.28 (0.32–5.16)		
			Tertile 3	8	1.59 (0.47–5.30)		
			Trend-test *P* value, 0.45				
		Lung, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	8	1.14 (0.49–2.25)		
			10–20 yr	11	0.83 (0.42–1.49)		
			≥ 20 yr	66	0.77 (0.60–0.98)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Lung, incidence	Duration of employment, part-time firefighters (SIR):			Age, calendar period	
			> 3 mo to 10 yr	4	0.56 (0.15–1.44)		
			10–20 yr	2	0.26 (0.03–0.94)		
			≥ 20 yr	9	0.43 (0.20–0.82)		
		Lung, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	54	0.83 (0.62–1.08)		
			1970–1994	28	0.76 (0.51–1.10)		
			1995 or after	4	0.91 (0.25–2.32)		
		Lung, incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	1	0.10 (0.00–0.55)		
			1970–1994	13	0.61 (0.33–1.05)		
			1995 or after	1	0.23 (0.01–1.27)		
		Mesothelioma, incidence	Firefighter status (SIR):				
			Full-time	11	1.33 (0.66–2.37)		
			Part-time	4	1.38 (0.37–3.52)		
			All	15	1.34 (0.75–2.21)		
		Mesothelioma, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	3	5.82 (1.20–17.00)		
			10–20 yr	2	2.01 (0.24–7.25)		
			≥ 20 yr	6	0.89 (0.33–1.94)		
		Mesothelioma, incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	1	2.00 (0.05–11.12)		
			10–20 yr	1	1.62 (0.04–9.04)		
			≥ 20 yr	2	1.12 (0.14–4.05)		
		Mesothelioma, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	3	0.59 (0.12–1.71)		
			1970–1994	6	2.08 (0.76–4.53)		
			1995 or after	2	6.65 (0.81–24.02)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Mesothelioma, incidence	Era of first employment, part-time firefighters (SIR):			Age, calendar period	
			Pre-1970	1	1.14 (0.03–6.37)		
			1970–1994	2	1.15 (0.14–4.14)		
			1995 or after	1	3.49 (0.09–19.46)		
Glass et al. (2016b) Victoria, Australia Enrolment, 1971–1999/follow-up, 1980–2011 (mortality), 1982–2012 (incidence) Cohort	614 male (611) and female (3) employed and volunteer Country Fire Authority trainers and a group of paid [career] Country Fire Authority firefighters who trained at the Fiskville site between 1971 and 1999; all analyses limited to men as no deaths or cancers were observed among women Exposure assessment method: employed or volunteer firefighter trainers and paid [career] firefighters who trained at training facility for any period of time from human resource records, categorized into risk of low, medium, and high chronic exposure to smoke and other agents based on job assignment	Respiratory system, incidence	Risk of chronic exposure (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Incorporated categorical level of exposure into assessment for each type of firefighter. Volunteers mainly rural, paid [career] firefighters were municipal. *Strengths*: included firefighter instructors with high potential exposure to smoke and other hazardous agents, assessed exposure based on job assignment. *Limitations*: low number of cases, young age at end of follow-up.
			Low	0	0		
			Medium	3	0.84 (0.17–2.46)		
			High	1	0.68 (0.02–3.77)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bates et al. (2001) New Zealand Enrolment, 1977 through June 1995/follow-up, 1977–1995 (mortality), 1977–1996 (incidence) Cohort	4305; the cohort comprised all male (4221) and female (84) firefighters (paid [career] and volunteer) employed as a career firefighter for ≥ 1 yr and who also worked as a career firefighter for ≥ 1 day between 1977 and 1995; all analyses limited to men due to small numbers of women Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Lung, incidence	Follow-up period (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job classification. May include urban [municipal] and rural firefighters. *Strengths*: ascertained both incidence and mortality outcomes. *Limitations*: little information on confounders; significant loss to follow-up.
			1977–1996	17	1.14 (0.7–1.8)		
			1990–1996	7	0.82 (0.3–1.7)		
		Lung, incidence	Duration of paid service (SIR):				
			0–10 yr	3	0.93 (0.2–2.7)		
			11–20 yr	4	1.45 (0.4–3.7)		
			> 20 yr	8	1.52 (0.7–3.0)		
			Trend-test *P* value, 0.48				
		Lung, incidence	Duration of paid and volunteer service (SIR):				
			0–10 yr	1	0.66 (0.0–3.7)		
			11–20 yr	4	2.04 (0.6–5.2)		
			> 20 yr	10	1.25 (0.6–2.3)		
			Trend-test *P* value, 0.85				
		Lung, mortality	SMR:				
			Firefighters vs male New Zealand population	10	0.86 (0.4–1.6)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2016) Europe, Canada, New Zealand, and China 1985–2010 Case–control	Cases: 14 748 adult male lung cancer cases with information on smoking or work history extracted from the SYNERGY-studies database of pooled case–control studies Controls: 17 543; control selection varied between individual studies and were drawn from the general population or hospitals Exposure assessment method: questionnaire; ever employed, and categorical duration of employment (years), from self-reports coded from interviews	Lung, incidence	Firefighter status (OR):			Age, study site	*Exposure assessment critique*: Satisfactory quality. Possible recall bias. May be heterogeneity of exposure, includes urban [municipal] and rural firefighters, from several countries, differing time periods and categories of firefighter. *Strengths*: large study size; smoking information is available. *Limitations*: potential for recall bias; lacking information on exposure; hospital controls were used for some studies, which may be a poor referent for healthy individuals selected into firefighting.
			Never	14 662	1		
			Ever	86	1.03 (0.77–1.38)		
		Lung, incidence	Duration of firefighter employment (OR):				
			Never	14 662	1		
			< 6 yr	32	1.56 (0.91–2.67)		
			6–21 yr	22	1.13 (0.64–2.00)		
			22–32 yr	14	0.69 (0.36–1.33)		
			≥ 33 yr	18	0.84 (0.46–1.53)		
			Trend-test *P* value, 0.46				
		Lung, incidence	Firefighter status (OR):			Age, study site, pack-years, and time since quitting smoking	
			Never	14 662	1		
			Ever	86	0.95 (0.68–1.32)		
		Lung, incidence	Duration of firefighter employment (OR):				
			Never	14 662	1		
			< 6 yr	32	1.19 (0.65–2.15)		
			6–21 yr	22	0.99 (0.52–1.86)		
			22–32 yr	14	0.70 (0.32–1.50)		
			≥ 33 yr	18	0.91 (0.47–1.77)		
			Trend-test *P* value, 0.58				
		Lung, incidence	Firefighter status (OR):			Age, study site, pack-years, and time since quitting smoking, employed in other exposed job (ever/never)	
			Never	14 662	1		
			Ever	86	0.95 (0.68–1.32)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2016) (cont.)		Lung, incidence	Duration of firefighter employment (OR):			Age, study site, pack-years, and time since quitting smoking, employed in other exposed job (ever/never)	
			Never	14 662	1		
			< 6 yr	32	1.21 (0.67–2.19)		
			6–21 yr	22	0.97 (0.51–1.84)		
			22–32 yr	14	0.69 (0.32–1.49)		
			≥ 33 yr	18	0.92 (0.48–1.78)		
			Trend-test *P* value, 0.58				
		Lung, incidence	Firefighter status, never smokers (OR):			Age, study site	
			Never	457	1		
			Ever	2	0.60 (0.14–2.58)		
		Lung, incidence	Firefighter status, former smokers (OR):			Age, study site, pack-years, and time since quitting smoking	
			Never	4922	1		
			Ever	25	0.75 (0.45–1.26)		
		Lung, incidence	Firefighter status, current smokers (OR):			Age, study site, smoking pack-years	
			Never	9278	1		
			Ever	59	1.18 (0.73–1.90)		
		Lung (adenocarcinoma), incidence	Firefighter status (OR):			Age, study site, pack-years, and time since quitting smoking	
			Never	3832	1		
			Ever	24	1.03 (0.64–1.67)		
		Lung (squamous cell carcinoma), incidence	Firefighter status (OR):				
			Never	5938	1		
			Ever	34	1.03 (0.66–1.60)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2016) (cont.)		Lung (small cell/ oat cell), incidence	Firefighter status (OR):			Age, study site, pack-years, and time since quitting smoking	
			Never	2263	1		
			Ever	15	1.03 (0.57–1.87)		
		Other (specify): lung (other/ unspecified histological type), incidence	Firefighter status (OR):				
			Never	2629	1		
			Ever	13	0.84 (0.46–1.55)		

9/11, World Trade Center disaster, 11 September 2001; BMI, body mass index; CFHS, Career Firefighter Health Study; CI, confidence interval; FDNY, Fire Department of the City of New York; HR, hazard ratio; HWSE, healthy-worker survivor effect; ICD-10, International Classification of Diseases, 10th revision; IDR, incidence density ratio; LRT, likelihood ratio test; mo, month; NJ, New Jersey; NR, not reported; OR, odds ratio; PMR, proportionate mortality ratio; RCS, restricted cubic splines; RIR, relative incidence ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; vs, versus; SRR, standardized rate ratio; vs, versus; WTC, World Trade Center; yr, year.

these studies were excluded because they largely represented earlier follow-up of other included studies (Heyer et al., 1990; Beaumont et al., 1991; Baris et al., 2001). The remaining two studies from the USA presented results from mortality analyses in cohorts from the State of New Jersey, and from Buffalo, New York, respectively (Feuer & Rosenman, 1986; Vena & Fiedler, 1987). Two cohort studies from Canada reported on cancer mortality among firefighters in Edmonton and Calgary, and in Toronto, respectively (Guidotti, 1993; Aronson et al., 1994). In Oceania, cancer incidence among firefighters has been reported in five occupational and population-based studies, of which four were from Australia (Glass et al., 2016a, b, 2017, 2019) and one from New Zealand (Bates et al., 2001).

In addition to ever-employment in the occupation, exposure was typically defined as duration of employment or firefighting activity, ever-employment in a fire combat role, time since first or last employment, age at exposure, or exposure calendar period. In some instances, the authors had developed quantitative metrics on the basis of work history records or job-exposure matrices to assign exposure to the number and type of incidents, the number of fire-runs, fire-hours (i.e. the time spent at fires), or exposure days. [Since these studies included exposure contrasts, they were generally more informative than studies relying on classification on the basis of job title only. Although long follow-up periods were generally a strength of many of these studies, long follow-up can also prove to be a challenge for exposure assessment, because exposures are likely to change over time, employment records may not capture time spent firefighting, and exposures were assessed retrospectively in the cohort studies] (see Section 1.8.1 for more detail).

A cohort mortality study of 33 442 male professional [career] emergency responders (of whom 29 453, or 88%, were firefighters) in the Republic of Korea, who had been employed for ≥ 1 month between 1980 and 2007 and followed up from 1992 through 2007, provided information on the risk of cancer of the lung and bronchus (Ahn & Jeong, 2015). Firefighters were identified from a national database of emergency responders using work history and job title information, and were defined as any individual with first-line (e.g. pump, ladder, and operation chief) or second-line (e.g. drivers and division chief) firefighting duties in their work history. Mortality information was ascertained through a national database with near complete follow-up. The male population of the Republic of Korea was used as the reference population for the standardized mortality ratio (SMR), which was adjusted for age and calendar year, with a 1-year lag. An internal analysis using Poisson regression models that adjusted for age and calendar year was also performed. Twenty-six deaths from lung cancer were identified among the firefighters. The overall SMR for lung cancer was decreased for firefighters compared with the population of the Republic of Korea (SMR, 0.58; 95% confidence interval, CI, 0.38–0.84), and SMRs in three categories of employment duration (< 10, 10 to < 20, and ≥ 20 years) were all less than one. The internal analyses suggested an increased risk [estimated using adjusted rate ratios] of lung cancer for firefighters with ≥ 20 years of employment (adjusted relative risk, ARR, 1.21; 95% CI, 0.46–3.18; 13 deaths) and a decreased risk for firefighters with 10 to < 20 years of employment (ARR, 0.71; 95% CI, 0.26–1.96; 7 deaths) compared with firefighters with < 10 years of employment and non-firefighters within the cohort, but the results were statistically imprecise. [The Working Group noted that this study was limited by little adjustment for confounding (no adjustment for smoking), a relatively short length of follow-up (mean follow-up, 11.3 years), the relatively young age of the cohort (mean age at the end of follow-up, 41.3 years), and the low number of cases. The consideration of employment duration and job title was a strength of the exposure assessment, although there was no

analysis of tasks performed. The study population included firefighting activity across the country, various work shifts (e.g. full-time and part-time work), and probably included both municipal and rural firefighters. Analyses by duration of employment and the use of internal analyses comparing firefighters with emergency responders and firefighters with < 10 years of experience was a strength and limited the influence of healthy-worker hire bias.]

An earlier study of the same cohort of 33 416 male professional [career] emergency responders (of whom 29 438, or 88%, were firefighters) in the Republic of Korea investigated incidence of rather than mortality from cancers of the respiratory system (Ahn et al., 2012). Follow-up for cancer incidence was conducted from 1996 through 2007 using data from a national cancer registry that had near complete follow-up. Stratified standardized incidence ratios (SIRs) were calculated for firefighters who had worked for ≥ 10 years and those who had worked for < 10 years, using the male population of the Republic of Korea as the referent. An internal analysis was also performed using age- and calendar year-adjusted standardized rate ratios (SRR) estimated through Poisson regression in which the incidence of cancer of the lung and bronchus among firefighters was compared with that among non-firefighters. In the external comparison, an apparent decreased risk was observed in the incidence of cancer of the lung and bronchus (SIR, 0.78; 95% CI, 0.55–1.09; 36 cases) and cancer of the larynx (SIR, 0.57; 95% CI, 0.11–1.67; 3 cases). The risk was not found to be increased among workers with an employment duration of > 10 years. There was also little evidence from the internal analysis for an increased risk of cancer of the lung in firefighters (SRR, 0.69; 95% CI, 0.21–2.26; 36 cases) compared with non-firefighter emergency responders, although the estimate was imprecise. [The Working Group noted that the SIR analysis in this study was limited by probable healthy-worker hire bias, limited adjustment for confounding (with no adjustment for smoking; the firefighter cohort reportedly smoked a little less and had less obesity than the comparison population), a relatively short length of follow-up (maximum follow-up, 12 years), the relatively young age of the cohort (mean age at the end of follow-up, 41.3 years), and the low number of cases. The analyses by employment duration and internal analyses comparing firefighters with non-firefighter emergency responders were strengths; however, most cohort members were classified as firefighters even though many were primarily medical/rescue technicians who only rotated temporarily through firefighter duties, potentially leading to non-differential exposure misclassification that would tend to bias the results towards the null. The study did not distinguish between typical exposure scenes (e.g. structure or wildland firefighting, and municipal or rural settings.]

An incidence and mortality study in a cohort of 3881 male professional [career] firefighters in Norway provided information on the risk of cancers of the respiratory system (larynx, lung, and mesothelioma) (Marjerrison et al., 2022a, b). Participants were firefighters employed in any of 15 fire departments covering 50% of the Norwegian population, with a geographical spread that was representative of the general population. The firefighters had worked in one of the departments at some time between 1950 and 2019, and most (92%) were engaged full-time throughout their employment. The cohort included firefighters with past or present positions entailing active firefighting duties; individuals who had worked exclusively as chimney sweeps, fire inspectors, or office personnel were excluded. [Results were also presented for the broader cohort that included never-active firefighting personnel, but the Working Group considered the results for active firefighters to be more informative.] Incidence data came from the Cancer Registry of Norway, for which there is mandatory reporting of cancers. Mortality

data came from the Norwegian Cause of Death Registry. The follow-up period for both the cancer incidence and mortality analyses was from 1960 through 2018 (mean follow-up length for cancer incidence, 28 years). The general male population of Norway was the reference population for SIRs and SMRs, which were standardized by age and calendar year. The results of analyses conducted by year of first employment, time since first employment, and duration of employment were reported in Marjerrison et al. (2022a), whereas results stratified by follow-up period and age at diagnosis were reported for both incidence and mortality in Marjerrison et al. (2022b). The estimated risk of cancer of the larynx among firefighters was higher than that in the general population, but the result was imprecise (SIR, 1.77; 95% CI, 0.91–3.08; 12 cases); the SMR point estimate was similar but had even less precision (SMR, 1.92; 95% CI, 0.52–4.91; < 5 deaths). There was little evidence to suggest that the risk of cancer of the lung was raised in firefighters compared with the general population, whether based on incidence (SIR, 0.98; 95% CI, 0.78–1.22; 81 cases) or mortality (SMR, 0.91; 95% CI, 0.69–1.16; 61 deaths). The risk of mesothelioma appeared to be considerably elevated compared with that in the general population, although the number of cases was small (SIR, 2.46; 95% CI, 0.99–5.06; 7 cases; and SMR, 2.40; 95% CI, 0.65–6.15; < 5 deaths). Separate stratified analyses were also conducted. Most of these were too imprecise to be informative for cancer of the larynx or for mesothelioma, but risk for cancer of the larynx in firefighters did appear to be elevated compared with that in the general population ≥ 40 years after first employment, after ≥ 30 years of employment, for follow-up from 1985 through 1994, and for cases diagnosed in firefighters aged ≥ 70 years. For mesothelioma, elevated risk was found for ≥ 40 years after first employment, after ≥ 30 years of employment, and for follow-up from 1995 onwards. The precision was better for analyses of cancer of the lung because of the larger number of cases, but there was no strong evidence of an increase in risk for any of the stratified analyses. [The Working Group noted that this study was limited by probable healthy-worker hire bias, the low number of cases of laryngeal cancer and mesothelioma, and the lack of data on potential confounders apart from age, calendar year, and sex. Although the analyses excluded individuals who had never performed active firefighting duties, the main limitations regarding the exposure assessment were that job changes over time were not accounted for, and that the proportion of rural to municipal firefighters was unknown. Healthy-worker hire bias may have influenced results because of the lack of internal analyses by specific job tasks and the use of an external reference group. The ascertainment of cancer incidence, the long length of follow-up, and the stratification of analyses on the basis of duration and time of employment were strengths. The presentation of both incidence and mortality data for the same sites and strata allowed for direct comparisons of the potential for surveillance bias.]

A study of cancer incidence in a cohort of 8136 male firefighters that used an extended follow-up of the Nordic Occupational Cancer (NOCCA) cohort in Sweden provided information on risk of cancers of the respiratory system (larynx, lung, and mesothelioma). Employment information was ascertained from national decennial censuses, starting in 1960 and ending in 1990 (eligible firefighters had to be aged between 30 and 64 years at the time of the relevant census and have worked as a firefighter for more than half of regular working hours that year). Cancer incidence data were ascertained from the Swedish Cancer Registry with follow-up from 1961 through 2009 (mean follow-up length, 28 years) (Bigert et al., 2020). The extent of any increased risk was assessed by external comparisons, including analyses of work duration as a proxy for exposure, and stratified by calendar period of follow-up. The male general population

of Sweden was the referent for all external comparisons. For external comparison estimates stratified by duration of employment categories, tests for a linear trend were conducted using a generalized linear model. There were no findings of elevated risk for cancer of the larynx or lung. The SIR for laryngeal cancer was 0.92 (95% CI, 0.48–1.61; 12 cases). For lung cancer, the overall SIR was 0.87 (95% CI, 0.72–1.05; 110 cases), with no elevated risk observed for analyses based on histological subtype, or after stratification by duration of employment ($P = 0.10$) or period of follow-up. Similar analyses specific to the incidence of adenocarcinoma were too imprecise to be informative. The incidence of mesothelioma was modestly elevated with an SIR of 1.11 (95% CI, 0.45–2.29; 7 cases). A separate analysis of mesothelioma stratified by duration of employment was too imprecise to be informative. [The Working Group noted that this study was limited by probable healthy-worker hire bias given the use of a single external general population referent, the lack of work history data from employment records, and the absence of data on potential confounders apart from age, sex, and calendar time. There was likely to have been error (non-differential misclassification) in the measurement of duration of employment as a firefighter given that data were collected from the decennial census. It was unclear whether individuals were active firefighters for the whole of their employment, and the cohort probably included a combination of full-time, part-time, municipal, and rural firefighters. Strengths of this study included the long follow-up period, the ascertainment of cancer incidence, and analyses stratified by calendar period of employment.]

A study of cancer incidence in a cohort of 1080 male firefighters in Stockholm, Sweden, provided information on the risk of cancer of the bronchus and lung combined, and cancer of the pleura (Kullberg et al., 2018). Firefighters were identified through annual enrolment records from 15 fire stations in Stockholm and had worked for ≥ 1 year between 1931 and 1983. This was an update to a previous study (Tornling et al., 1994) and added 26 years of follow-up for cancer incidence (from 1958 through 2012) from the Swedish Cancer Registry. For the incidence results, only those from the more recent study are discussed here. External comparisons were made with reference rates for the male general population of Stockholm County. Analyses were also stratified by age, employment duration, and starting year of employment for some cancer outcomes. The overall SIR for bronchus and lung cancer combined was less than one (SIR, 0.79; 95% CI, 0.52–1.15; 27 cases). There were only two cases of cancer of the pleura although 0.8 cases were expected. [The Working Group noted that this study was limited by probable healthy-worker hire bias, because of the reliance on an external reference population, and by a lack of data on important potential confounders, particularly smoking. Strengths of this study included the ascertainment of cancer incidence, the long follow-up period, and analyses stratified by duration and era of employment, although stratified results were not reported for cancers of the respiratory system. Although the long follow-up period was a strength, it could also lead to misclassification of exposure because job activities and exposures probably changed over the study period and no results were reported for an association with job tasks or number of fires attended. It was unclear to what extent individuals had undertaken active firefighting duties during their employment.]

The earlier study of the same cohort also investigated mortality outcomes in a slightly larger population of 1116 male firefighters and provided information on risk of lung cancer mortality (Tornling et al., 1994). Vital status was determined through linkage with the census, death register, and emigration register. The cause of death was obtained from official death certificates. Mortality follow-up was from 1951 to the end of 1986. Exposure to fire events was assessed

using reports of fires fought by the Stockholm fire brigade between 1933 and 1983, although associations were not reported for cancers of the respiratory tract. With male regional mortality as the referent, the overall SMR for lung cancer (SMR, 0.90; 95% CI, 0.53–1.42; 18 deaths) was not elevated. [The Working Group noted that this study was limited by probable healthy-worker hire bias and a lack of data on important potential confounders, particularly smoking. A strength of the exposure assessment was the differentiation of exposure on the basis of number of fires fought accounting for job position, station, and year of exposure, although associations were reported for few outcomes.]

A cancer incidence study in a cohort of 9061 male full-time, part-time, and volunteer firefighters in Denmark provided information on risk of cancers of the larynx and lung, and mesothelioma (Petersen et al., 2018a). Firefighters were identified using employer, trade union, and Danish Civil Registration System records that contained information on work history. Firefighters from all municipal districts in Denmark were represented in the cohort. Cohort members had been employed as firefighters at some time between 1964 and 2004, and cancer incidence follow-up was conducted in the Danish Cancer Registry from 1968 through 2014. Several proxy measures of exposure were used, including duration of employment, era of first employment, employment type (e.g. full-time, other), and job function (e.g. regular, specialized). The subpopulation of firefighters identified as "specialized" were smoke divers, who were considered to have a heavier exposure to smoke than the other firefighters. Three populations served as reference populations in external SIR analyses: the national male general population of Denmark, a random sample of Danish male employees, and Danish military personnel. Internal comparisons were also conducted, but results contributed little new information and were not reported. A total of 132 cases of lung cancer were identified, with overall SIRs of close to one using all three comparison populations (estimates ranging from 0.91 to 1.06). The SIRs were also less than, but generally close to, the null for analyses based on all proxy measures of exposure, including full-time versus other employment types. The exception was employment duration, for which the SIR estimate was modestly raised (SIR, 1.13; 95% CI, 0.85–1.49; 50 cases) for < 1 year of employment, but less than one for longer durations of employment, including ≥ 1 year (SIR, 0.81; 95% CI, 0.65–1.00; 82 cases), ≥ 10 years (SIR, 0.73; 95% CI, 0.57–0.93; 65 cases), and ≥ 20 years (SIR, 0.70; 95% CI, 0.53–0.93; 49 cases). For cancer of the larynx (SIRs ranging from 0.92 to 1.01; 16 cases) and mesothelioma (SIRs ranging from 0.65 to 0.71; 4 cases), point estimates were below or close to one. For mesothelioma, results were imprecise and were not stratified by full-time versus part-time employment status or other proxies of exposure. [The Working Group noted that this study was limited by a lack of adjustment for confounders, particularly smoking. Also, more than half of the cohort consisted of part-time/volunteer firefighters, which could have biased the result for mesothelioma towards the null. Strengths of this study included the use of working and military reference populations to reduce the influence of healthy-worker hire bias, the long period of follow-up, the ascertainment of cancer incidence outcomes, and the analyses by various proxies of exposure, such as job task. The study population excluded those without actual firefighting exposure based on job title/function.]

Cancer mortality was investigated in the same cohort of Danish firefighters over a similar calendar period (Petersen et al., 2018b). An expanded study population of 11 775 male firefighters was identified using the same methods as described in Petersen et al. (2018a). Firefighters were followed for mortality and cause of death in the Danish national death registry from 1970 through 2014. The mean length of follow-up was

28 years for full-time firefighters and 17 years for part-time and volunteer firefighters. Two reference populations were used for external comparison analyses – a random sample of the Danish working male population and a sample of Danish military personnel. Seventy-six deaths from cancers of the larynx, trachea, and lung were identified, with a modest excess of deaths from this cause (SMR, 1.13; 95% CI, 0.91–1.42), in the subsample of full-time firefighters (n = 4659) compared with the military reference population. The SMR among part-time and volunteer firefighters was also modestly elevated (SMR, 1.16; 95% CI, 0.86–1.57; 42 deaths) compared with the military referent. For full-time firefighters, the SMRs based on duration of employment were imprecise but close to one, apart from that for firefighters who had worked for < 1 year (SMR, 1.30; 95% CI, 0.96–1.77; 41 deaths). There was no test for trend in risk across employment duration categories. [The Working Group noted that this study was largely subject to the same strengths and limitations as the cancer incidence study by Petersen et al. (2018a). The reliance on mortality outcomes in this study may have contributed to a survival bias, in the sense that occupational exposure as a firefighter may have conferred survival advantage because of earlier detection or better treatment availability than that for non-firefighters.]

A series of studies in the USA evaluated the cancer experience of firefighters from the Fire Department of New York (FDNY) who were involved in the WTC disaster response in 2001 (Zeig-Owens et al., 2011; Moir et al., 2016; Webber et al., 2021). These studies reported various lengths of follow-up for certain cancer sites, in addition to an assessment of exposure at the disaster site and evaluation of medical surveillance bias. Comparisons were also made with a separate cohort study of United States (US) municipal firefighters in which an assessment of exposure to firefighting activities was conducted (Daniels et al., 2014, 2015; Pinkerton et al., 2020).

The most recent study was of cancer incidence in a cohort of 10 786 male firefighters from the FDNY and 8813 male firefighters from the Career Firefighter Health Study (CFHS), which included firefighters from Philadelphia, Chicago, and San Francisco fire departments, USA, and provided information on the risk of lung cancer (Webber et al., 2021) [a previous study by Moir et al. (2016) was not reviewed here since it did not report the latest follow-up for lung cancer]. Firefighters were included if they had been employed on 11 September 2001, and the FDNY firefighters had to have worked at the WTC disaster site for ≥ 1 day between 11 September 2001 and 25 July 2002. Cancer incidence follow-up was conducted using several state cancer registries selected on the basis of residential history information, beginning on 11 September 2001 and ending in 2016. Exposure for FDNY firefighters was categorized into one of five groups on the basis of the time of arrival and first day of work at the WTC site. All CFHS firefighters were considered to be unexposed using this exposure metric. External comparisons were made using the US male general population as the referent. In addition, internal comparisons were made comparing incidence rates in the FDNY to rates in the CFHS using Poisson regression, controlling for age and race or ethnicity. Several secondary and sensitivity analyses were performed. These included attempting to take into account increased medical surveillance of the FDNY cohort by adding a 2-year and 5-year lag to external comparison analyses for lung cancers diagnosed within 6 months of a routine computerized tomography (CT) scan of the chest, adjusting for smoking in internal regression analyses among the subset of firefighters for whom smoking data were available (FDNY, 10 723; CFHS, 2856), and examining a dose–response relation in regression analyses between WTC exposure category and cancer in the FDNY cohort only. [The Working Group noted the low proportions of (self-reported) smokers in both cohorts (FDNY, 3.5%

current smokers, 30.2% former smokers; CFHS, 6.6% current, 37.0% former) compared with the general population of the USA, suggesting that negative confounding by smoking might have been present in many of the studies considered, unless smoking was explicitly adjusted for in the analyses.]

SIRs for lung cancer were decreased in both the FDNY (SIR, 0.53; 95% CI, 0.39–0.72; 44 cases) and CFHS (SIR, 0.71; 95% CI, 0.57–0.89; 83 cases) cohorts using the general population reference rates. After adjustment for medical surveillance bias, the SIR for lung cancer for the FDNY cohort was even lower (SIR, 0.47; 95% CI, 0.34–0.65). In internal analyses, the risk of lung cancer appeared to be lower in FDNY firefighters than in CFHS firefighters, but the estimate was imprecise (relative rate, RR [rate ratio], 0.87; 95% CI, 0.57–1.33). This was also the case after adjustment for surveillance bias (RR, 0.77; 95% CI, 0.50–1.19). [The Working Group noted that this study was limited by a possible incompletely controlled effect of greater medical surveillance bias in FDNY firefighters than in CFHS firefighters or the US general population, although this bias may be less influential for lung cancer than for other cancer sites. Limitations also included the relatively young age of the cohort, and the relatively short follow-up period (15 years). Further, the exposure being assessed was WTC disaster response, rather than all firefighting activity up to 2001, which limited the applicability of these studies to an assessment of the cancer hazard arising from all firefighting activities. Strengths of this study included the ascertainment of cancer incidence outcomes, the comparison of two firefighter cohorts to evaluate the impact of surveillance bias in this specialized cohort, and the adjustment for smoking in sensitivity analyses.]

Cancer incidence associated with exposure at the WTC disaster site was also investigated in an earlier study of an overlapping cohort of 9853 FDNY male firefighters (Zeig-Owens et al., 2011). The firefighters included had been employed for ≥ 18 months, were active on 1 January 1996 with no previous history of cancer, and aged < 60 years on 11 September 2001 ("9/11"). Follow-up time was classified as "unexposed" before 9/11 for all firefighters and after 9/11 for firefighters who did not attend the WTC site (n = 926), and as "exposed" from 9/11 for firefighters who did attend the WTC site for ≥ 1 day (n = 8927). Separate results were available for these "exposed" and "unexposed" periods of person-time. [A later methods study by Zeig-Owens et al. (2016) did not provide additional information that was informative to the deliberations of the Working Group.] Cancer incidence follow-up was conducted in state cancer registries from 1996 through 2008. SIRs, adjusted for age, race, ethnic origin, and calendar year, were calculated using the US male general population reference rates. In addition, "SIR ratios" were calculated using the unexposed person-time as the reference group. [The Working Group noted that "SIR ratio" is not a standard epidemiological effect measure. It was presumed to be interpretable as the ratio of an SIR for an exposed period to an SIR for an unexposed period, although the SIRs were not standardized to the same population. The SIR ratios in the study were subject to confounding by age, race, and ethnic origin, and were considered to be of limited informativeness.] SIR ratios for some cancers were presented with and without correction for medical surveillance bias. The "corrected" SIR ratios lagged the diagnosis date by 2 years for three cases of lung cancer. For lung cancer incidence, the corrected SIR restricted to exposed person-time was less than one (SIR, 0.28; 95% CI, 0.13–0.62; 6 cases), as was the corrected SIR ratio (SIR ratio, 0.53; 95% CI, 0.18–1.54; 14 cases, 6 exposed versus 8 unexposed), although the former estimate was imprecise. [The Working Group noted that this study was limited by probable healthy-worker hire bias, young age at end of follow-up of the cohort, and short follow-up period after exposure at the

WTC disaster site (mean duration, 12.7 years). The analysis was probably subject to residual medical surveillance bias, although this bias may be less influential for lung cancer than for other sites.]

The CFHS is a separate cohort study conducted by the National Institute for Occupational Safety and Health (NIOSH) of cancer incidence and mortality among 29 992 municipal career firefighters from San Francisco, Chicago, and Philadelphia, USA (Pinkerton et al., 2020). The firefighters included were men and women who had worked for ≥ 1 day between 1950 and 2009. Firefighters were identified through personnel records and data from a previous study (Beaumont et al., 1991; Baris et al., 2001). The most recent mortality follow-up study by Pinkerton et al. (2020) included an additional 7 years of follow-up relative to the previous studies (Daniels et al., 2014, 2015). Mortality follow-up was conducted through national death registry, state vital records, and retirement board data sources from 1950 through 2016. The US general population was the referent in external comparison analyses using the SMR, which was standardized by gender, race, age, and calendar year. Sensitivity analyses were also conducted using state mortality reference rates. Three measures of exposure to firefighting activities were available for a subset of 19 287 male firefighters: exposed-days, fire-runs (Chicago and Philadelphia cohorts only), and fire-hours (Chicago cohort only). Exposure was defined as exposure to the combustion by-products of fire and assessed by linking detailed work histories with job-exposure matrices based on job, location, and firefighting apparatus assignments (Dahm et al., 2015). With the US general population referent, the overall SMR for lung cancer among firefighters was 1.08 (95% CI, 1.02–1.15; 1197 deaths), with considerable heterogeneity ($P < 0.01$) between results for the three included cohorts: San Francisco SMR, 0.71 (95% CI, 0.60–0.83); Chicago SMR, 1.20 (95% CI, 1.11–1.30); Philadelphia SMR, 1.14 (95% CI, 1.03–1.26). This heterogeneity diminished but was still significant ($P < 0.01$) when state reference rates were used. For mesothelioma mortality, the overall SMR was considerably elevated at 1.86 (95% CI, 1.10–2.94; 18 deaths), with little heterogeneity ($P = 0.71$). Internal regression analyses were conducted to estimate associations with the three exposure metrics and applying a 10-year lag. Models were adjusted for age, race, birthdate, and fire department, with partial adjustment for the healthy-worker survivor effect in some models by including a variable on employment duration. For internal analyses, the hazard rate at the 75th percentile of the exposure distribution was compared with that at the 25th percentile. For lung cancer mortality, there was a positive association with number of exposed days (hazard ratio, HR for 8700 days versus 2500 days, 1.38; 95% CI, 1.08–1.78), fire-runs (HR for 8800 versus 2100 runs, 1.21; 95% CI, 1.05–1.38) and fire-hours (HR for 2300 versus 600 hours, 1.48; 95% CI, 1.21–1.80). In analyses of fire-runs, there was little evidence of differences in risk according to time since exposure, age at exposure, or exposure period. [The Working Group noted that some external comparison results were limited by probably healthy-worker hire bias. Internal analyses were not subject to this bias, and regression modelling attempted to control for a healthy-worker survivor effect through covariate adjustment of employment duration. There was a lack of data on important potential confounders, including smoking. However, confounding by smoking was considered less likely in the internal regression analyses. Strengths of this study included the long follow-up period, and the use of quantitative exposure metrics in internal analyses.]

An earlier study of a subset of firefighters from the same CFHS cohort examined internal exposure–response associations for both cancer mortality and incidence with follow-up to the end of 2009 (Daniels et al., 2015). The study included 19 309 firefighters of known race hired in 1950

or later and employed for ≥ 1 year. Methods were similar to those used in Pinkerton et al. (2020); however, results in the present study were not adjusted for employment duration. Mortality results in the two studies were similar. For lung cancer incidence, a positive exposure–response association was observed for number of fire-hours (HR for 2300 hours versus 600 hours, 1.39; 95% CI, 1.10–1.74), but not exposed days (HR for 8700 versus 2500 days, 1.05; 95% CI, 0.84–1.33) or fire-runs (HR for 8800 versus 2100 runs, 1.10; 95% CI, 0.94–1.28). Consistent with Pinkerton et al. (2020), there were no important differences in lung cancer mortality according to time since exposure, age at exposure, or exposure period. [The Working Group noted that an important difference between the models in Daniels et al. (2015) and Pinkerton et al. (2020) was that the earlier study did not adjust for employment duration. Confounding by employment duration appeared to be strong for lung cancer mortality in Pinkerton et al. (2020).]

An additional study of the CFHS cohort investigated both cancer mortality and incidence in 29 993 municipal career firefighters and reported external and internal comparison analyses with follow-up to the end of 2009 (Daniels et al., 2014). The methods were similar to those in the updated mortality study by Pinkerton et al. (2020), and only the incidence results are reviewed here. Cancer incidence follow-up was conducted in state cancer registries relevant to each fire department to the end of 2009, with start years varying between 1985 and 1988. Residential history information was used to select state registries for follow-up. US general population reference rates were used in external comparison analyses with SIRs standardized by gender, race, age, and calendar year. Separate analyses were conducted for two end-points, first primary cancer diagnosis and all primary cancer diagnoses, although results were similar for each [only results for all primary cancers were reported]. With the US general population as the referent, the SIR among firefighters was raised for laryngeal cancer (SIR, 1.50; 95% CI, 1.19–1.85; 84 cases). For lung cancer, the overall SIR was modestly raised (SIR, 1.12; 95% CI, 1.04–1.21; 716 cases). The excess was observed among Caucasian [White] men (SIR, 1.15; 95% CI, 1.07–1.24; 689 cases) but not among men of other racial groups (SIR, 0.67; 95% CI, 0.43–1.00; 24 cases). There was evidence of heterogeneity in the lung cancer SIRs between the three fire departments ($P < 0.001$). For mesothelioma, the overall SIR for firefighters was considerably raised (SIR, 2.29; 95% CI, 1.60–3.19; 35 cases). [The Working Group noted that evidence of risk heterogeneity by department suggested that differences in exposures or other risk factors (e.g. smoking habits) across departments may not have been adequately addressed. Limitations included the lack of data on important potential confounders, particularly smoking. Strengths included the long period of follow-up, the ascertainment of incidence outcomes, and the inclusion of female firefighters.]

A cohort study of 2447 male municipal firefighters from Seattle and Tacoma, USA, reported on incidence of lung and laryngeal cancer compared with that in the local male general population and in a cohort of male police officers from Washington state (Demers et al., 1994). Firefighters had been employed for ≥ 1 year between 1944 and 1979, and cancer incidence follow-up was conducted from 1974 through 1989 in the regional Surveillance, Epidemiology, and End Results (SEER) cancer registry. Residential history information from pension and other sources was used to reduce loss to follow-up attributable to migration outside of the catchment area of the cancer registry. Information on exposure duration was available for the subcohort of Seattle firefighters, for whom exposure was assessed on the basis of information from employment records about the duration (in years) of active-duty employment in direct firefighting positions (i.e. administrative or support positions excluded). SIRs and incidence density

ratios (IDR) [the IDR can be interpreted as a rate ratio] were adjusted for age and calendar year. There were 45 cases of cancer of the lung, trachea, and bronchus, and 5 cases of cancer of the larynx, with estimates of effect close to or equal to one regardless of whether comparison was made with the local general population (SIR for lung, 1.0; 95% CI, 0.7–1.3; and SIR for larynx, 1.0; 95% CI, 0.3–2.3) or with police officers (IDR for lung, 1.1; 95% CI, 0.6–1.9; and IDR for larynx, 0.8; 95% CI, 0.2–3.5). When considering lung cancer by histological type, SIRs for adenocarcinoma, squamous cell carcinoma (SCC), small cell carcinoma, and large cell carcinoma did not differ from expected estimates. For lung cancer overall, SIR estimates using the general population referent appeared to decrease with increasing duration of employment and with time since first employment, although no formal test for trend was performed. [The Working Group noted that this study was limited by little adjustment for confounding, and no adjustment for smoking. The assessment of the duration of years involved in direct firefighting (intended as a surrogate for cumulative fire-smoke exposure) was a strength, although it was not measured equally in the Seattle and Tacoma study populations. The use of police officers as a comparison group was a strength that limited healthy-worker hire bias.]

An earlier study of 4401 municipal firefighters, which included the Portland, Seattle, and Tacoma firefighters described above, reported findings for risk of mortality for cancers of the respiratory system (Demers et al., 1992a). Firefighters had been employed between 1944 and 1979, and mortality follow-up was conducted in national and state sources from 1945 through 1989. An earlier publication of the mortality findings of the Seattle portion of the cohort was published with shorter follow-up (Heyer et al., 1990), as was a study of both cancer incidence and mortality including only Seattle and Tacoma (Demers et al., 1992b). [Since the results of these previous studies were subsumed by those of the later studies, the results from these publications were not given a full review by the Working Group.] Fire department records were used to assign years of active duty in positions involving fire combat (in the Seattle and Portland firefighters) or employment as a firefighter (in Tacoma firefighters). Mortality rates were compared to those in the US White male general population and in a cohort of local male police officers. There were 95 deaths from cancer of the trachea, bronchus, and lung among firefighters, with estimates of close to one using both comparison groups (compared with the general population, SMR, 0.96; 95% CI, 0.77–1.17; and compared with police officers, IDR, 0.95; 95% CI, 0.67–1.33). Two deaths from cancer of the larynx provided a very imprecise estimate indicating no excess risk. There were no results for cancers of the respiratory system stratified by any employment, age, or exposure characteristics, including duration of employment in active firefighting positions. [Although this study evaluated mortality outcomes only, it had similar limitations and strengths to those of the later study by Demers et al. (1994).]

A mortality study in a cohort of 1867 White male municipal firefighters who worked for the City of Buffalo, USA, provided information on the risk of cancers of the respiratory system (Vena & Fiedler, 1987). Firefighters had been employed for ≥ 1 year between 1950 and 1979, and mortality follow-up was from 1950 through 1979. The US White male general population was the reference population in external comparison analyses. Stratification by year of hire, year of death, duration of firefighter employment, and latency was used for some cancer sites, but an analysis stratified only by duration of employment was performed for cancers of the respiratory system (International Classification of Diseases, ICD-8, 160–163). The observed number of deaths from cancer of the respiratory system was close to that expected (SMR, 0.94; 95% CI, 0.62–1.36; 28 deaths), with no apparent relation

to duration of employment as a firefighter. [The Working Group noted that this study was limited by probable healthy-worker hire bias and a lack of data on important potential confounders (particularly smoking). The number of deaths was low for analyses by duration of employment. No formal tests for trend were conducted. It was unclear whether individuals were active firefighters for the whole of their employment. The long follow-up period was a strength. Confidence intervals for stratified analyses were calculated by the Working Group.]

A proportionate mortality study of deceased police and firefighters was conducted in New Jersey, USA (Feuer & Rosenman, 1986). Analyses were based on 263 deaths in White male firefighters reported to the state comprehensive retirement system for police officers and firefighters in 1974–1980. Three reference populations were used to compare mortality proportions among firefighters, including the US general population, the New Jersey general population, and police officers identified in the same data source. No excesses of mortality from cancer of the respiratory system were observed among firefighters compared with any reference group, and there was no association with duration of employment. [A strength of this study was the comparison with another uniformed service occupation. The proportionate mortality study design, lack of information on potential confounders, and short observation period limited the informativeness of this study. Confidence intervals were calculated by the Working Group.]

A mortality study in a cohort of 5414 male municipal firefighters in Toronto, Canada, who worked for ≥ 6 months between 1950 and 1989 provided information on the risk of cancers of the respiratory system (Aronson et al., 1994). Mortality follow-up was conducted in a national mortality database from 1950 through 1989. The male general population of Ontario was the reference population for external comparison analyses using the SMR. Analyses were also stratified by years since first employment, duration of employment, and age (analysis by duration of employment was restricted to 5373 firefighters). Employment information was ascertained from fire-department employment records. The overall SMR for cancers of the trachea, bronchus, and lung was close to one (SMR, 0.95; 95% CI, 0.71–1.24; 54 deaths). There was no evidence of increasing risk of lung cancer with increasing employment duration or time since first employment. There was little difference in the results when the analysis was stratified by age. There was only one death from cancer of the larynx. [The Working Group noted that this study was limited by probable healthy-worker hire bias, a lack of data on important potential confounders such as smoking, and the ascertainment of mortality outcomes only, which may contribute to survival bias. Also, the extent of active firefighting duties and exposure in the cohort over the employment period of 39 calendar years was unclear. Strengths of this study included the long follow-up period and the analysis by duration of employment.]

A mortality study of 3328 municipal firefighters in two cohorts from Calgary and Edmonton, Canada, who worked at some time between 1927 and 1987 provided information on risk of cancers of the respiratory system (Guidotti, 1993). Mortality follow-up was conducted in both provincial and national sources from 1927 through 1987. The male general population of Alberta was the reference population for external comparison analyses. [The number of female firefighters in the cohort was described as "negligible" by the study author.] Analyses were also stratified by year of cohort entry, latency, duration of employment, and an exposure index. The exposure index was based on years of firefighter service weighted by an estimate of the relative time spent in proximity to fires according to job classification. Interviews with Edmonton firefighters were used to generate the weighted estimates for all job types. With the general

population of Alberta as the referent, the overall SMR among firefighters for cancer of the trachea, bronchus, and lung was elevated (SMR, 1.42; 95% CI, 0.91–2.11; 24 deaths). However, the excess was confined to the Edmonton cohort, and the authors raised the possibility that the lung cancer results were confounded by smoking. There was no apparent relation with year of cohort entry, latency, duration of employment, or the exposure index. No deaths from cancer of the larynx were identified. [The Working Group noted that this study was limited by probable healthy-worker hire bias and a lack of data on important potential confounders, particularly smoking. The considerable follow-up during the middle and later part of the last century suggested that the availability and use of effective personal protective equipment (PPE) may have been lower than for firefighters included in studies in more recent decades. The long follow-up period and use of the exposure index based on duration of employment and job classification were strengths.]

Four studies investigated cancer risk among diverse types of firefighter in Australia (Glass et al., 2016a, b, 2017, 2019). These studies involved male and female volunteer, career, full-time, part-time, and instructor firefighters in urban and rural environments. Each study also assessed exposure to specific events involved in firefighting. The methods used to enumerate and analyse the cohorts in each study were broadly similar.

The most recent of the four studies was on cancer incidence in an entirely female cohort of 37 962 volunteer firefighters in Australia, which provided information on risk of cancers of the respiratory system (Glass et al., 2019). The cohort included firefighters from fire agencies representing all except two states of Australia. Firefighters entered the cohort at various calendar periods depending on the fire agency. Work history information describing the number and type of incidents attended was ascertained from fire agency personnel records. Cancer incidence follow-up was conducted in a national cancer registry from 1982 through 2010. [Mortality results and results for 1682 career firefighters were not reported for specific cancer sites.] In external comparison analyses, the female general population of Australia was the referent. Internal regression analyses were also conducted according to duration of service, whether fire incidents were attended, the number of incidents attended, and incident type. Among volunteer firefighters who attended incidents (n = 16 320), an excess of lung cancer cases was observed with the general population as the referent (SIR, 1.30; 95% CI, 0.90–1.82; 34 cases). There was no excess of lung cancer among all volunteer firefighters (n = 37 097). For mesothelioma, SIR estimates were statistically imprecise but suggested excess risk. There were three cases of mesothelioma diagnosed among all volunteer firefighters and one case diagnosed among volunteers who attended incidents. In internal analyses, the relative incidence ratios (RIRs) [equivalent to rate ratios] for the association between the number of incidents attended and lung cancer were statistically imprecise but indicated elevated rates among volunteers who had ever attended incidents versus never attended incidents. Trend tests using tertile categories did not suggest a relation between risk of lung cancer and the total number of incidents attended overall (P = 0.51), or all fire incidents (P = 0.46), structure fire incidents (P = 0.17), landscape [wildland] fire incidents (P = 0.56), or vehicle fire incidents (P = 0.18). [The Working Group noted that this study was limited by probable healthy-worker hire bias, the young age of the volunteer cohort at the end of follow-up (mean, 46 years), a lack of information on important potential confounders such as smoking, and a short follow-up period (approximate mean, 7 years). Strengths of this study included the internal comparison analyses and the exposure assessment involving the number and type of attended incidents, including landscape fires. This study was also based on a large population

of female firefighters and included many firefighters working in rural environments.]

Using the same methods as those in the study of female firefighters, cancer incidence was also investigated in a parallel cohort of 163 094 male volunteer firefighters in Australia (Glass et al., 2017). The data collection, follow-up period, and analysis were similar to those described in the cohort study in female firefighters (Glass et al., 2019), although the cohort of male firefighters was drawn from five fire agencies, and analyses were additionally reported by duration of service. With the male general population of Australia as the referent, SIRs among all volunteer firefighters (n = 157 931) were decreased for all cancers of the respiratory system combined (SIR, 0.49; 95% CI, 0.45–0.54; 429 cases) and for lung cancer (SIR, 0.48; 95% CI, 0.44 to 0.54; 371 cases), cancer of the larynx (SIR, 0.45; 95% CI, 0.31–0.62; 36 cases), and mesothelioma (SIR, 0.64; 95% CI, 0.64–0.87; 42 cases). Results were similar for volunteer firefighters who had attended incidents (n = 100 126). In internal regression analyses, the RIR [equivalent to rate ratio] for all volunteer firefighters was decreased in the longest duration of service category (≥ 20 years) compared with the shortest (> 3 months to 10 years) for incidence of cancers of the respiratory system combined (P < 0.01) and for incidence of lung cancer (P = 0.03). Results were similar for firefighters who had attended incidents. In internal regression analyses, the RIRs did not suggest a positive relation between the tertile of number of incidents attended (overall or by incident type) and the risk of cancers of the respiratory system combined or lung cancer, although the estimates were imprecise. [The Working Group noted that this study exhibited the same strengths and limitations as the study of female volunteer firefighters in Australia. This study was similarly limited by a short follow-up period (mean follow-up, 9.4 years) and the young age of the cohort (mean age at end of follow-up, 48.7 years). It was also noted that the exposure tertiles were based on exposure in a separate cohort of career firefighters and the distribution of cases was unequal, with very few cases in the highest tertiles for all cancer sites in this cohort of volunteer firefighters. This may indicate that volunteers participated in fewer fire incidents.]

A cancer incidence study in a cohort of 30 057 paid full-time and part-time male firefighters in Australia provided information on the risk of cancers of the respiratory system (Glass et al., 2016a). The methods used to enumerate and analyse the cohort were similar to those previously described for the studies of volunteer firefighters (Glass et al., 2017, 2019), although 8 out of 10 fire agencies supplied records to identify the study population, and the study included firefighters who were employed full-time (n = 17 394) or part-time (n = 12 663) and had worked for ≥ 3 months between 1976 and 2003. The cohort consisted primarily of municipal and semi-metropolitan firefighters. Cancer incidence follow-up was conducted in a national registry to the end of 2010. With the male general population of Australia as the referent, overall SIRs for firefighters were decreased for cancers of the respiratory system combined (SIR, 0.71; 95% CI, 0.59–0.85; 117 cases), lung cancer (SIR, 0.71; 95% CI, 0.58 to 0.86; 101 cases), and laryngeal cancer (SIR, 0.70; 95% CI, 0.36–1.22; 12 cases). There was an excess risk of mesothelioma (SIR, 1.34; 95% CI, 0.75–2.21; 15 cases). In internal regression analyses adjusted for age and calendar year, there was no evidence of a positive trend in lung cancer risk with increasing employment duration in all firefighters (P = 0.84) or in strata of full-time (P = 0.60) or part-time firefighters (P = 0.46). There was also no evidence of a positive trend in lung cancer risk with increasing number of incidents (overall or by incident type) in full-time firefighters who had ever attended incidents. [The Working Group noted that this study was limited by probable healthy-worker hire bias, a lack of data on potential confounders (particularly smoking), the short follow-up period, and

the relatively young age of the cohort at the end of follow-up (mean age, 49.9 and 44.5 years, for full-time and part-time firefighters, respectively). The study benefited from an enhanced assessment to differentiate exposure based on the number and type of incidents attended, but early exposure was extrapolated from more recent data. The internal analyses comparing risk across exposure categories within the cohort reduced the influence of biases related to using an external reference group.]

A study of cancer incidence was conducted in a cohort of 614 firefighters and trainers who attended a firefighter-training facility in Australia (Glass et al., 2016b). Three female firefighters were excluded from the analysis. Cancer incidence follow-up was conducted from 1982 through 2012. The study assessed exposure to hazardous substances at the training facility rather than to typical firefighter work. The male general population of Victoria was the reference group in external comparison analyses. Participants were grouped into risk categories of low, medium, and high chronic exposure (to smoke and other hazardous agents) on the basis of job assignment. The "high risk of chronic exposure" group comprised paid [career] instructors and operators, the medium-risk group comprised career and volunteer regional instructors, and the low-risk group comprised career practical firefighting trainees. There were only four cases of cancer of the respiratory system (expected, 6.17 cases) and the SIRs across three categories of exposure were based on too few cases to be informative. [The Working Group noted that this was the only study reviewed that specifically investigated firefighter instructors, a group assumed to have greater potential for high exposure. This study was limited by the small number of cases and the young age of the participants. Strengths of this study included the long follow-up period and the internal comparison analysis by exposure level.]

A study of mortality and cancer incidence in a cohort of 4305 paid [career] and volunteer firefighters in New Zealand provided information on risk of cancers of the respiratory system (Bates et al., 2001). The cohort included 84 female firefighters who were excluded from the analysis. The included firefighters had worked for ≥ 1 year as a career firefighter and been employed for ≥ 1 day between 1977 and 1995. Follow-up for cancer mortality and incidence was conducted in a national data source to the end of 1995 (for mortality) or 1996 (for incidence). The male general population of New Zealand was the reference population in external comparison analyses. Analyses were stratified by calendar year, years of service, and employment type (e.g. career, volunteer service). With the general population as the referent, overall mortality from lung cancer among firefighters was decreased (SMR, 0.86; 95% CI, 0.4–1.6; 10 cases) and incidence was increased (SIR, 1.14; 95% CI, 0.7–1.8; 17 cases). There was some evidence of a positive relation between lung cancer incidence and duration of career service (P = 0.48), although estimates were based on few cases and were imprecise. [The Working Group noted that this study was limited by probable healthy-worker hire bias and a lack of data on potential confounders, particularly smoking. A significant proportion of the cohort was lost to follow-up. It was unclear the extent to which the study population included municipal versus rural firefighters.]

Bigert et al. (2016) analysed pooled information from the IARC SYNERGY study that included 14 case–control studies conducted in Canada, China, Europe, and New Zealand. The SYNERGY study was designed to evaluate confounding and effect modification in the assessment of occupational lung carcinogens and risk of lung cancer. Study information was collected by questionnaire between 1985 and 2010. The average response proportion among individual studies was 78% (range, 41–100%). Selection of controls varied by study and

included hospital patients, general populations, or both. Participants were restricted to working males with detailed "lifetime" work histories and smoking information, resulting in a study group comprising 14 748 incident cases of lung cancer and 17 543 controls. Firefighters (n = 190; 86 cases of lung cancer, 104 controls) were identified from self-reported lifetime work histories. Age- and smoking-adjusted logistic regression models were fitted to calculate odds ratios (ORs), with firefighting as the exposure of interest. The adjustment for smoking comprised cumulative cigarette smoking (pack-years), and time since quitting smoking cigarettes. Models were also fit including adjustment for employment in a job known to present an excess risk of lung cancer (e.g. mining industry, asbestos production, metals industry, construction industry, and shipbuilding). Outcomes included lung cancer overall and stratified by histology. Analyses for all lung cancers were repeated after stratification by smoking status (never, former, current) and work duration (< 6, 6–21, 22–32, and > 32 years). Meta-analysis was used to examine heterogeneity across the studies. There was no evidence of increased lung cancer risk in models either with (OR, 0.95; 95% CI, 0.68–1.32) or without (OR, 1.03; 95% CI, 0.77–1.38) adjustment for smoking. Further adjustment for high-risk employment did not substantively change the estimate (OR, 0.95; 95% CI, 0.68–1.32). There was no evidence of increasing lung cancer risk with employment duration (P = 0.58). There was also no evidence of differences in lung cancer risk across categories of smoking status, although there were only two lung cancers among firefighters classified as never smokers. In analyses for major histological types of lung cancer, there was no evidence of increased risk of adenocarcinoma, SCC, small cell carcinoma, or other/unspecified types in firefighters compared with other occupations. There was no evidence of study heterogeneity (I^2 = 0.0%, P = 0.738). [The Working Group noted that control for smoking was a strength of this study, as was the detailed occupational history collected for every participant. Limitations included the small number of cases in stratified analyses, a lack of information on exposures and other risk factors, and the use of hospital controls in some individual studies.]

2.1.2 *Studies only reporting having ever worked as a firefighter*

(a) Occupational cohort studies

See Table S2.2 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Between 1978 and 2021, there were eight studies examining the risk of cancers of the respiratory system in firefighters compared with non-firefighter populations (Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Giles et al., 1993; Deschamps et al., 1995; Ma et al., 2005, 2006; Amadeo et al., 2015). Of these studies, three had an exposure assessment of satisfactory quality (Musk et al., 1978; Eliopulos et al., 1984; Deschamps et al., 1995), whereas the remaining studies were found to have exposure assessments of minimal quality (see Table 1.8.1). Exposures probably stemmed mostly from structure fires in urban settings. Cancer sites considered included the trachea, lung and bronchus, larynx, and mesothelioma. All studies conducted external comparisons that did not examine exposure–response associations using direct measures or proxies for exposure. Most studies had longitudinal cohort designs that included information on the firefighter population at risk; however, one study conducted only a proportionate mortality ratio (PMR) analysis (Grimes et al., 1991). In all the studies, only career firefighters were specifically identified, and most were probably assigned to tasks common to fighting structure fires. Most studies examined cancers observed in career firefighters employed at a single municipal department (Musk et al., 1978; Eliopulos

et al., 1984; Grimes et al., 1991; Giles et al., 1993; Deschamps et al., 1995); however, multidepartment cohorts were also evaluated (Ma et al., 2005, 2006; Amadeo et al., 2015). [The Working Group noted that the reliance on external reference populations for occupational cohorts, leading to potential downward bias from healthy-worker effects, was a shared limitation among all studies reviewed. In general, informativeness was considered to be superior in studies on cancer incidence compared with studies on cancer mortality; the latter having a greater potential for information and selection biases. Among other limitations, studies lacked individual information on occupational exposures and important risk factors other than demographic characteristics such as age and sex. Also, this group of studies covered a long time period, such that fire environments in earlier studies (e.g. Musk et al., 1978; Eliopulos et al., 1984) probably differed greatly from those experienced in later studies. The Working Group noted that, in the absence of information on the population of interest, risk estimates from PMR studies relied heavily on strong assumptions that may not be valid for firefighter cohorts. The Working Group also noted the sparse information available on the risk of mesothelioma because of its long latency, rarity, and lack of a widely available disease classification before the late 1990s.]

Amadeo et al. (2015) examined mortality among civilian male career firefighters in France (n = 10 829), actively employed in 1979 and followed to the end of 2008 (308 089 person-years). Firefighter status was determined by employment records covering 93% of all French municipal fire departments. Vital status and causes of death were determined from linkage to national vital records. Cause-specific cancer risk was assessed in age- and calendar year-adjusted SMRs using the general male population of France as the referent. The mean age at entry was 30 years (range, 17–64 years). About 15% of the cohort was deceased at the end of follow-up. Mortality from cancers of the lung and bronchus was lower than expected (SMR, 0.86; 95% CI, 0.74–0.99; 187 deaths). There was no evidence of excess mortality from cancers of the larynx and trachea (SMR, 1.10; 95% CI, 0.73–1.59; 28 deaths). There were six deaths from mesothelioma, which was reported to be near the expected number, although the specific SMR was not reported. [The large study size, firefighter identification, and long follow-up period were notable strengths. The Working Group also noted that all-cause mortality was significantly below that expected in the cohort. The SMRs tended to be low among young firefighters and to increase with age. These findings suggested relatively strong downward bias from healthy-worker selection.]

Deschamps et al. (1995) examined mortality in male career firefighters (n = 830) (with specialized military status) who were employed by the *Brigade des sapeurs-pompiers de Paris* (Paris Fire Brigade) for a minimum of 5 years by 1977 and were followed to the end of 1990 (11 414 person-years). Occupation was determined by employment records. Vital status was ascertained from pension records, and the underlying cause of death was determined via linkage with the national mortality registry. Age- and calendar-year adjusted cause-specific SMRs were calculated using the male general population of France as the referent. The duration of fire combat was assessed among decedents; however, this information was not used when estimating cancer rate ratios. By the end of the study, less than 4% (n = 32) of the participants were deceased, which was about half that expected. Mortality from cancers of the respiratory system was close to that expected, with wide confidence intervals (SMR, 1.12; 95% CI, 0.45–2.30; 7 deaths). [The Working Group noted that the small study size and young cohort led to few deaths during observation, and necessitated analysis restricted to a heterogenous group of all cancers of the respiratory system combined. There was also a strong potential for downward

bias from healthy-worker effects, given the short mortality follow-up and use of a specialized group of firefighters who had been selected for good physical and psychological health, received annual medical examinations, and were required to meet high standards of physical training.]

Ma et al. (2006) examined cancer incidence in a cohort of 36 813 career firefighters employed in Florida, USA, beginning in 1972, who were followed from 1981 through 1999 (431 865 person-years). Employment was determined by state firefighter certification records. The cohort was mostly White (90.1%) and relatively young, with an average age of < 60 years at the end of the study. The median follow-up time was 13 years. Follow-up time was shorter for female firefighters (5.5% of the cohort) than for males. Incident cases were identified by linkage with the state cancer registry. Age- and calendar year-adjusted SIRs were determined separately for men and women, with state cancer rates as the referent. The incidence rate of cancers of bronchus and lung combined was greater than expected among female firefighters (SIR, 1.51; 95% CI, 0.30–4.40), although there were only three cases, and the confidence interval was wide. The incidence rate of cancers of the bronchus and lung was lower than expected among male firefighters (SIR, 0.65; 95% CI, 0.54–0.78; 128 cases).

Ma et al. (2005) also examined cancer mortality between 1972 and 1999 in the same cohort of Florida career firefighters described above. The cause of death was ascertained via linkage with state vital records. Age- and calendar year-adjusted SMRs were calculated separately for male (n = 34 796) and female (n = 2017) firefighters. Comparisons were made with state general-population rates as the referent. The patterns of mortality from cancers of the bronchus and lung in men (SMR, 0.93; 95% CI, 0.79–1.09; 155 deaths) and women (SMR, 2.22; 95% CI, 0.45–6.49; 3 deaths) were compatible with the incidence results. [The Working Group noted the large study size and sex-specific risk estimates as strengths of the Florida cohort studies, although risk estimates for women were limited by small numbers. The follow-up period may have been insufficient to observe excess incidence or mortality for cancers of the respiratory system, and the Florida firefighter cohort was still relatively young at the end of follow-up. The significant deficit in all-cause mortality among males in the Florida firefighter cohort suggests the potential for strong downward bias from healthy-worker effects.]

Grimes et al. (1991) examined proportionate mortality in male firefighters with ≥ 1 year of service in the fire department of the City of Honolulu, USA, and followed from 1969 through 1988. Information on the cause of death was abstracted from death certificates obtained from state vital records. Analyses were stratified by ethnic group ("Caucasian" [White] and "Hawaiian"). The expected numbers were based on all deaths among males aged > 20 years in the state population. There were 205 deaths observed. The PMR for deaths from cancer of the respiratory system in the full cohort was 1.28 (95% CI, 0.82–2.00; [18] deaths). There was no indication of effect modification by ethnic group (Caucasian [White] versus Hawaiian). [Reporting estimates stratified by ethnicity was a notable strength. However, in addition to the general limitations of study designs without denominator data, the Working Group noted that the PMRs were not standardized by age or calendar period.]

Musk et al. (1978) examined mortality patterns among 5655 male career firefighters with ≥ 3 years of service in the Boston Fire Department, Massachusetts, USA, who were followed for mortality from 1915 through 1975 (142 975 person-years). Occupation as a firefighter was determined by employment records. Causes of death were ascertained from death certificates obtained from state vital records. Death certificates were not available for nearly 8% of known decedents. Relative risk associated with employment as a firefighter was estimated from

age- and calendar period-adjusted cause-specific SMRs using mainly Massachusetts state rates as the referent. The number of expected deaths was determined from rates for the state (all men) and national (White men) population. Nearly all participants (99.7%) were White and 246 people (4.4%) were lost to follow-up. A total of 2470 deaths were observed (43.7%), which was 91% of that expected. Observed deaths from cancers of the respiratory system were fewer than expected (SMR, 0.88; 95% CI, [0.69–1.10]; 70 deaths). [The long observation period was a notable study strength that also lessened the potential for strong bias from healthy-worker effects. The Working Group also noted that, given the relatively few cancer deaths, the analysis was restricted to all cancers of the respiratory system combined rather than to specific types. Confidence intervals were calculated by the Working Group.]

Giles et al. (1993) examined cancer incidence among 2865 male firefighters from Melbourne, Australia, who were first employed between 1917 and 1989 and followed from 1980 through 1989 (20 853 person-years). Information on cancer incidence was obtained via linkage with the Victorian Cancer Registry. Age- and calendar year-adjusted cause-specific SIRs were calculated using the male population of Victoria as the referent. The incidence of cancers of the trachea, bronchus, and lung was lower than expected among the firefighters (SIR, 0.77; 95% CI, 0.28–1.68; 6 cases). [The Working Group noted that the long period between first employment and observation would result in potential selection bias from survivor effects caused by the exclusion of firefighters who may have died before the start of follow-up in 1980, and whose deaths would therefore not have been observed. The study also had limited power given the small study size and short observation period.]

Eliopulos et al. (1984) examined mortality among 990 Australian men first employed as full-time firefighters between 1939 and 1978 and followed through 1978 (16 876 person-years). More than half (64.5%) were still employed at the end of follow-up, with about 3% lost to follow-up after accounting for emigration. Vital status was obtained from a variety of information sources, and the underlying cause of death was abstracted from death certificates. Age- and calendar period-adjusted SMRs were calculated using the adult male population of Western Australia as the reference group. [The Working Group noted that PMRs were also calculated but did not consider them informative for the evaluation, given the availability of SMRs for cancer of the respiratory system.] A total of 116 deaths (11.7%) were observed in the cohort, which was 80% of that expected. There were fewer than expected deaths from cancers of the respiratory system (SMR, 0.84; 95% CI, 0.33–1.71; 7 deaths). [The Working Group noted that the observed trends in all-cause mortality were consistent with strong healthy-worker effects and that this study had limited power, given the small study size.]

(b) Population-based studies

See Table S2.2 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Between 1989 and 2021, five population-based cohort studies were published that included findings on the risk of cancers of the respiratory system among firefighters (Hansen, 1990; Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020; Sritharan et al., 2022), and ten case–control or mortality surveillance studies reporting risk estimates for cancers of the respiratory system from employment as a firefighter (Sama et al., 1990; Burnett et al., 1994; Ma et al., 1998; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Muegge et al., 2018; Langevin et al., 2020; Lee et al., 2020; McClure et al., 2021). Of all the studies in this section, only the study by Langevin et al. (2020) was found to have an exposure assessment of satisfactory quality. Exposure assessments in the remaining studies were considered to be

of minimal quality (see Table S1.28, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.fr/615).

The cohort studies compared incidence or mortality of cancer in firefighters to that expected in the general population overall or in a non-firefighting reference population. Four cohort studies used national census data to enumerate the cohort (Hansen, 1990; Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020), whereas one study examined a cohort formed using an occupational injury and disease claims database and linkage to person and cancer registries (Sritharan et al., 2022). All cohort studies determined firefighter employment status from self- or proxy-reported information gathered at the time of census or death.

Six case–control studies had event-only designs using cancer registry information to identify individuals with cancers of the respiratory system as cases and other cancers as controls (Sama et al., 1990; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Lee et al., 2020; McClure et al., 2021). Two case–control studies used death certificate information in similar event-only designs (Ma et al., 1998; Muegge et al., 2018). The remaining case–control study was a multicentre population-based case–control study of laryngeal cancer incidence among residents in a large metropolitan area (Langevin et al., 2020). An additional study used information from death certificates obtained from a national occupational mortality surveillance database to calculate PMRs specifically focused on firefighters (Burnett et al., 1994).

In general, cancer incidence was considered more informative than mortality, although exceptions may apply on the basis of other considerations, such as the potential for cancer screening bias. The Working Group noted that the reliance on external reference populations, leading to probable healthy-worker selection bias, was a shared limitation among the cohort studies, given the strong potential for bias in a highly selected population of interest. Another limitation of all studies in this section was the reliance on a one-time qualitative measure of exposure, employment as a firefighter, from censuses, claims data, or death certificates. Occupational information abstracted from death certificates was subject to additional errors. Most studies lacked individual information on important risk factors (e.g. tobacco use) other than demographic characteristics such as age and sex, although the case–control study by Langevin et al. (2020) was a notable exception. Finally, long latency, rarity of occurrence, and lack of disease classification before the late 1990s limited the informativeness of studies on mesothelioma risk. The Working Group noted that a shared strength of the event-only case–control studies was the availability of large case numbers, resulting in improved statistical power. There were also important shared limitations. First, event-only designs used other incident cancers, cancer deaths, or non-cancer deaths as controls. As such, the effect measure is a valid measure of relative risk only if the rate of control events among the exposed is the same as that among the unexposed. In the absence of this condition, a serious bias in either direction can occur. Second, cancer registries and death certificates contain only limited information on occupation, which can result in considerable exposure misclassification. This misclassification can be differential with respect to case status, leading to potential bias in either direction.]

Zhao et al. (2020) examined mortality patterns by occupation in a longitudinal study of the male population of Spain as reported in the 2001 census and followed to the end of 2011. At baseline, the study included nearly 10 million working men aged 20–64 years, of whom 27 365 were firefighters (266 562 person-years among firefighters and 93 752 897 person-years among other occupations). Occupation was determined from census report at baseline. The underlying cause of death was ascertained by linkage with

the national mortality registry. Age-adjusted mortality rate ratios (MRRs) were calculated to compare rates for firefighters to rates for men in all other occupations. The rate ratio for laryngeal cancer mortality was increased (MRR, 1.77; 95% CI, 1.01–3.09; 14 deaths). There was no evidence of increased lung cancer risk among firefighters (MRR, 0.94; 95% CI, 0.77–1.15; 104 deaths). With only one death observed, there was also no evidence of excess mortality from mesothelioma. [The large sample size and use of a working population as the reference group were notable strengths; however, the short follow-up period and young age of the cohort resulted in limited informativeness, especially for cancers with a long latency such as lung cancer and mesothelioma.]

Pukkala et al. (2014) examined cancer incidence in the NOCCA cohort, a large cohort of male career firefighters (n = 16 422), using data from five Nordic countries for the period 1961–2005 (412 991 person-years). Firefighter status was determined by national census questionnaire. Cancer incidence was determined by linkage with national cancer registries. In the full cohort, lung cancer incidence (310 cases) did not differ meaningfully from the expected number, with the national population as the referent; however, an excess of lung cancer was observed in Danish firefighters (SIR, 1.37; 95% CI, 1.03–1.77; 56 cases), which was consistent with the results of an earlier census-based mortality study of Danish male firefighters followed from 1970 through 1980 (Hansen, 1990). [The earlier study (Hansen, 1990) will not be further discussed here because of its overlap with Pukkala et al. (2014).] The authors attributed this excess to increased relative risk of adenocarcinoma of the lung among older Danish firefighters. The incidence of lung adenocarcinoma was greater than expected in the full cohort (SIR, 1.29; 95% CI, 1.02–1.60; 80 cases), which was largely attributable to the findings among Danish firefighters, although tests of heterogeneity among countries were not reported. The SIR for adenocarcinoma was greatest for attained age ≥ 70 years compared with that for younger firefighters. The SIR was also greatest in the most recent observation period (1991–2005) compared with earlier periods, although differences were much less pronounced. There was no evidence of an increased risk of SCC or small cell carcinoma. Pukkala et al. (2014) also reported that the incidence of mesothelioma was greater than expected, although this was based on small numbers of cases (SIR, 1.55; 95% CI, 0.90–2.48; 17 cases). The SIR for mesothelioma was substantially elevated among those aged ≥ 70 years (SIR, 2.59; 95% CI, 1.24–4.77; 10 cases). [The Working Group noted that this finding was consistent with the long latency between asbestos exposure and occurrence of mesothelioma observed in other studies.] The mesothelioma risk appeared largely attributable to a substantial excess in Norwegian firefighters (SIR, 2.78; 95% CI, 1.02–6.06; 6 cases). [Strengths of the study included the use of cancer incidence as the end-point; increased statistical power resulting from the pooling of information from multiple countries; the long follow-up period and the large number of firefighters; and the examination of risk by attained age, period of follow-up, histological type, and country. The Working Group noted as limitations the likelihood of healthy-worker selection bias, the infrequent ascertainment of firefighting status through use of the decennial census, and the lack of information on potential confounders.]

Sritharan et al. (2022) investigated cancer incidence in a cohort of 13 642 firefighters employed in Ontario, Canada. The study group was enumerated using information from an occupational injury and disease claims database and linkage to person registries. Information was abstracted for claimants (n = 2 368 226) between 1983 and 2019 who were aged ≥ 15 years and had complete information on sex, birthdate, claim date, and occupation and industry information. The cohort was then linked to the Ontario Cancer

Registry to obtain information on site-specific cancer incidence. People with a cancer diagnosis recorded before 1983 or who entered the cohort for an occupational cancer claim were excluded. Workers were followed from first claim date to date of first cancer diagnosis, emigration out of Ontario, attained age 85 years, death, or study end (2020), whichever was earliest. Site-specific cancer risk was assessed using Cox proportional hazards regression, controlling for age at start of follow-up, birth year, and sex. Models compared cancer incidence in firefighters to that in all other occupations and in police. There was no evidence of an increased incidence of cancers of the lung or larynx among firefighters compared with either reference group. The incidence rate of mesothelioma among firefighters was three times that among police (HR, 3.21; 95% CI, 1.10–10.20; 11 cases). This excess was greatly attenuated in comparisons using all workers as the reference group (HR, 1.56; 95% CI, 0.86–2.84). [The Working Group noted that the large study size and access to tumour information were important strengths. Another study strength was the inclusion of female firefighters. Among limitations, exposure information consisted only of the job title available at the time of the worker compensation claim. The type of compensation claims used to identify the cohort may have differed by occupation, which could also introduce bias. Additional information would be needed to determine whether exposure misclassification was differentially distributed, which could result in a bias in either direction.]

Harris et al. (2018) examined cancer incidence by occupation in the Canadian Census Health and Environment Cohort (CanCHEC) (1991–2010). The cohort was created from the 1991 national census that collected data on about 20% of Canadian households. Occupation was determined from self-report of the longest-held job in the previous year. The study roster was probabilistically matched to the national cancer registry to ascertain cancer cases. Cox proportional hazards regression models adjusting for age, region, and education level were fitted to estimate the cancer risk associated with work as a firefighter compared with that for other occupations. The analyses were restricted to working adult men aged 25–74 years at baseline and included 1 108 410 people (of whom 4535 were firefighters). The average follow-up length among firefighters was 17.9 years. With other workers as the referent, firefighters in this study did not have an increased risk of lung cancer (HR, 0.90; 95% CI, 0.71–1.15; 65 cases). [A notable strength was the use of a large population-based cohort that supported several comparisons of firefighters with a working population, thereby reducing the potential for strong bias from healthy-worker effects. The Working Group also noted that analyses were restricted to outcomes with more than five events. Therefore, size restrictions precluded information on rare events, such as mesothelioma and laryngeal cancer. The lack of accounting for race or ethnicity in fitted models was considered to be a minor limitation.]

Lee et al. (2020) examined site-specific cancer incidence in a registry-based case–control study using data from Florida, USA. Employment records for people certified as firefighters in 1972–2012 (n = 109 009) were linked with state cancer registry data (1981–2014) to identify 3760 male and 168 female firefighters aged ≥ 20 years at diagnosis of their first primary cancer. Logistic regression was used to calculate age- and calendar year-adjusted ORs separately for men and women, with firefighting as the exposure of interest. Results stratified by tumour stage and age (< 50 years, ≥ 50 years) were also reported for men. The controls in primary analyses comprised all cancer cases identified in the state registry except for cases of the cancer of interest. In post hoc analyses, ORs for men were calculated using controls excluding smoking-related cancers (lung, larynx, oesophagus, bladder, oral/pharynx) because the smoking rate among firefighters was assumed to be lower than that in

the general population. Most firefighters were non-Hispanic (95.1%) or White (93.6%) and diagnosed between age 45 and 64 years. There was no evidence of increased lung cancer risk among male (OR, 0.79; 95% CI, 0.72–0.87; 466 cases) or female (OR, 0.54; 95% CI, 0.28–1.02; 10 cases) firefighters compared with other occupations. Among men, lung cancer ORs were higher in the older age group and the late-stage tumour group than in the younger group and the early-stage tumour group, respectively; however, all ORs were below one. The OR for mesothelioma was increased among male firefighters but had wide confidence intervals (OR, 1.26; 95% CI, 0.70–2.29; 11 cases). There were no mesothelioma cases among women. Laryngeal cancer was less likely to occur in male firefighters than in non-firefighters (OR, 0.48; 95% CI, 0.34–0.67; 35 cases), with no cases observed among female firefighters. Excluding smoking-related cancers from the control group only slightly attenuated ORs, suggesting little potential for a strong bias from smoking. [A strength of the study was the linkage to the Florida state firefighter certification database, which was a superior source of information on firefighter status when compared with the cancer registry. The Working Group noted overlap with the previous cohort study of Florida firefighters by Ma et al. (2006), which had follow-up through 1999. That study used a standard longitudinal cohort design rather than the event-only case–control design of Lee et al. (2020). Comparing estimates from Ma et al. (2006) with those from Lee et al. (2020) revealed notable inconsistencies between findings, which might have stemmed from differences in analytical methods, follow-up, or both. These differences could have been more thoroughly explored by replicating the previous cohort study methods using the extended follow-up for comparison with current findings.]

McClure et al. (2021) extended the Florida cancer registry-based case–control study to assess whether results differed according to the method by which firefighter status was identified, either by cancer registry data alone (n = 1831) or by linkage between the registry and the state firefighter certification records, as reported by Lee et al. (2020). The OR for cancers of the respiratory system in male firefighters identified from certification records (OR, 0.73; 95% CI, 0.67–0.81; 505 cases) was lower than that obtained from data restricted to registry information (OR, 0.99; 95% CI, 0.87–1.11; 311 cases). The study confirmed that occupational data were frequently missing from registry records, and that the absence of these data was not random but was differentially distributed by sociodemographic and diagnostic characteristics. Female firefighters, less-recent diagnoses, and older-aged patients were less likely to have information on firefighter occupation listed in the cancer registry (McClure et al., 2019). [The Working Group noted that differentially distributed exposure misclassification could result in bias in either direction and concluded that all studies relying on cancer registry information for occupation merited cautious interpretation.]

Langevin et al. (2020) conducted a population-based case–control study of head and neck cancers among men in the Boston area, Massachusetts, USA. Cases (718 people, of whom 11 were firefighters) were ascertained from records in major area hospitals and verified through linkage with the state cancer registry. Controls (905 people, of whom 13 were firefighters) were identified through municipal and state records as living within the catchment area and having no history of head and neck cancer. Controls were frequency-matched to cases on age, sex, and location of residence. Enrolment occurred in two phases: December 1999 to December 2003 (phase I) and October 2006 and June 2011 (phase II). Self-reported information on occupational histories, sociodemographic factors, alcohol consumption, and tobacco use were collected using questionnaires. Firefighters were defined as those reporting a current or former job as a career firefighter with job duties that involved

firefighting. The classification excluded volunteer firefighters, fire inspectors, and fire administration staff. Participation rates were 78% and 47% for cases and controls, respectively. The odds of laryngeal SCC were increased among firefighters compared with non-firefighters (OR, 1.70; 95% CI, 0.45–6.41); however, there were only three cases in firefighters. In analyses stratified by smoking status, there was a strong association between firefighting and SCCs of the hypopharynx and larynx combined in people with a history of smoking of < 18.4 pack-years (OR, 8.06; 95% CI, 1.74–37.41; 3 cases in firefighters). The exposure–response relation per decade firefighting was also substantially elevated (OR, 2.10; 95% CI, 1.06–4.14). These associations were not found among heavy smokers (> 18.4 pack-years). [Analysis adjusting for several important risk factors, such as age, race, education, smoking, and alcohol consumption, was a notable strength. However, the Working Group also noted that few firefighters participated in the study, and that stratified analyses were adversely affected by small numbers. The Working Group also noted a potential for bias because of reliance on self-report, although the contribution of information on occupation to this bias was expected to be small, given that self-reported firefighter status is likely to be more accurately reported than for some other occupations. There was also a potential upward selection bias given that firefighters were less likely to participate as controls.]

Muegge et al. (2018) examined firefighter mortality in a registry-based case–control study using death certificate information obtained from the vital records system in Indiana, USA (1985–2013). Decedents aged ≥ 18 years at death and of known race and ethnicity were identified as either firefighters or non-firefighters using industry and occupation information recorded at time of death. Each firefighter death record (n = 2818) was matched to four randomly selected non-firefighter deaths (n = 11 272) without replacement. Matching variables were exact on attained age, sex, race, ethnicity, and year of death. Conditional logistic regression was used to calculate site-specific cancer mortality ORs. There were 318 deaths from cancers of the respiratory system among firefighters. The authors stated that there was no evidence of increased odds of death attributable to cancers of the respiratory system among firefighters, although point estimates were not shown. Post hoc calculation of PMRs and standardized mortality odds ratios (SMORs) was said to have provided similar findings (excluding deaths attributable to assault and homicide), although results were not shown. [The Working Group noted the use of a non-standard analysis approach applied to event-only data as a limitation. Reporting of results from analysis of alternative approaches (e.g. PMRs and SMORs) would have better supported study findings. Among other limitations, the Working Group noted the lack of a risk measure for cancers of the respiratory system and the reliance on death certificates for exposure status.]

Tsai et al. (2015) examined site-specific cancer incidence in a registry-based event-only case–control study of firefighters in California, USA, in 1988–2007. Researchers obtained data from the state cancer registry, including demographic information, cancer characteristics, and information on industry and occupation for the longest held job by each study participant. Keyword searches of occupation and industry fields were used to identify firefighters using codes related to firefighting from the 1990 revision of the US Census Bureau. The study was restricted to first malignant primary tumours among male participants aged 18–97 years at diagnosis for whom information on occupation and industry was available (n = 678 132). About 44% of records meeting all other eligibility criteria were excluded because of missing occupation. The control group comprised cancers of the pharynx, stomach, liver, and pancreas, which were selected on the basis of review of the literature suggesting that

cancers at these sites were not associated with firefighting. These cancers were removed from the control group when selected as the cancer of interest. Logistic regression models were fitted to calculate ORs adjusted for age at diagnosis, year of diagnosis, and race. The study included 3996 male firefighters, most of whom (90.2%) were White. Among cancers of the respiratory system, the risk of non-specific, non-small cell lung cancer (International Classification of Diseases for Oncology, ICD-O, 8046) was substantially increased (OR, 2.01; 95% CI, 1.38–2.93; 42 cases). There was no evidence of increased risk of other lung cancer histological types or of all lung cancers combined. The OR for mesothelioma was elevated (OR, 1.40; 95% CI, 0.89–2.21; 21 cases). In contrast, the risk of laryngeal cancer was decreased in firefighters (OR, 0.59; 95% CI, 0.39–0.89; 25 cases) compared with other occupations. Bates (2007) conducted a similar study with the California Cancer Registry, USA, in 1988–2003, but these data were included in the study conducted by Tsai et al. (2015). [The Working Group noted that study strengths included the large number of incident cancers with histological confirmation of diagnosis and analyses by lung cancer histological type. Several limitations were also noted, including largely incomplete information on occupation, and lack of information on exposure and potential confounding factors (e.g. smoking).]

Kang et al. (2008) extended a previous cancer registry-based case–control study of White male firefighters in Massachusetts, USA (Sama et al., 1990). Study data (1987–2003) were obtained from the registry and included age, sex, smoking status, detailed tumour information, and self-reported information on occupation and industry. Occupational information was available for 62.5% of all cancer cases listed in the registry. Among eligible cases (n = 161 778), the occupational fields were searched by keyword to identify firefighting as the exposure of interest (n = 2125). Two unexposed reference groups (police, all other occupations) were used, with police preferred in most analyses. Smoking information, which was available for 84.5% of firefighters, 85.4% of police, and 82.2% of other occupations, was used to define smoking status as never, past, current, or unknown. Standardized morbidity odds ratios (SMBORs), adjusted for age and smoking, were calculated for 25 cancer types of concern (lip, buccal cavity, nasopharynx, pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, larynx, lung, cutaneous melanoma (hereafter referred to as "melanoma"), soft tissue sarcoma, breast, prostate, testis, kidney, bladder, brain, thyroid, leukaemia, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, multiple myeloma), with each site compared individually to the group of control [comparison] cancers (i.e. cancer sites other than those of concern) among each of the two unexposed reference groups. SMBORs were also calculated for age groups 18–54, 55–74, and ≥ 75 years. The numbers of lung and larynx cancers among firefighters were 379 and 38, respectively. There was no evidence of increased risk of cancers of the lung or larynx among firefighters in analyses using either reference group or within any age group. [The Working Group noted that the availability of information on smoking and control for smoking in estimating ORs were important strengths. However, the methods used for control for smoking (including the handling of missing data) were not clear. The Working Group noted differences in ORs by reference group. There was not an obvious pattern of differences by reference group across all outcomes; therefore, the choice of referent appeared inconsequential. Another notable limitation was the largely incomplete information on occupation. The effect of the missing information was unclear given some evidence that missingness may be differentially distributed by important sociodemographic variables (McClure et al., 2021).]

Sama et al. (1990) conducted a registry-based cancer incidence study using information from the cancer registry in Massachusetts, USA, for the 4 years (1982–1986) before the start of the study by Kang et al. (2008). The study examined nine cancer types, including cancers of the trachea, bronchus, and lung combined. The cancer cases included White men aged ≥ 18 years at diagnosis, with confirmed primary tumours coded in accordance with ICD-O. Occupational information was available for only about half of all registry cases. Information on occupation was coded according to the US Census Bureau on the basis of the self-reported longest job held, as identified at the time of cancer diagnosis. Firefighters (n = 315) were identified as those with jobs listed as firefighter or fire chief. SMBORs, adjusted for age, were calculated using two groups as referent: (i) registry cases with any occupational information other than firefighter; and (ii) cases among protective services, identified as police, police chief, sheriff, and correctional officers. For each cancer of a priori interest, control cancers included all other cancers except those of the organ systems of concern, namely cancers of the digestive and respiratory systems, and lymphatic and haematopoietic tissues. Smoking status included information on cigarettes, and participants were categorized as current, former, or never smokers; this information was available for 89% of firefighters, 85% of police controls, and 86% of state controls. Analyses were not adjusted for smoking, although the prevalence of current smoking among firefighters was 46.3% compared with 40.1% and 41.6% for police and state cases, respectively. Incident lung cancer was more likely among firefighters compared with either reference group – SMBOR for all occupations other than firefighter referent, 1.22 (95% CI, 0.87–1.69); and SMBOR for police referent, 1.30 (95% CI, 0.84–2.03) – although confidence intervals were wide. [The Working Group noted that information on occupation was substantially incomplete. This is a common limitation of cancer registries. The effect of incomplete information on risk estimates was not clear, given evidence that data gaps might not be random (McClure et al., 2021). Other limitations included the lack of control for smoking, as well as limitations inherent to the study design restricted to cancer event data.]

Using the occupational mortality surveillance system in the PMR study by Burnett et al. (1994) (described below), Ma et al. (1998) examined race-specific cancer risk among male firefighters in a case–control study of decedents from 24 states in the USA. The database contained information on causes of death and occupation that was abstracted from death certificates obtained from 24 US states between 1984 and 1993. Race-specific cancer mortality odds ratios (MORs) were calculated with all non-cancer deaths as referent and adjusting for year and age at death. There were 6607 deaths and 1883 cancer deaths among firefighters. Among firefighter cancer deaths, 96.5% and 3.5% were observed in White and Black firefighters, respectively. Lung cancer risk was marginally increased among White firefighters (MOR, 1.1; 95% CI, 1.0–1.2; 633 deaths) but not among Black firefighters (MOR, 0.8; 95% CI, 0.5–1.3; 15 deaths). There was no evidence of increased risk of laryngeal cancer for either racial group. Mesothelioma was not directly investigated; however, the MOR for cancers of the pleura among White firefighters was elevated (MOR, 1.8; 4 deaths). There were no pleural cancers observed among Black firefighters. [The use of a large and geographically diverse national occupational mortality database was a notable strength. The Working Group noted that analyses of certain outcomes and of Black firefighters were limited by small numbers.]

In a mortality surveillance study, Burnett et al. (1994) calculated PMRs using death certificate data collected from 27 US states in 1984–1990 that were coded into a national occupational surveillance database. Firefighter status was determined from death certificate information about the usual occupation and industry over the

decedent's lifetime that was provided by a proxy (e.g. next of kin) at the time of death. Age-adjusted PMRs compared the proportion of deaths from specific causes in White male firefighters to the proportion of deaths from the same causes for all White male decedents. Separate analyses were conducted for all deaths and for deaths occurring before age 65 years. The lung cancer PMR was as expected for all firefighter deaths (PMR, 1.02; 95% CI, 0.94–1.11; 562 deaths) and for deaths before age 65 years (PMR, 0.98; 95% CI, 0.86–1.12; 236 deaths). Other cancers of the respiratory system were not investigated. The authors acknowledged the potential for error in the information on occupation from death certificates because of a tendency among firefighters to retire early and seek other employment. Information on the duration of employment or occupational exposure was not available. [The use of information from a national occupational surveillance database spanning several states was a notable strength. Among the substantial limitations of this study was that the potential for incomplete or erroneous information on occupation from death certificates may have resulted in downward bias from differential misclassification based on occupation status. The Working Group also noted that a PMR analysis may overestimate risk for specific causes of death among firefighters, given the relatively low overall death rate among this occupational group.]

2.2 Cancers of the urogenital system

2.2.1 Studies reporting occupational characteristics of firefighters

See Table 2.3.

Studies first described in Section 2.1.1 are described in less detail in the present section.

The Working Group identified 23 occupational and population-based cohort studies on the relation between occupational exposure as a firefighter and risk of cancers of the genitourinary system, including the prostate, testis, bladder, and kidney (Vena & Fiedler, 1987; Demers et al., 1992a, 1994; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Bates et al., 2001; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014, 2015; Glass et al., 2016a, b, 2017, 2019; Petersen et al., 2018a, b; Kullberg et al., 2018; Bigert et al., 2020; Pinkerton et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a, b). Of these studies, one was from Asia, seven from Europe, fourteen from North America, and five from Oceania. Four of these studies were excluded because they largely represented earlier follow-up of included studies (Heyer et al., 1990; Beaumont et al., 1991; Baris et al., 2001) or covered similar data to that in an included study (Demers et al., 1992b). [The Working Group noted that the study strengths and limitations pertaining to design that were previously described for cancers of the respiratory system in Section 2.1.2(b) also apply to outcomes in the present section.]

A cohort study of cancer incidence in 33 416 male professional [career] emergency responders (29 438, or 88%, were firefighters) in the Republic of Korea provided information on the risk of cancers of the genitourinary system (Ahn et al., 2012). Emergency responders were employed between 1980 and 2007, and cancer incidence follow-up was carried out from 1996 through 2007. With the male population of the Republic of Korea as the referent, the SIRs for firefighters were raised for cancers of the kidney (SIR, 1.56; 95% CI, 1.01–2.41; 20 cases), urinary bladder (SIR, 1.60; 95% CI, 1.01–2.56; 17 cases), and prostate (SIR, 1.32; 95% CI, 0.60–2.51; 9 cases), but the evidence was less clear for prostate cancer because of the wide confidence interval. The age- and calendar year-adjusted SRRs from internal analyses (with non-firefighter emergency responders as the referent) were not elevated for cancers of the prostate, kidney, or bladder.

An incidence and mortality study in a cohort of 3881 male professional [career] firefighters from several departments in Norway provided

Table 2.3 Cohort studies reporting occupational characteristics of firefighters and cancers of the urogenital system

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) Republic of Korea Enrolment, 1980–2007/follow-up, 1996–2007 Cohort	33 416 men employed as emergency responders for ≥ 1 mo in 1980–2007 with (29 438) and without (3978) firefighting experience and not deceased in 1995 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Prostate, incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include rural and municipal firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: no information on personal characteristics or confounders (except the firefighter cohort had a lower BMI and smoked less than the comparison population for the SIR analysis); follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	1	0.75 (0.01–4.16)		
			≥ 10 yr	8	1.47 (0.63–2.89)		
			Total	9	1.32 (0.60–2.51)		
		Prostate, incidence	SRR:				
			Non-firefighters	2	1		
			Ever employed as a firefighter	9	0.22 (0.05–1.05)		
		Kidney, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	6	1.62 (0.59–3.52)		
			≥ 10 yr	14	1.54 (0.84–2.58)		
			Total	20	1.56 (1.01–2.41)		
		Kidney, incidence	SRR:				
			Non-firefighters	2	1		
			Ever employed as a firefighter	20	0.69 (0.16–2.99)		
		Urinary bladder, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	1	0.39 (0.01–2.18)		
			≥ 10 yr	16	1.98 (1.13–3.22)		
			Total	17	1.60 (1.01–2.56)		
		Urinary bladder, incidence	SRR:				
			Non-firefighters	3	1		
			Ever employed as a firefighter	17	0.40 (0.12–1.40)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Kidney, incidence	SIR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions, may include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	29	1.28 (0.86–1.84)		
		Kidney, incidence	Year of first employment (SIR):				
			Pre-1950	10	1.61 (0.77–2.96)		
			1950–1969	9	1.24 (0.57–2.35)		
			1970 or after	10	1.09 (0.52–2.01)		
		Kidney, incidence	Time since first employment (SIR):				
			< 20 yr	1	0.47 (0.01–2.64)		
			20–39 yr	15	1.41 (0.79–2.32)		
			≥ 40 yr	13	1.32 (0.70–2.26)		
		Kidney, incidence	Duration of employment (SIR):				
			< 10 yr	3	1.32 (0.27–3.85)		
			10–19 yr	3	1.07 (0.22–3.14)		
			20–29 yr	6	0.95 (0.35–2.06)		
			≥ 30 yr	17	1.51 (0.88–2.42)		
		Urinary tract (ICD-10, C65–C68), incidence	SIR:				
			Firefighters	69	1.25 (0.97–1.58)		
		Urinary tract (ICD-10, C65–C68), incidence	Year of first employment (SIR):				
			Pre-1950	35	1.71 (1.19–2.38)		
			1950–1969	22	1.04 (0.65–1.58)		
			1970 or after	12	0.88 (0.45–1.54)		
		Urinary tract (ICD-10, C65–C68), incidence	Time since first employment (SIR):				
			< 20 yr	3	1.13 (0.23–3.30)		
			20–39 yr	17	0.86 (0.50–1.38)		
			≥ 40 yr	49	1.49 (1.10–1.97)		
		Urinary tract (ICD-10, C65–C68), incidence	Duration of employment (SIR):				
			< 10 yr	8	1.82 (0.79–3.60)		
			10–19 yr	3	0.55 (0.11–1.60)		
			20–29 yr	22	1.54 (0.97–2.34)		
			≥ 30 yr	36	1.16 (0.81–1.60)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Prostate, incidence	SIR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions, may include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	214	1.18 (1.03–1.35)		
		Prostate, mortality	SMR:				
			Firefighters	54	1.07 (0.80–1.39)		
		Prostate, incidence	Period of follow-up (SIR):				
			1984 or before	14	0.83 (0.45–1.39)		
			1985–1994	32	1.33 (0.91–1.88)		
			1995 or after	168	1.20 (1.02–1.39)		
		Prostate, mortality	Period of follow-up (SMR):				
			1984 or before	6	0.91 (0.33–1.97)		
			1985–1994	7	0.70 (0.28–1.44)		
			1995 or after	41	1.21 (0.87–1.64)		
		Prostate, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	2.65 (0.72–6.79)		
			50–69 yr	109	1.22 (1.01–1.48)		
			≥ 70 yr	101	1.11 (0.91–1.35)		
		Prostate, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–22.03)		
			50–69 yr	7	0.72 (0.29–1.48)		
			≥ 70 yr	47	1.16 (0.85–1.54)		
		Testis, incidence	SIR:				
			Firefighters	17	1.39 (0.81–2.22)		
		Testis, mortality	SMR:				
			Firefighters	0	0 (0.00–3.07)		
		Testis, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	1.64 (0.45–4.21)		
			1985–1994	0	0 (0.00–1.34)		
			1995 or after	13	1.72 (0.91–2.93)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Testis, mortality	Period of follow-up (SMR):			Age, calendar year	
			1984 or before	0	0 (0.00–5.24)		
			1985–1994	0	0 (0.00–25.3)		
			1995 or after	0	0 (0.00–10.5)		
		Testis, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	15	1.47 (0.82–2.43)		
			50–69 yr	< 5	1.10 (0.13–3.97)		
			≥ 70 yr	0	0 (0.00–12.7)		
		Testis, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–4.86)		
			50–69 yr	0	0 (0.00–12.3)		
			≥ 70 yr	0	0 (0.00–25.8)		
		Kidney, mortality	SMR:				
			Firefighters	10	0.97 (0.46–1.78)		
		Kidney, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	1.07 (0.29–2.74)		
			1985–1994	8	2.40 (1.04–4.74)		
			1995 or after	17	1.09 (0.64–1.75)		
		Kidney, mortality	Period of follow-up (SMR):				
			1984 or before	< 5	0.43 (0.01–2.37)		
			1985–1994	< 5	2.00 (0.54–5.11)		
			1995 or after	5	0.83 (0.27–1.95)		
		Kidney, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	0.78 (0.09–2.80)		
			50–69 yr	12	0.97 (0.50–1.69)		
			≥ 70 yr	15	1.96 (1.10–3.23)		
		Kidney, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	< 5	3.01 (0.36–10.9)		
			50–69 yr	< 5	0.83 (0.23–2.13)		
			≥ 70 yr	< 5	0.82 (0.22–2.11)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Urinary tract (ICD-10, C65–C68), mortality	SMR:			Age, calendar year	
			Firefighters	15	1.14 (0.64–1.88)		
		Urinary tract (ICD-10, C65–C68), incidence	Period of follow-up (SIR):				
			1984 or before	13	1.42 (0.76–2.43)		
			1985–1994	15	1.47 (0.82–2.43)		
			1995 or after	41	1.14 (0.82–1.55)		
		Urinary tract (ICD-10, C65–C68), mortality	Period of follow-up (SMR):				
			1984 or before	< 5	1.20 (0.25–3.51)		
			1985–1994	< 5	1.58 (0.43–4.05)		
			1995 or after	8	0.99 (0.43–1.94)		
		Urinary tract (ICD-10, C65–C68), incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	1.05 (0.22–3.06)		
			50–69 yr	23	0.96 (0.61–1.44)		
			≥ 70 yr	43	1.52 (1.10–2.04)		
		Urinary tract (ICD-10, C65–C68), mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–12.0)		
			50–69 yr	< 5	0.79 (0.16–2.30)		
			≥ 70 yr	12	1.32 (0.68–2.31)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2020) Sweden Enrolment, 1960–1990/follow-up, 1961–2009 Cohort	8136 male firefighters identified from national censuses in 1960, 1970, 1980, and 1990 Exposure assessment method: questionnaire; ever employed and categorical duration of employment (years) as firefighter from census surveys	Prostate, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. May include full-time, part-time, municipal, and rural firefighters. *Strengths*: precise linkage to high-quality outcome data; near complete ascertainment of cancer incidence, long length of follow-up (mean, 28 yr); analyses stratified by calendar period of employment. *Limitations*: no data on job duties, employment type, or potential confounders (aside from age, sex, and calendar year); probable healthy-worker hire bias; potential non-differential misclassification of employment duration.
			Firefighters	444	1.06 (0.96–1.16)		
		Prostate, incidence	Duration of employment (SIR):				
			1–9 yr	2	0.50 (0.06–1.81)		
			10–19 yr	76	0.94 (0.74–1.18)		
			20–29 yr	114	0.98 (0.81–1.17)		
			≥ 30 yr	252	1.14 (1.01–1.29)		
			Trend-test *P* value, 0.13				
		Prostate, incidence	Time period (SIR):				
			1961–1975	8	0.68 (0.29–1.34)		
			1976–1990	77	1.09 (0.86–1.36)		
			1991–2009	359	1.06 (0.95–1.18)		
		Testis, incidence	SIR:				
			Firefighters	4	0.39 (0.11–1.01)		
		Kidney, incidence	SIR:				
			Firefighters	41	0.84 (0.61–1.14)		
		Urinary bladder and ureter, incidence	SIR:				
			Firefighters	109	1.08 (0.89–1.31)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1958–2012 Cohort	1080 men who worked ≥ 1 year as a firefighter in Stockholm in 1931–1983 Exposure assessment method: ever employed and categorical duration of employment (years) as an urban [municipal] firefighter from annual enrolment records	Prostate, incidence	Follow-up period (SIR):			Birth year, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole of employment. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence; analyses of duration and era of employment. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year); lack of exposure assessment based on job tasks or fire responses.
			Full: 1958–2012	60	0.68 (0.52–0.87)		
			Former: 1958–1986	29	1.19 (0.80–1.72)		
			Extended: 1958–2012	31	0.48 (0.33–0.69)		
		Prostate, incidence	Age at risk (SIR):				
			< 50 yr	1	4.24 (0.11–23.6)		
			50–64 yr	10	0.50 (0.24–0.92)		
			≥ 65 yr	49	0.72 (0.53–0.95)		
			Trend-test *P* value, 0.52				
		Prostate, incidence	Duration of employment (SIR):				
			1–9 yr	7	0.64 (0.30–1.33)		
			10–19 yr	3	0.41 (0.13–1.26)		
			20–29 yr	17	1.06 (0.66–1.70)		
			≥ 30 yr	33	0.61 (0.43–0.86)		
			Trend-test *P* value, 0.75				
		Prostate, incidence	Period of first employment (SIR):				
			1902–1939	24	0.87 (0.59–1.31)		
			1940–1959	31	0.87 (0.61–1.23)		
			1960–1986	5	0.20 (0.08–0.47)		
			Trend-test *P* value, < 0.01				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) (cont.)		Kidney, incidence	Follow-up period (SIR):			Birth year, calendar period	
			Full: 1958–2012	6	0.57 (0.21–1.23)		
			Former: 1958–1986	2	0.37 (0.04–1.33)		
			Extended: 1987–2012	4	0.78 (0.21–1.99)		
		Urinary organs (ICD-7 181), incidence	Follow-up period (SIR):				
			Full: 1958–2012	16	0.72 (0.41–1.17)		
			Former: 1958–1986	8	0.95 (0.41–1.88)		
			Extended: 1987–2012	8	0.58 (0.25–1.14)		
Tornling et al. (1994) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1951–1986 (mortality), 1958–1986 (incidence) Cohort	1116 for mortality/1091 for incidence; male firefighters employed for ≥ 1 yr by the City of Stockholm between 1931 and 1983, identified from annual enrolment records Exposure assessment method: ever firefighter and duration (years) of firefighting employment from annual enrolment records; number of fires fought ascertained from exposure index developed from fire reports	Prostate, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Enhanced exposure assessment (but based on 10% sample of reports) to differentiate exposure based on number of fires fought accounting for job position, station, and year of exposure. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence and mortality; assessed exposure to fire responses for some outcomes *Limitations*: no data on potential confounders (aside from age, sex, and calendar year).
			Firefighters	14	1.21 (0.66–2.02)		
		Prostate, incidence	SIR:				
			Firefighters	28	1.14 (0.76–1.65)		
		Kidney, mortality	SMR:				
			Firefighters	4	1.10 (0.30–2.81)		
		Kidney, incidence	SIR:				
			Firefighters	2	0.36 (0.04–1.29)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) Denmark Enrolment, 1964–2004/follow-up, 1968–2014 Cohort	9061 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born 2 April 1928 or later, employed before age 60 yr and 31 December 2004, no cancer diagnosis before employment as a firefighter, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years), as well as employment type, job title/function, and work history, ascertained from civil registration, pension, employer personnel, and trade union membership records	Prostate, incidence	Reference group (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; near-complete ascertainment of cancer incidence; use of three reference groups to evaluate healthy-worker bias; analyses by proxies of exposure including job task. *Limitations*: little information on potential confounders.
			Firefighters vs general population	202	1.10 (0.95–1.26)		
			Firefighters vs sample of employees	202	1.15 (1.00–1.32)		
			Firefighters vs military	202	1.02 (0.88–1.17)		
		Prostate, incidence	Employment type (SIR):				
			Full-time	130	1.12 (0.95–1.33)		
			Part-time or volunteer	72	1.05 (0.83–1.32)		
		Prostate, incidence	Era of first employment (SIR):				
			Pre-1970	108	1.16 (0.96–1.40)		
			1970–1994	85	1.05 (0.85–1.30)		
			1995 or after	9	0.90 (0.47–1.73)		
		Prostate, incidence	Job function (SIR):				
			Regular	188	1.09 (0.95–1.26)		
			Specialized	14	1.15 (0.68–1.94)		
		Prostate, incidence	Age at first employment (SIR):				
			< 25 yr	100	1.12 (0.92–1.36)		
			25–34 yr	56	1.08 (0.83–1.41)		
			≥ 35 yr	46	1.06 (0.80–1.42)		
		Prostate, incidence	Duration of employment (SIR):				
			< 1 yr	59	1.12 (0.87–1.45)		
			≥ 1 yr	143	1.09 (0.92–1.28)		
			≥ 10 yr	125	1.09 (0.91–1.29)		
			≥ 20 yr	101	1.12 (0.92–1.36)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Testis, incidence	Reference group (SIR):			Age, calendar period	
			Firefighters vs general population	47	1.30 (0.97–1.73)		
			Firefighters vs sample of employees	47	1.04 (0.78–1.39)		
			Firefighters vs military	47	0.98 (0.73–1.30)		
		Testis, incidence	Employment type (SIR):				
			Full-time	23	1.23 (0.82–1.86)		
			Part-time or volunteer	24	1.36 (0.91–2.04)		
		Testis, incidence	Era of first employment (SIR):				
			Pre-1970	8	1.55 (0.77–3.09)		
			1970–1994	28	1.32 (0.91–1.91)		
			1995 or after	11	1.12 (0.62–2.02)		
		Testis, incidence	Job function (SIR):				
			Regular	43	1.27 (0.94–1.71)		
			Specialized	4	1.65 (0.62–4.39)		
		Testis, incidence	Age at first employment (SIR):				
			< 25 yr	25	1.33 (0.90–1.97)		
			25–34 yr	17	1.21 (0.75–1.94)		
			≥ 35 yr	5	1.48 (0.62–3.56)		
		Testis, incidence	Duration of employment (SIR):				
			< 1 yr	10	1.72 (0.92–3.19)		
			≥ 1 yr	37	1.22 (0.88–1.68)		
			≥ 10 yr	25	1.07 (0.73–1.59)		
			≥ 20 yr	14	0.99 (0.58–1.67)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Other genitals (ICD-10, C60, C63), incidence	Reference group (SIR):			Age, calendar period	
			Firefighters vs general population	3	0.78 (0.25–2.41)		
			Firefighters vs sample of employees	3	0.82 (0.26–2.54)		
			Firefighters vs military	3	0.70 (0.23–2.18)		
		Kidney, incidence	Reference group (SIR):				
			Firefighters vs general population	32	1.04 (0.74–1.47)		
			Firefighters vs sample of employees	32	1.02 (0.72–1.44)		
			Firefighters vs military	32	1.04 (0.74–1.48)		
		Kidney (urinary pelvis/upper urinary tract), incidence	Reference group (SIR):				
			Firefighters vs general population	10	1.46 (0.79–2.72)		
			Firefighters vs sample of employees	10	1.59 (0.85–2.95)		
			Firefighters vs military	10	1.35 (0.73–2.51)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Urinary bladder (ICD-10, C67, D09.0, D30.3, D41.4), incidence	Firefighters vs general population	88	1.09 (0.89–1.35)	Age, calendar period	
			Firefighters vs sample of employees	88	1.11 (0.90–1.37)		
			Firefighters vs military	88	1.05 (0.86–1.30)		
		Urinary bladder (ICD-10, C67, D09.0, D30.3, D41.4), incidence	Employment type (SIR):				
			Full-time	59	1.14 (0.89–1.48)		
			Part-time of volunteer	29	1.01 (0.70–1.45)		
		Urinary bladder (ICD-10, C67, D09.0, D30.3, D41.4), incidence	Era of first employment (SIR):				
			Pre-1970	51	1.21 (0.92–1.59)		
			1970–1994	35	1.05 (0.75–1.46)		
			1995 or after	2	0.41 (0.10–1.66)		
		Urinary bladder (ICD-10, C67, D09.0, D30.3, D41.4), incidence	Job function (SIR):				
			Regular	83	1.10 (0.89–1.37)		
			Specialized	5	0.95 (0.39–2.28)		
		Urinary bladder (ICD-10, C67, D09.0, D30.3, D41.4), incidence	Age at first employment (SIR):				
			< 25 yr	54	1.32 (1.01–1.73)		
			25–34 yr	17	0.76 (0.47–1.22)		
			≥ 35 yr	17	0.98 (0.61–1.58)		
		Urinary bladder (ICD-10, C67, D09.0, D30.3, D41.4), incidence	Duration of employment (SIR):				
			< 1 yr	31	1.28 (0.90–1.82)		
			≥ 1 yr	57	1.01 (0.78–1.32)		
			≥ 10 yr	51	1.04 (0.79–1.37)		
			≥ 20 yr	37	0.97 (0.70–1.34)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018b) Denmark Enrolment, 1964–2014/follow-up, 1970–2014 Cohort	11 775 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born in 1928 or later, employed before age 60 yr and 31 December 2004, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years) as a firefighter ascertained from civil registration, pension, employer personnel, and trade union membership records	Prostate, mortality	Employment type (SMR, military reference group):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; use of military reference group to evaluate healthy-worker bias; analyses by duration of employment. *Limitations*: little information on potential confounders.
			Full-time	16	0.66 (0.40–1.07)		
			Part-time/ volunteer	20	1.89 (1.22–2.93)		
		Prostate, mortality	Duration of employment (SMR, military reference group), full-time firefighters:				
			< 1 yr	7	0.56 (0.27–1.17)		
			≥ 1 yr	9	0.77 (0.40–1.47)		
			≥ 10 yr	8	0.75 (0.37–1.50)		
			≥ 20 yr	7	0.74 (0.35–1.56)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Webber et al. (2021) USA 2001–2016 Cohort	10 786 FDNY, 8813 CFHS; FDNY and CFHS cohorts; male firefighters who were active on 11 September 2001; FDNY cohort included men who worked at the WTC site any time between 11 September 2001 and 25 July 2002; CFHS cohort included men who were actively employed on 11 September 2001 and assumed not to be working at the WTC site Exposure assessment method: presence at WTC site from employment records and duty rosters	Prostate, incidence	Group (SIR, US reference rates):			Age, calendar year, race/ethnicity	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. Qualitative assessment based on presence at the WTC site, exposures complex and probably unique to 9/11 disaster. Municipal firefighters. *Strengths*: ascertainment of cancer incidence; comparison of two firefighter cohorts to evaluate bias. *Limitations*: medical surveillance bias; young age of cohort; relatively short length of follow-up.
			CFHS firefighters	358	1.22 (1.11–1.35)		
			FDNY WTC firefighters	332	1.70 (1.53–1.88)		
		Prostate, incidence	SIR (2-yr adjustment for potential surveillance bias):				
			FDNY WTC firefighters	NR	1.55 (1.39–1.73)		
		Prostate, incidence	Group (RR):			Age on 11 September 2001, race/ethnicity	
			CFHS firefighters	358	1		
			FDNY WTC firefighters	332	1.39 (1.19–1.63)		
		Prostate, incidence	Group RR (2-yr adjustment for potential surveillance bias):				
			CFHS firefighters	NR	1		
			FDNY WTC firefighters	NR	1.28 (1.09–1.51)		
		Kidney, incidence	Group (SIR, US reference rates):			Age, calendar year, race/ethnicity	
			CFHS firefighters	55	1.19 (0.90–1.56)		
			FDNY WTC firefighters	39	0.93 (0.67–1.28)		
		Kidney, incidence	SIR (2-yr adjustment for potential surveillance bias):				
			FDNY WTC firefighters	NR	0.85 (0.61–1.19)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Webber et al. (2021) (cont.)		Kidney, incidence	Group (RR):			Age on 11 September 2001, race/ethnicity	
			CFHS firefighters	55	1		
			FDNY WTC firefighters	39	0.82 (0.52–1.30)		
		Kidney, incidence	Group RR (2-yr adjustment for potential surveillance bias)				
			CFHS firefighters	NR	1		
			FDNY WTC firefighters	NR	0.75 (0.47–1.20)		
Zeig-Owens et al. (2011) New York City, USA Enrolment, 1996/follow-up, 1996–2008 Cohort	9853 male FDNY firefighters who were employed for ≥ 18 mo, were active firefighters on 1 January 1996, with no prior cancer, and, if alive on 12 September 2001, also had known WTC exposure status Exposure assessment method: WTC-exposed and non-exposed firefighter from employment records and questionnaires	Prostate, incidence	WTC exposure status (SIR, 2-yr adjustment for potential surveillance bias):			Age, race, ethnic origin, calendar year	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. WTC exposure self-reported using three methods. WTC site exposures complex and probably unique to 9/11 disaster. *Strengths*: evaluation of medical surveillance bias. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Non-exposed	45	1.35 (1.01–1.81)		
			Exposed	73	1.21 (0.96–1.52)		
			SIR ratio (exposed vs non-exposed)	NR	0.90 (0.62–1.30)		
		Testis, incidence	WTC exposure status (SIR):				
			Non-exposed	11	1.54 (0.85–2.78)		
			Exposed	≤ 5	0.86 (0.36–2.06)		
			SIR ratio (exposed vs non-exposed)	NR	0.56 (0.19–1.60)		
		Kidney, incidence	WTC exposure status (SIR):				
			Non-exposed	5	0.30 (0.07–1.18)		
			Exposed	10	0.86 (0.46–1.60)		
			SIR ratio (exposed vs non-exposed)	NR	2.91 (0.64–13.30)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeig-Owens et al. (2011) (cont.)		Urinary bladder, incidence	WTC exposure status (SIR):			Age, race, ethnic origin, calendar year	
			Non-exposed	6	0.79 (0.36–1.76)		
			Exposed	11	1.01 (0.56–1.83)		
			SIR ratio (exposed vs non-exposed)	NR	1.28 (0.47–3.46)		
Pinkerton et al. (2020) San Francisco, Chicago and Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2016 Cohort	29 992 municipal career firefighters in the CFHS cohort employed by the fire departments of San Francisco, Chicago, or Philadelphia for ≥ 1 day between 1950 and 2009; exposure–response analyses limited to 19 287 male firefighters of known race hired in 1950 or later and employed for ≥ 1 yr Exposure assessment method: ever employed as a firefighter, and number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Prostate, mortality	Fire department (SMR):			Gender, race, age, calendar period	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices; adjustment for HWSE. *Limitations*: healthy-worker selection bias in external comparison analyses; little information on potential confounders.
			San Francisco	60	0.89 (0.68–1.15)		
			Chicago	176	1.23 (1.05–1.42)		
			Philadelphia	98	0.99 (0.81–1.21)		
			Overall	334	1.08 (0.97–1.20)		
			Heterogeneity *P* value, 0.06				
		Prostate, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	126	0.88 (0.62–1.25)		
			RCS without HWSE adjustment	126	0.80 (0.52–1.27)		
			Fully adjusted loglinear	126	1.04 (0.65–1.71)		
			Fully adjusted RCS	126	0.85 (0.47–1.62)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Prostate, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	104	0.87 (0.66–1.14)		
			RCS without HWSE adjustment	104	0.81 (0.58–1.13)		
			Fully adjusted loglinear	104	0.92 (0.67–1.25)		
			Fully adjusted RCS	104	0.86 (0.58–1.27)		
		Prostate, mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag):				
			Loglinear without HWSE adjustment	76	0.78 (0.53–1.14)		
			RCS without HWSE adjustment	76	0.63 (0.40–1.01)		
			Fully adjusted loglinear	76	0.82 (0.52–1.27)		
			Fully adjusted RCS	76	0.66 (0.39–1.12)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Other male genital (ICD-10, C60, C62–C63), mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	< 5	0.52 (0.01–2.90)		
			Chicago	0	0 (NR)		
			Philadelphia	< 5	0.85 (0.18–2.49)		
			Overall	< 5	0.39 (0.11–1.00)		
			Heterogeneity *P* value, 0.15				
		Kidney, mortality	Fire department (SMR):				
			San Francisco	15	0.85 (0.48–1.40)		
			Chicago	66	1.57 (1.22–2.00)		
			Philadelphia	27	0.93 (0.61–1.36)		
			Overall	108	1.22 (1.00–1.47)		
			Heterogeneity *P* value, 0.02				
		Kidney, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	62	1.15 (0.64–2.13)		
			RCS without HWSE adjustment	62	1.23 (0.64–2.52)		
			Fully adjusted loglinear	62	1.03 (0.50–2.24)		
			Fully adjusted RCS	62	1.16 (0.50–2.92)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Kidney, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	55	1.03 (0.67–1.53)		
			RCS without HWSE adjustment	55	1.15 (0.69–1.94)		
			Fully adjusted loglinear	55	0.94 (0.59–1.46)		
			Fully adjusted RCS	55	1.08 (0.61–1.96)		
		Kidney, mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag)				
			Loglinear without HWSE adjustment	42	1.26 (0.72–2.14)		
			RCS without HWSE adjustment	42	1.55 (0.78–3.22)		
			Fully adjusted loglinear	42	1.15 (0.63–2.08)		
			Fully adjusted RCS	42	1.56 (0.72–3.58)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Urinary bladder, mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	23	1.01 (0.64–1.52)		
			Chicago	48	0.98 (0.72–1.30)		
			Philadelphia	33	0.96 (0.66–1.34)		
			Overall	104	0.98 (0.80–1.18)		
			Trend-test *P* value, 0.98				
		Urinary bladder, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	37	0.71 (0.37–1.38)		
			RCS without HWSE adjustment	37	0.71 (0.33–1.67)		
			Fully adjusted loglinear	37	1.23 (0.50–3.41)		
			Fully adjusted RCS	37	2.66 (0.67–14.7)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2015) San Francisco, Chicago, Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	19 309, all male career firefighters in the CFHS cohort of known race who were on active duty ≥ 1 day in 1950–2009 in the fire departments of Chicago, Philadelphia, or San Francisco, with ≥ 1 yr of employment Exposure assessment method: number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Prostate, incidence	Exposed-days model (HR, RCS model, 10-yr lag):			Age, race, fire department, birth cohort	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices. *Limitations*: little information on potential confounders.
			8700 days vs 2500 days	832	0.90 (0.77–1.05)		
		Prostate, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, log-linear model, 10-yr lag):				
			8800 runs vs 2100 runs	678	1.02 (0.91–1.14)		
		Prostate, incidence	Fire-hours (Chicago only) model (HR, power model, 10-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	419	0.98 (0.90–1.09)		
		Prostate, incidence	Time since exposure in fire-runs (Chicago and Philadelphia only) loglinear model (HR at 4600 runs, 10-yr lag):			Age, race, fire department, birth cohort	
			Lag to lag + 10 yr	NR	0.60 (0.21–1.53)		
			Lag + 10 to lag + 20 yr	NR	0.68 (0.35–1.23)		
			> lag + 20 yr	NR	0.80 (0.52–1.18)		
			LRT *P* value, 0.807				
		Prostate, incidence	Age at exposure in fire-runs (Chicago and Philadelphia only) loglinear model (HR at 4600 runs, 10-yr lag):				
			< 40 yr	NR	0.72 (0.42–1.16)		
			≥ 40 yr	NR	0.73 (0.50–1.04)		
			LRT *P* value, 0.953				
		Prostate, incidence	Exposure period in fire-runs (Chicago and Philadelphia only) loglinear model (HR at 4600 runs, 10-yr lag):				
			Pre-1970	NR	0.91 (0.55–1.44)		
			1970 or after	NR	0.63 (0.43–0.91)		
			LRT *P* value, 0.299				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2015) (cont.)		Urinary bladder, incidence	Exposed-days model (HR, power model, 10-yr lag):			Age, race, fire department, birth cohort	
			8700 days vs 2500 days	174	1.01 (0.89–1.19)		
		Urinary bladder, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, power model, 10-yr lag):				
			8800 runs vs 2100 runs	144	1.05 (0.89–1.27)		
		Urinary bladder, incidence	Fire-hours (Chicago only) model (HR, power model, 10-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	95	0.98 (0.79–1.27)		
Daniels et al. (2014) Chicago, San Francisco, and Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	29 993 (24 453 for incidence analyses) male and female career firefighters in the CFHS cohort employed for ≥ 1 day in Chicago, San Francisco, or Philadelphia fire departments between 1950 and 2009 Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Male genital organs, incidence	Fire department (SIR, all cancers):			Race, age, calendar period	*Exposure assessment critique*: Satisfactory quality. Minimum exposure was 1 day of work as a municipal firefighter. *Strengths*: long period of follow-up; ascertained incidence outcomes; included female firefighters. *Limitations*: healthy-worker hire bias in external comparisons; little information on potential confounders.
			San Francisco	278	1.21 (1.07–1.36)		
			Chicago	602	0.98 (0.91–1.07)		
			Philadelphia	398	0.98 (0.89–1.09)		
		Prostate, incidence	SIR:				
			All cancers	1261	1.03 (0.98–1.09)		
			First primary cancer	1176	1.03 (0.97–1.09)		
		Prostate, incidence	Fire department (SIR, all cancers):				
			San Francisco	276	1.22 (1.08–1.37)		
			Chicago	592	0.99 (0.91–1.07)		
			Philadelphia	393	0.99 (0.90–1.10)		
			Heterogeneity *P* value, 0.078				
		Prostate, incidence	Race (SIR, all cancers):			Age, calendar period	
			Caucasian [White]	1167	1.02 (0.96–1.08)		
			Other	94	1.26 (1.02–1.54)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Prostate, incidence	Age (SIR, all cancers):			Race, age, calendar period	
			17–64 yr	426	1.21 (1.10–1.33)		
			65 to ≥ 85 yr	835	0.96 (0.90–1.03)		
			Heterogeneity *P* value, < 0.001				
		Other male genital (ICD-10, C60, C62–C63), incidence	SIR:				
			All cancers	17	0.62 (0.36–0.99)		
			First primary cancer	17	0.67 (0.39–1.07)		
		Other and unspecified male genital (ICD-10, C60, C63), incidence	Fire department (SIR, all cancers):				
			San Francisco	0	0 (NR)		
			Chicago	< 5	0.53 (0.06–1.92)		
			Philadelphia	0	0 (NR)		
		Other male genital (ICD-10, C60, C62–C63), incidence	Race (SIR, all cancers):			Age, calendar period	
			Caucasian [White]	16	0.64 (0.37–1.04)		
			Other	< 5	0.38 (0.01–2.13)		
		Testis, incidence	SIR:			Race, age, calendar period	
			All cancers	15	0.75 (0.42–1.24)		
			First primary cancer	15	0.79 (0.44–1.30)		
		Testis, incidence	Fire department (SIR, all cancers):			Gender, race, age, calendar period	
			San Francisco	< 5	0.74 (0.09–2.67)		
			Chicago	8	0.76 (0.33–1.50)		
			Philadelphia	5	0.75 (0.24–1.75)		
		Urinary organs (ICD-10, C64–C68), incidence	Fire department (SIR, all cancers):				
			San Francisco	89	1.15 (0.93–1.42)		
			Chicago	234	1.17 (1.02–1.32)		
			Philadelphia	159	1.17 (1.00–1.37)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Kidney, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	166	1.27 (1.09–1.48)		
			First primary cancer	129	1.24 (1.04–1.48)		
		Kidney, incidence	Fire department (SIR, all cancers):				
			San Francisco	26	1.10 (0.72–1.61)		
			Chicago	83	1.30 (1.04–1.61)		
			Philadelphia	57	1.33 (1.00–1.72)		
			Heterogeneity *P* value, 1.00				
		Kidney, incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men: Caucasian [White]	151	1.26 (1.06–1.47)		
			Other	14	1.46 (0.80–2.45)		
		Kidney, incidence	Age (SIR, all cancers):			Gender, race, age, calendar period	
			17–64 yr	79	1.41 (1.12–1.76)		
			65 to ≥ 85 yr	87	1.17 (0.94–1.44)		
			Heterogeneity *P* value, 1.00				
		Urinary bladder, incidence	SIR:				
			All cancers	316	1.12 (1.00–1.25)		
			First primary cancer	272	1.18 (1.05–1.33)		
		Urinary bladder, incidence	Fire department (SIR, all cancers):				
			San Francisco	63	1.18 (0.91–1.51)		
			Chicago	151	1.10 (0.93–1.29)		
			Philadelphia	102	1.10 (0.90–1.33)		
			Heterogeneity *P* value, 1.00				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Urinary bladder, incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men: Caucasian [White]	305	1.11 (0.99–1.24)		
			Other	7	0.92 (0.37–1.91)		
		Urinary bladder, incidence	Age (SIR, all cancers):			Gender, race, age, calendar period	
			17–64 yr	133	1.33 (1.08–1.62)		
			65 to ≥ 85 yr	219	1.04 (0.91–1.19)		
			Heterogeneity *P* value, 0.002				
Demers et al. (1994) Seattle and Tacoma, USA Enrolment, 1944–1979/follow-up, 1974–1989 Cohort	2447 male firefighters employed for ≥ 1 yr between 1944 and 1979, alive as of 1 January 1974 and known to be a resident of one of thirteen counties in the catchment area of the tumour registry for ≥ 1 mo; reference group included 1878 male local police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration of employment (years) in direct firefighting positions from employment records	Prostate, incidence	SIR (local county rates):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Duration (years) involved in direct firefighting (surrogate for fire smoke) was not measured equally in the two study populations. Municipal firefighters. *Strengths*: use of two comparison groups; including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders.
			Firefighters	66	1.4 (1.1–1.7)		
		Prostate, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	7	1.4 (0.6–2.8)		
			10–19 yr	6	1.2 (0.4–2.6)		
			20–29 yr	47	1.5 (1.1–2.0)		
			≥ 30 yr	6	0.9 (0.3–1.9)		
		Prostate, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	1	7.4 (0.2–41)		
			20–29 yr	5	1.8 (0.6–4.3)		
			≥ 30 yr	60	1.3 (1.0–1.7)		
		Prostate, incidence	IDR:				
			Local police	28	1		
			Firefighters	66	1.1 (0.7–1.8)		
		Kidney, incidence	SIR (local county rates):				
			Firefighters	3	0.5 (0.1–1.6)		
		Kidney, incidence	IDR:				
			Local police	4	1		
			Firefighters	3	0.4 (0.1–2.1)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		Urinary bladder, incidence	SIR (local county rates):			Age, calendar period	
			Firefighters	18	1.2 (0.7–1.9)		
		Urinary bladder, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	4	2.2 (0.6–5.6)		
			10–19 yr	2	0.9 (0.1–3.4)		
			20–29 yr	9	1.0 (0.4–1.8)		
			≥ 30 yr	3	1.6 (0.3–4.8)		
		Urinary bladder, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	1	1.4 (0.0–7.5)		
			20–29 yr	4	2.0 (0.5–5.1)		
			≥ 30 yr	13	1.0 (0.6–1.8)		
		Urinary bladder, incidence	IDR:				
			Local police	6	1		
			Firefighters	18	1.7 (0.7–4.3)		
Demers et al. (1992a) Seattle and Tacoma, Washington; Portland, Oregon, USA Enrolment, 1944–1979/follow-up, 1945–1989 Cohort	4401 male firefighters employed for ≥ 1 yr between 1944 and 1979 in Seattle, Tacoma, or Portland, USA; reference group included 3676 local police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration (years) of exposure to fire combat from employment records	Prostate, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Duration (years) involved in fire combat (surrogate for fire smoke) was not measured equally in the three municipal firefighter populations. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders; ascertained mortality outcomes only.
			Firefighters	30	1.34 (0.90–1.91)		
		Prostate, mortality	Duration of exposed employment (SMR):				
			< 10 yr	3	2.24 (0.5–7.1)		
			10–19 yr	2	1.12 (0.1–4.1)		
			20–29 yr	14	1.23 (0.7–2.1)		
			≥ 30 yr	11	1.36 (0.7–2.4)		
		Prostate, mortality	Years since first employment (SMR):				
			< 20 yr	0	0 (0.0–26.6)		
			20–29 yr	0	0 (0.0–3.1)		
			≥ 30 yr	30	1.42 (1.0–2.0)		
		Prostate, mortality	Age at risk (SMR):				
			18–39 yr	0	0 (0.0–178)		
			40–64 yr	4	0.86 (0.2–2.2)		
			≥ 65 yr	26	1.46 (1.0–2.1)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1992a) (cont.)		Prostate, mortality	IDR:			Age, calendar period	
			Local police	11	1		
			Firefighters	30	1.43 (0.71–2.85)		
		Kidney, mortality	SMR:				
			Firefighters	2	0.27 (0.03–0.97)		
		Bladder and other urinary cancers (ICD-9, 188, 189.3–189.9), mortality	SMR:				
			Firefighters	2	0.23 (0.03–0.83)		
		Bladder and other urinary cancers (ICD-9, 188, 189.3–189.9), mortality	IDR:				
			Local police	4	1		
			Firefighters	2	0.16 (0.02–1.24)		
Vena & Fiedler (1987) Buffalo, New York, USA 1950–1979 Cohort	1867 White male career firefighters employed by the City of Buffalo for ≥ 5 yr, with ≥ 1 yr as a firefighter Exposure assessment method: ever-employment, timing, and duration of employment from employment records	Prostate, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Minimal quality. Only assessed ever-employment and duration of employment as a municipal firefighter. *Strengths*: long length of follow-up. *Limitations*: healthy-worker hire bias; little information on potential confounders or exposure to firefighting activities.
			Overall	5	0.71 (0.23–1.65)		
		Kidney, mortality	SMR:				
			Overall	3	1.30 (0.26–3.80)		
		Urinary bladder, mortality	Years worked as a firefighter (SMR):				
			1–9 yr	1	[5.00 (0.3–24.7)]		
			10–19 yr	0	0 (NR)		
			20–29 yr	1	[1.25 (0.1–6.2)]		
			30–39 yr	3	[2.14 (0.5–5.8)]		
			≥ 40 yr	4	[5.71 (1.8–13.8)]		
			Overall	9	2.86 (1.3–5.4)		
		Urinary bladder, mortality	Calendar year of death (SMR):				
			1950–1959	1	[1.56 (0.1–8.2)]		
			1960–1969	7	[6.36 (2.8–12.6)]		
			1970–1979	1	[0.67 (0.0–3.3)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena & Fiedler (1987) (cont.)		Urinary bladder, mortality	Year of hire (SMR):			Age, calendar period	
			Prior to 1930	9	[4.74 (2.3–8.7)]		
			1930–1939	0	0 (NR)		
			1940–1949	0	0 (NR)		
			1950 or after	0	0 (NR)		
		Urinary bladder, mortality	Years of latency (SMR):				
			< 20 yr	0	0 (NR)		
			20–29 yr	0	0 (NR)		
			30–39 yr	1	[1.04 (0.1–5.5)]		
			40–49 yr	5	[4.53 (1.7–10.3)]		
			≥ 50 yr	3	[6.38 (1.5–16.3)]		
Aronson et al. (1994) Toronto, Canada 1950–1989 Cohort	5414 male firefighters employed for ≥ 6 mo at one of six fire departments in Metropolitan Toronto any time between 1950 and 1989 Exposure assessment method: ever employed and categorical duration of employment (years) as municipal firefighter from employment records	Prostate, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Probably municipal firefighters. *Strengths*: long period of follow-up; analysis of employment duration. *Limitations*: healthy-worker hire bias; little information on confounders or exposure; ascertained mortality outcomes only.
			Any employment	16	1.32 (0.76–2.15)		
		Prostate, mortality	Years since first employment (SMR):				
			< 20 yr	0	0 (0–16.04)		
			20–29 yr	2	2.44 (0.30–8.81)		
			≥ 30 yr	14	1.27 (0.69–2.13)		
		Prostate, mortality	Years of employment (SMR):				
			< 15 yr	1	1.61 (0.04–8.99)		
			15–29 yr	5	2.43 (0.79–5.66)		
			≥ 30 yr	9	0.97 (0.44–1.84)		
		Prostate, mortality	Age (SMR):				
			< 60 yr	2	1.53 (0.19–5.52)		
			≥ 60 yr	14	1.30 (0.71–2.18)		
		Testis, mortality	SMR:				
			Any employment	3	2.52 (0.52–7.37)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aronson et al. (1994) (cont.)		Testis, mortality	Years since first employment (SMR):			Age, calendar period	
			< 20 yr	3	3.26 (0.67–9.53)		
			20–29 yr	0	0 (0–24.59)		
			≥ 30 yr	0	0 (0–30.74)		
		Testis, mortality	Years of employment (SMR):				
			< 15 yr	3	3.66 (0.75–10.69)		
			15–29 yr	0	0 (0–14.19)		
			≥ 30 yr	0	0 (0–36.89)		
		Testis, mortality	Age (SMR):				
			< 60 yr	3	2.75 (0.57–8.04)		
			≥ 60 yr	0	0 (0–40.99)		
		Kidney and ureter (ICD-9, 189), mortality	SMR:				
			Any employment	2	0.43 (0.05–1.56)		
		Urinary bladder, mortality	SMR:				
			Any employment	7	1.28 (0.51–2.63)		
Guidotti (1993) Edmonton and Calgary, Canada 1927–1987 Cohort	3328, all firefighters employed between 1927–1987 by either of the fire departments of Edmonton or Calgary Exposure assessment method: ever employed and categorical duration of employment (years) from employment records; exposure index of years of employment weighted by time spent in proximity to fires based on job classification	Prostate, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Good quality. Good approach to differentiate exposure between ranks. Municipal firefighters. *Strengths*: long length of follow-up; analyses by duration of employment and exposure index. *Limitations*: little information on potential confounders; ascertained mortality outcomes only; low number of cases for stratified analyses.
			Any employment	8	1.46 (0.63–2.88)		
		Prostate, mortality	Latency (SMR):				
			< 20 yr	0	0		
			20–29 yr	1	[2.86 (0.13–12.7)]		
			30–39 yr	2	[1.65 (0.28–5.46)]		
			40–49 yr	2	[1.2 (0.20–3.96)]		
			≥ 50 yr	3	[1.45 (0.37–3.96)]		
		Kidney and ureter (ICD-9, 189), mortality	SMR:				
			Any employment	7	4.14 (1.66–8.53)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) (cont.)		Kidney and ureter (ICD-9, 189), mortality	Year of cohort entry (SMR):			Age, calendar period	
			Pre-1920	4	[17.28 (5.50–41.8)]		
			1920–1929	0	0		
			1930–1939	0	0		
			1940–1949	0	0		
			1950–1959	2	[3.34 (0.56–11.0)]		
			1960–1969	1	[5.16 (0.26–25.4)]		
			1970–1979	0	0		
		Kidney and ureter (ICD-9, 189), mortality	Latency (SMR):				
			< 20 yr	1	[4.08 (0.20–19.7)]		
			20–29 yr	2	[3.92 (0.66–13.0)]		
			30–39 yr	0	0		
			40–49 yr	4	[21.29 (6.69–50.8)]		
			≥ 50 yr	0	0		
		Kidney and ureter (ICD-9, 189), mortality	Duration of employment (SMR):				
			< 1 yr	0	0		
			1–9 yr	0	0		
			10–19 yr	1	[4.3 (0.21–21.2)]		
			20–29 yr	2	[3.84 (0.64–12.7)]		
			30–39 yr	2	[3.38 (0.57–11.2)]		
			≥ 40 yr	2	[36.12 (6.10–120)]		
		Kidney and ureter (ICD-9, 189), mortality	Exposure opportunity (year × weight) (SMR):				
			0	1	[8.9 (0.45–44.0)]		
			> 0, < 1	0	0		
			1–4	0	0		
			5–9	0	0		
			10–14	1	[8.54 (0.43–42.2)]		
			15–19	1	[6.54 (0.33–32.2)]		
			20–24	0	0		
			25–29	2	[5.22 (0.88–17.3)]		
			30–35	0	0		
			≥ 35	2	[35.42 (5.99–118)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) (cont.)		Urinary bladder, mortality	SMR:			Age, calendar period	
			Any employment	4	3.16 (0.86–8.08)		
		Urinary bladder, mortality	Year of cohort entry (SMR):				
			Pre-1920	3	[7.10 (1.80–19.3)]		
			1920–1929	0	0		
			1930–1939	0	0		
			1940–1949	1	[3.44 (0.17–17.0)]		
			1950–1959	0	0		
			1960–1969	0	0		
			1970–1979	0	0		
		Urinary bladder, mortality	Latency (SMR):			Age and time period	
			< 20 yr	0	0		
			20–29 yr	0	0		
			30–39 yr	1	[2.78 (0.14–13.7)]		
			40–49 yr	3	[13.93 (3.47–37.1)]		
			≥ 50 yr	0	0		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) Australia Enrolment, varied by agency/follow-up, 1980–2011 (mortality); 1982–2010 (incidence) Cohort	39 644 female firefighters, both paid [career] (1682) and volunteer (37 962), from nine fire agencies in Australia Exposure assessment method: ever career or volunteer firefighter, ever attended an incident, tertiles of cumulative number of incidents and type of incidents attended from personnel records	Female reproductive cancer (ICD-10, C51–C58), incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents for volunteer firefighters. Included specific incident types, but early exposure was extrapolated from more recent data. Volunteers mainly rural. *Strengths*: study of female firefighters; includes predominantly rural firefighters; ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			All volunteer firefighters	88	0.80 (0.64–0.98)		
			Volunteers who attended incidents	37	0.81 (0.57–1.11)		
		Female reproductive cancer (ICD-10, C51–C58), incidence	No. of incidents, all volunteers (RIR) [equivalent to rate ratios]:				
			Zero incidents	32	1		
			Tertile 1	9	0.97 (0.46–2.05)		
			Tertile 2	11	1.04 (0.53–2.08)		
			Tertile 3	15	1.70 (0.91–3.16)		
			Trend-test *P* value, 0.16				
		Female reproductive cancer (ICD-10, C51–C58), incidence	No. of fire incidents, all volunteers (RIR):				
			Zero incidents	35	1		
			Tertile 1	8	0.87 (0.40–1.89)		
			Tertile 2	9	0.96 (0.46–2.01)		
			Tertile 3	15	1.74 (0.94–3.21)		
			Trend-test *P* value, 0.09				
		Female reproductive cancer (ICD-10, C51–C58), incidence	No. of structure fire incidents, all volunteers (RIR):				
			Zero incidents	55	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	6	1.16 (0.50–2.70)		
			Tertile 3	6	1.22 (0.52–2.85)		
			Trend-test *P* value, 0.06				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Female reproductive cancer (ICD-10, C51–C58), incidence	No. of landscape fire incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	35	1		
			Tertile 1	8	1.15 (0.53–2.49)		
			Tertile 2	9	1.09 (0.52–2.27)		
			Tertile 3	15	1.92 (1.05–3.54)		
			Trend-test *P* value, 0.18				
		Female reproductive cancer (ICD-10, C51–C58), incidence	No. of vehicle fire incidents, all volunteers (RIR):				
			Zero incidents	56	1		
			Tertile 1	2	0.66 (0.16–2.72)		
			Tertile 2	3	0.86 (0.27–2.76)		
			Tertile 3	6	1.76 (0.75–4.10)		
			Trend-test *P* value, 0.18				
		Cervix/uterine cervix, incidence	SIR:				
			All volunteer firefighters	12	0.53 (0.28–0.93)		
			Volunteers who attended incidents	5	0.48 (0.16–1.13)		
		Urinary tract (ICD-10, C64–C68), incidence	SIR:				
			All volunteer firefighters	23	0.78 (0.49–1.17)		
			Volunteers who attended incidents	7	0.62 (0.25–1.28)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Urinary tract (ICD-10, C64–C68), incidence	No. of incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	12	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	3	0.74 (0.21–2.61)		
			Tertile 3	4	1.12 (0.36–3.48)		
			Trend-test *P* value, 0.09				
		Urinary tract (ICD-10, C64–C68), incidence	No. of fire incidents, all volunteers (RIR):				
			Zero incidents	12	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	3	0.92 (0.26–3.25)		
			Tertile 3	4	1.26 (0.41–3.93)		
			Trend-test *P* value, 0.09				
		Urinary tract (ICD-10, C64–C68), incidence	No. of structure fire incidents, all volunteers (RIR):				
			Zero incidents	14	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	1	0.74 (0.10–5.60)		
			Tertile 3	4	3.04 (1.00–9.27)		
			Trend-test *P* value, 0.08				
		Urinary tract (ICD-10, C64–C68), incidence	No. of landscape fire incidents, all volunteers (RIR):				
			Zero incidents	13	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	2	0.64 (0.14–2.85)		
			Tertile 3	4	1.29 (0.42–3.97)		
			Trend-test *P* value, 0.09				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Urinary tract (ICD-10, C64–C68), incidence	No. of vehicle fire incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	15	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	2	2.06 (0.47–9.02)		
			Tertile 3	2	2.06 (0.47–9.03)		
			Trend-test *P* value, 0.31				
		Kidney, incidence	SIR:				
			All volunteer firefighters	19	0.98 (0.59–1.53)		
			Volunteers who attended incidents	6	0.77 (0.28–1.69)		
		Kidney, incidence	No. of incidents, all volunteers (RIR):				
			Zero incidents	10	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	3	0.87 (0.24–3.18)		
			Tertile 3	3	0.99 (0.27–3.60)		
			Trend-test *P* value, 0.16				
		Kidney, incidence	No. of fire incidents, all volunteers (RIR):				
			Zero incidents	10	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	3	1.09 (0.30–3.95)		
			Tertile 3	3	1.12 (0.31–4.09)		
			Trend-test *P* value, 0.16				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Kidney, incidence	No. of structure fire incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	12	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	1	0.85 (0.11–6.51)		
			Tertile 3	3	2.61 (0.73–9.31)		
			Trend-test *P* value, 0.13				
		Kidney, incidence	No. of landscape fire incidents, all volunteers (RIR):				
			Zero incidents	11	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	2	0.75 (0.17–3.40)		
			Tertile 3	3	1.14 (0.32–4.08)		
			Trend-test *P* value, 0.16				
		Kidney, incidence	No. of vehicle fire incidents, all volunteers (RIR):				
			Zero incidents	13	1		
			Tertile 1	0	0 (NR)		
			Tertile 2	1	1.17 (0.15–8.96)		
			Tertile 3	2	2.33 (0.52–10.39)		
			Trend-test *P* value, 0.24				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) Australia Enrolment, date varied by agency (1998–2000)/ follow-up through 30 November 2011 (mortality) and 31 December 2010 (cancer incidence) Cohort	163 094, all male volunteer firefighters from five fire agencies enrolled on or after the date on which the agency's roll was complete and who had ever held an active firefighting role Exposure assessment method: ever volunteer firefighter, categorical volunteer duration (years) and era from service records; ever volunteer firefighter who attended an incident, tertiles of cumulative emergency incidents from contemporary incident data	Male reproductive (ICD-10, C60–C63), incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents. Included specific incident types but early exposure extrapolated from more recent data. Firefighters from rural or peri-urban areas. *Strengths*: includes predominantly rural firefighters; ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			All volunteers	2763	1.08 (1.04–1.12)		
			Volunteers who attended incidents	1777	1.09 (1.04–1.14)		
		Male reproductive (ICD-10, C60–C63), incidence	Era of first service (SIR):				
			Pre-1970	860	1.13 (1.06–1.21)		
			1970–1994	1073	1.11 (1.05–1.18)		
			1995 or after	830	0.99 (0.92–1.06)		
		Male reproductive (ICD-10, C60–C63), incidence	Duration of service, all volunteers (RIR) [equivalent to rate ratios]:				
			> 3 mo to < 10 yr	752	1		
			10–20 yr	497	1.07 (0.96–1.20)		
			≥ 20 yr	1480	1.13 (1.04–1.24)		
			Trend-test *P* value, 0.01				
		Male reproductive (ICD-10, C60–C63), incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	347	1		
			10–20 yr	293	1.12 (0.96–1.31)		
			≥ 20 yr	1148	1.18 (1.04–1.34)		
			Trend-test *P* value, 0.01				
		Male reproductive (ICD-10, C60–C63), incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	1659	1		
			Group 2	80	1.04 (0.83–1.30)		
			Group 3	38	1.00 (0.73–1.38)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Male reproductive (ICD-10, C60–C63), incidence	No. of fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	1664	1		
			Group 2	77	0.95 (0.75–1.19)		
			Group 3	36	1.06 (0.77–1.48)		
		Male reproductive (ICD-10, C60–C63), incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	1699	1		
			Group 2	52	1.10 (0.83–1.45)		
			Group 3	26	1.03 (0.70–1.51)		
		Male reproductive (ICD-10, C60–C63), incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	1408	1		
			Group 2	276	1.08 (0.94–1.22)		
			Group 3	93	0.95 (0.77–1.17)		
		Male reproductive (ICD-10, C60–C63), incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	1657	1		
			Group 2	87	1.08 (0.87–1.34)		
			Group 3	33	1.05 (0.74–1.48)		
		Prostate, incidence	SIR:				
			All volunteers	2655	1.12 (1.08–1.16)		
			Volunteers who attended incidents	1692	1.13 (1.08–1.19)		
		Prostate, incidence	Era of first service (SIR):				
			Pre-1970	851	1.18 (1.10–1.26)		
			1970–1994	1022	1.15 (1.08–1.22)		
			1995 or after	782	1.03 (0.96–1.11)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Prostate, incidence	Duration of service, all volunteers (RIR):			Age, calendar period	
			> 3 mo to < 10 yr	701	1		
			10–20 yr	470	1.06 (0.95–1.19)		
			≥ 20 yr	1452	1.12 (1.02–1.23)		
			Trend-test *P* value, 0.02				
		Prostate, incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	315	1		
			10–20 yr	266	1.07 (0.91–1.26)		
			≥ 20 yr	1123	1.15 (1.01–1.31)		
			Trend-test *P* value, 0.03				
		Prostate, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	1578	1		
			Group 2	77	1.04 (0.83–1.31)		
			Group 3	38	1.04 (0.75–1.43)		
		Prostate, incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	1581	1		
			Group 2	76	0.97 (0.77–1.23)		
			Group 3	36	1.10 (0.79–1.53)		
		Prostate, incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	1615	1		
			Group 2	52	1.15 (0.87–1.52)		
			Group 3	26	1.06 (0.72–1.57)		
		Prostate, incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	1337	1		
			Group 2	264	1.07 (0.94–1.22)		
			Group 3	92	0.97 (0.78–1.19)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Prostate, incidence	No. of vehicle fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	1577	1		
			Group 2	83	1.08 (0.87–1.35)		
			Group 3	33	1.09 (0.77–1.54)		
		Testis, incidence	SIR:				
			All volunteers	99	0.92 (0.75–1.13)		
			Volunteers who attended incidents	81	1.10 (0.88–1.37)		
		Testis, incidence	Era of first service (SIR):				
			Pre-1970	7	1.99 (0.80–4.10)		
			1970–1994	47	1.07 (0.79–1.43)		
			1995 or after	45	0.75 (0.55–1.01)		
		Testis, incidence	Duration of service, all volunteers (RIR):				
			> 3 mo to < 10 yr	48	1		
			10–20 yr	25	1.36 (0.83–2.21)		
			≥ 20 yr	25	1.76 (1.00–3.08)		
			Trend-test *P* value, 0.04				
		Testis, incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	32	1		
			10–20 yr	25	1.66 (0.98–2.81)		
			≥ 20 yr	23	1.62 (0.86–3.02)		
			Trend-test *P* value, 0.08				
		Testis, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	78	1		
			Group 2	3	0.94 (0.30–2.97)		
			Group 3	0	0 (NR)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Testis, incidence	No. of fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	80	1		
			Group 2	1	0.33 (0.05–2.35)		
			Group 3	0	0 (NR)		
		Testis, incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	81	1		
			Group 2	0	0 (NR)		
			Group 3	0	0 (NR)		
		Testis, incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	69	1		
			Group 2	11	1.16 (0.61–2.21)		
			Group 3	1	0.41 (0.06–2.99)		
		Testis, incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	77	1		
			Group 2	4	1.13 (0.42–3.10)		
			Group 3	0	0 (NR)		
		Urinary tract (ICD-10, C64–C68), incidence	SIR:				
			All volunteers	334	0.72 (0.65–0.81)		
			Volunteers who attended incidents	205	0.70 (0.60–0.80)		
		Urinary tract (ICD-10, C64–C68), incidence	Era of first service (SIR):				
			Pre-1970	101	0.72 (0.59–0.88)		
			1970–1994	123	0.69 (0.57–0.82)		
			1995 or after	110	0.77 (0.63–0.93)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Urinary tract (ICD-10, C64–C68), incidence	Duration of service, all volunteers (RIR):			Age, calendar period	
			> 3 mo to < 10 yr	105	1		
			10–20 yr	56	0.86 (0.62–1.19)		
			≥ 20 yr	169	0.94 (0.73–1.22)		
			Trend-test *P* value, 0.72				
		Urinary tract (ICD-10, C64–C68), incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	46	1		
			10–20 yr	31	0.90 (0.57–1.42)		
			≥ 20 yr	133	1.15 (0.80–1.64)		
			Trend-test *P* value, 0.35				
		Urinary tract (ICD-10, C64–C68), incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	187	1		
			Group 2	12	1.40 (0.78–2.52)		
			Group 3	6	1.47 (0.65–3.31)		
		Urinary tract (ICD-10, C64–C68), incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	184	1		
			Group 2	17	1.95 (1.18–3.20)		
			Group 3	4	1.13 (0.42–3.06)		
		Urinary tract (ICD-10, C64–C68), incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	188	1		
			Group 2	10	1.94 (1.03–3.66)		
			Group 3	7	2.63 (1.24–5.59)		
		Urinary tract (ICD-10, C64–C68), incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	154	1		
			Group 2	35	1.27 (0.88–1.84)		
			Group 3	16	1.59 (0.95–2.67)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Urinary tract (ICD-10, C64–C68), incidence	No. of vehicle fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	187	1		
			Group 2	15	1.68 (0.99–2.84)		
			Group 3	3	0.88 (0.28–2.74)		
		Kidney, incidence	SIR:				
			All volunteers	196	0.82 (0.71–0.94)		
			Volunteers who attended incidents	130	0.83 (0.70–0.99)		
		Kidney, incidence	Era of first service (SIR):				
			Pre-1970	56	0.93 (0.70–1.21)		
			1970–1994	74	0.75 (0.59–0.94)		
			1995 or after	66	0.81 (0.63–1.04)		
		Kidney, incidence	Duration of service, all volunteers (RIR):				
			> 3 mo to < 10 yr	65	1		
			10–20 yr	32	0.81 (0.53–1.24)		
			≥ 20 yr	98	1.00 (0.72–1.40)		
			Trend-test *P* value, 0.92				
		Kidney, incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	31	1		
			10–20 yr	18	0.78 (0.43–1.40)		
			≥ 20 yr	84	1.19 (0.77–1.84)		
			Trend-test *P* value, 0.31				
		Kidney, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	115	1		
			Group 2	9	1.70 (0.86–3.34)		
			Group 3	6	2.37 (1.04–5.38)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Kidney, incidence	No. of fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	114	1		
			Group 2	12	2.22 (1.22–4.02)		
			Group 3	4	1.84 (0.68–4.99)		
		Kidney, incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	116	1		
			Group 2	7	2.15 (1.00–4.62)		
			Group 3	7	4.23 (1.97–9.08)		
		Kidney, incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	91	1		
			Group 2	26	1.58 (1.02–2.45)		
			Group 3	13	2.24 (1.25–4.01)		
		Kidney, incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	114	1		
			Group 2	13	2.34 (1.32–4.16)		
			Group 3	3	1.41 (0.45–4.44)		
		Urinary bladder, incidence	SIR:				
			All volunteers	117	0.60 (0.50–0.72)		
			Volunteers who attended incidents	67	0.55 (0.43–0.7)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) Australia Enrolment, 1976–2003/follow-up, 1976–2011 (mortality), 1982–2010 (incidence, except two states, 2009) Cohort	30 057; full- (17 394) or part-time (12 663) paid male firefighters employed at one of eight Australian fire agencies for ≥ 3 mo from start of personnel records (1976–2003, depending on agency) Exposure assessment method: employed as a part- or full-time firefighter for ≥ 3 mo, categorical employment duration (years) and era from employment records; tertiles of cumulative emergency incidents and type of incident attended from contemporary incident data	Male reproductive (ICD-10, C60–C63), incidence	Firefighter status (SIR):			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents, including specific incident types. Included specific incident types, but early exposure was extrapolated from more recent data. Municipal firefighters. *Strengths*: internal analysis by exposure to number and type of incidents; ascertained cancer incidence. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Full-time	357	1.20 (1.08–1.33)		
			Part-time	167	1.41 (1.20–1.64)		
			All	524	1.26 (1.15–1.37)		
		Male reproductive (ICD-10, C60–C63), incidence	Duration of employment, full-time firefighters (RIR) [equivalent to rate ratios]:				
			> 3 mo to 10 yr	40	1		
			10–20 yr	37	0.82 (0.53–1.30)		
			≥ 20 yr	277	1.23 (0.83–1.81)		
			Trend-test *P* value, 0.14				
		Male reproductive (ICD-10, C60–C63), incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	32	1		
			10–20 yr	47	1.52 (0.94–2.46)		
			≥ 20 yr	86	1.10 (0.68–1.80)		
			Trend-test *P* value, 0.99				
		Male reproductive (ICD-10, C60–C63), incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	72	1		
			10–20 yr	84	1.21 (0.88–1.68)		
			≥ 20 yr	363	1.21 (0.90–1.64)		
			Trend-test *P* value, 0.26				
		Male reproductive (ICD-10, C60–C63), incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	20	1		
			Tertile 2	37	2.14 (1.24–3.70)		
			Tertile 3	58	1.96 (1.17–3.27)		
			Trend-test *P* value, 0.02				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Male reproductive (ICD-10, C60–C63), incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	23	1		
			Tertile 2	26	1.42 (0.81–2.49)		
			Tertile 3	66	1.91 (1.21–3.09)		
			Trend-test *P* value, 0.01				
		Male reproductive (ICD-10, C60–C63), incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	23	1		
			Tertile 2	27	1.41 (0.81–2.47)		
			Tertile 3	65	1.96 (1.21–3.17)		
			Trend-test *P* value, 0.01				
		Male reproductive (ICD-10, C60–C63), incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	25	1		
			Tertile 2	36	1.64 (0.99–2.74)		
			Tertile 3	54	1.49 (0.92–2.40)		
			Trend-test *P* value, 0.14				
		Male reproductive (ICD-10, C60–C63), incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	22	1		
			Tertile 2	30	1.80 (1.03–3.13)		
			Tertile 3	63	2.13 (1.31–3.48)		
			Trend-test *P* value, < 0.01				
		Male reproductive (ICD-10, C60–C63), incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	40	1.36 (0.98–1.86)		
			10–20 yr	37	0.98 (0.69–1.35)		
			≥ 20 yr	277	1.21 (1.07–1.36)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Male reproductive (ICD-10, C60–C63), incidence	Duration of employment, part-time firefighters (SIR):			Age, calendar period	
			> 3 mo to 10 yr	32	1.11 (0.76–1.57)		
			10–20 yr	47	1.85 (1.36–2.46)		
			≥ 20 yr	86	1.34 (1.07–1.66)		
		Male reproductive (ICD-10, C60–C63), incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	17	1.12 (0.96–1.3)		
			1970–1994	161	1.27 (1.08–1.48)		
			1995 or after	26	1.29 (0.84–1.89)		
		Male reproductive (ICD-10, C60–C63), incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	37	1.33 (0.93–1.83)		
			1970–1994	101	1.42 (1.16–1.73)		
			1995 or after	29	1.47 (0.98–2.11)		
		Male reproductive (ICD-10, C60–C63), incidence	No. of incidents attended by part-time firefighters (RIR):				
			Tertile 1	10	1		
			Tertile 2	25	1.51 (0.72–3.18)		
			Tertile 3	33	0.83 (0.40–1.73)		
			Trend-test *P* value, 0.24				
		Male reproductive (ICD-10, C60–C63), incidence	No. of fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	14	1		
			Tertile 2	21	0.90 (0.46–1.79)		
			Tertile 3	33	0.61 (0.32–1.18)		
			Trend-test *P* value, 0.10				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Male reproductive (ICD-10, C60–C63), incidence	No. of structure fire incidents attended by part-time firefighters (RIR):			Age, calendar period	
			Tertile 1	12	1		
			Tertile 2	20	1.12 (0.55–2.31)		
			Tertile 3	36	0.75 (0.38–1.48)		
			Trend-test *P* value, 0.26				
		Male reproductive (ICD-10, C60–C63), incidence	No. of landscape fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	13	1		
			Tertile 2	22	1.11 (0.56–2.21)		
			Tertile 3	33	0.75 (0.39–1.45)		
			Trend-test *P* value, 0.26				
		Male reproductive (ICD-10, C60–C63), incidence	No. of vehicle fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	19	1		
			Tertile 2	21	0.95 (0.51–1.78)		
			Tertile 3	28	0.50 (0.28–0.91)		
			Trend-test *P* value, 0.01				
		Prostate, incidence	Firefighter status (SIR):				
			Full-time	325	1.23 (1.10–1.37)		
			Part-time	153	1.51 (1.28–1.77)		
			All	478	1.31 (1.19–1.43)		
		Prostate, incidence	Duration of employment, full-time firefighters (RIR):				
			> 3 mo to 10 yr	23	1		
			10–20 yr	30	1.05 (0.61–1.82)		
			≥ 20 yr	270	1.56 (0.98–2.51)		
			Trend-test *P* value, 0.02				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Prostate, incidence	Duration of employment, part-time firefighters (RIR):			Age, calendar period	
			> 3 mo to 10 yr	26	1		
			10–20 yr	41	1.51 (0.90–2.54)		
			≥ 20 yr	86	1.16 (0.70–1.95)		
			Trend-test *P* value, 0.86				
		Prostate, incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	49	1		
			10–20 yr	71	1.29 (0.89–1.88)		
			≥ 20 yr	356	1.32 (0.94–1.85)		
			Trend-test *P* value, 0.15				
		Prostate, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	14	1		
			Tertile 2	29	2.49 (1.32–4.72)		
			Tertile 3	54	2.45 (1.35–4.41)		
			Trend-test *P* value, 0.01				
		Prostate, incidence	No. of fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	15	1		
			Tertile 2	20	1.78 (0.91–3.48)		
			Tertile 3	62	2.55 (1.45–4.50)		
			Trend-test *P* value, < 0.01				
		Prostate, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	16	1		
			Tertile 2	20	1.57 (0.81–3.04)		
			Tertile 3	61	2.45 (1.40–4.26)		
			Trend-test *P* value, < 0.01				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Prostate, incidence	No. of landscape fire incidents by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	18	1		
			Tertile 2	27	1.78 (0.98–3.24)		
			Tertile 3	52	1.88 (1.09–3.22)		
			Trend-test *P* value, 0.03				
		Prostate, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	16	1		
			Tertile 2	22	1.95 (1.02–3.73)		
			Tertile 3	59	2.60 (1.50–4.54)		
			Trend-test *P* value, < 0.01				
		Prostate, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	23	1.26 (0.8–1.89)		
			10–20 yr	30	1.01 (0.68–1.44)		
			≥ 20 yr	269	1.26 (1.11–1.42)		
		Prostate, incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	26	1.42 (0.93–2.08)		
			10–20 yr	41	1.84 (1.32–2.49)		
			≥ 20 yr	85	1.41 (1.13–1.75)		
		Prostate, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	16	1.19 (1.02–1.39)		
			1970–1994	141	1.29 (1.09–1.52)		
			1995 or after	15	1.14 (0.64–1.88)		
		Prostate, incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	37	1.43 (1.01–1.97)		
			1970–1994	95	1.50 (1.22–1.84)		
			1995 or after	21	1.76 (1.09–2.68)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Prostate, incidence	No. of incidents attended by part-time firefighters (RIR):			Age, calendar period	
			Tertile 1	7	1		
			Tertile 2	24	2.30 (0.99–5.36)		
			Tertile 3	31	1.37 (0.60–3.14)		
			Trend-test *P* value, 0.97				
		Prostate, incidence	No. of fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	11	1		
			Tertile 2	20	1.21 (0.58–2.54)		
			Tertile 3	31	0.90 (0.44–1.80)		
			Trend-test *P* value, 0.55				
		Prostate, incidence	No. of structure fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	9	1		
			Tertile 2	19	1.54 (0.70–3.42)		
			Tertile 3	34	1.17 (0.56–2.48)		
			Trend-test *P* value, 0.95				
		Prostate, incidence	No. of landscape fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	10	1		
			Tertile 2	21	1.41 (0.66–3.00)		
			Tertile 3	31	1.05 (0.51–2.16)		
			Trend-test *P* value, 0.83				
		Prostate, incidence	No. of vehicle fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	16	1		
			Tertile 2	20	1.08 (0.56–2.09)		
			Tertile 3	26	0.66 (0.35–1.23)		
			Trend-test *P* value, 0.13				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Testis, incidence	Firefighter status (SIR):			Age, calendar period	
			Full-time	31	1.44 (0.98–2.05)		
			Part-time	12	0.93 (0.48–1.63)		
			All	43	1.25 (0.91–1.69)		
		Testis, incidence	Duration of employment, full-time firefighters (RIR):				
			> 3 mo to 10 yr	17	1		
			10–20 yr	7	0.60 (0.24–1.52)		
			≥ 20 yr	7	0.67 (0.20–2.31)		
			Trend-test *P* value, 0.39				
		Testis, incidence	Duration of employment, part-time firefighters: (RIR):				
			> 3 mo to 10 yr	6	NR		
			10–20 yr	5	NR		
			≥ 20 yr	0	0 (NR)		
		Testis, incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	23	1		
			10–20 yr	12	1.18 (0.57–2.48)		
			≥ 20 yr	7	0.93 (0.31–2.75)		
			Trend-test *P* value, 0.96				
		Testis, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	6	1		
			Tertile 2	8	1.27 (0.44–3.66)		
			Tertile 3	4	0.62 (0.17–2.25)		
			Trend-test *P* value, 0.51				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Testis, incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	8	1		
			Tertile 2	6	0.71 (0.25–2.04)		
			Tertile 3	4	0.46 (0.13–1.60)		
			Trend-test *P* value, 0.21				
		Testis, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	7	1		
			Tertile 2	7	0.97 (0.34–2.78)		
			Tertile 3	4	0.54 (0.15–1.89)		
			Trend-test *P* value, 0.35				
		Testis, incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	7	1		
			Tertile 2	9	1.21 (0.45–3.26)		
			Tertile 3	2	0.26 (0.05–1.28)		
			Trend-test *P* value, 0.13				
		Testis, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	6	1		
			Tertile 2	8	1.26 (0.44–3.65)		
			Tertile 3	4	0.62 (0.17–2.26)		
			Trend-test *P* value, 0.51				
		Testis, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	17	1.65 (0.96–2.63)		
			10–20 yr	7	0.99 (0.40–2.05)		
			≥ 20 yr	7	1.85 (0.74–3.81)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Testis, incidence	Duration of employment, part-time firefighters (SIR):			Age, calendar period	
			> 3 mo to 10 yr	6	0.61 (0.22–1.33)		
			10–20 yr	5	2.32 (0.75–5.41)		
			≥ 20 yr	0	0 (NR):		
		Testis, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	0	0 (NR):		
			1970–1994	20	1.46 (0.89–2.25)		
			1995 or after	11	1.66 (0.83–2.98)		
		Testis, incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	0	0 (NR):		
			1970–1994	4	0.74 (0.20–1.91)		
			1995 or after	8	1.09 (0.47–2.14)		
		Urinary tract (ICD-10, C64–C68), incidence	Firefighter status (SIR):				
			Full-time	59	0.91 (0.69–1.17)		
			Part-time	25	1.04 (0.67–1.53)		
			All	84	0.94 (0.75–1.17)		
		Urinary tract (ICD-10, C64–C68), incidence	Duration of employment, full-time firefighters (RIR):				
			> 3 mo to 10 yr	2	1		
			10–20 yr	12	5.63 (1.25–25.30)		
			≥ 20 yr	45	5.92 (1.33–23.30)		
			Trend-test *P* value, 0.03				
		Urinary tract (ICD-10, C64–C68), incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	4	1		
			10–20 yr	9	4.42 (1.26–15.44)		
			≥ 20 yr	12	4.32 (1.12–16.72)		
			Trend-test *P* value, 0.05				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Urinary tract (ICD-10, C64–C68), incidence	Duration of employment (RIR):			Age, calendar period	
			> 3 mo to 10 yr	6	1		
			10–20 yr	21	4.29 (1.71–10.78)		
			≥ 20 yr	57	4.32 (1.71–10.89)		
			Trend-test *P* value, 0.01				
		Urinary tract (ICD-10, C64–C68), incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	5	1		
			Tertile 2	7	1.57 (0.50–4.95)		
			Tertile 3	8	0.99 (0.32–3.06)		
			Trend-test *P* value, 0.91				
		Urinary tract (ICD-10, C64–C68), incidence	No. of fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	4	1		
			Tertile 2	6	1.80 (0.51–6.39)		
			Tertile 3	10	1.51 (0.47–4.86)		
			Trend-test *P* value, 0.55				
		Urinary tract (ICD-10, C64–C68), incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	5	1		
			Tertile 2	7	1.58 (0.50–4.99)		
			Tertile 3	8	1.00 (0.32–3.09)		
			Trend-test *P* value, 0.92				
		Urinary tract (ICD-10, C64–C68), incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	3	1		
			Tertile 2	6	2.18 (0.54–8.72)		
			Tertile 3	11	2.37 (0.66–8.57)		
			Trend-test *P* value, 0.21				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Urinary tract (ICD-10, C64–C68), incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	4	1		
			Tertile 2	4	1.23 (0.31–4.96)		
			Tertile 3	12	2.01 (0.66–6.46)		
			Trend-test *P* value, 0.19				
		Urinary tract (ICD-10, C64–C68), incidence	Duration of employment attended by full-time firefighters (SIR):				
			> 3 mo to 10 yr	2	0.32 (0.04–1.14)		
			10–20 yr	12	1.14 (0.59–1.99)		
			≥ 20 yr	45	0.95 (0.69–1.27)		
		Urinary tract (ICD-10, C64–C68), incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	4	0.58 (0.16–1.49)		
			10–20 yr	9	1.60 (0.73–3.04)		
			≥ 20 yr	12	1.05 (0.54–1.83)		
		Urinary tract (ICD-10, C64–C68), incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	30	0.92 (0.62–1.31)		
			1970–1994	28	1.00 (0.66–1.45)		
			1995 or after	1	0.23 (0.01–1.30)		
		Urinary tract (ICD-10, C64–C68), incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	7	1.37 (0.55–2.83)		
			1970–1994	16	1.11 (0.63–1.80)		
			1995 or after	2	0.44 (0.05–1.60)		
		Kidney, incidence	Firefighter status (SIR):				
			Full-time	33	0.97 (0.67–1.36)		
			Part-time	19	1.34 (0.81–2.10)		
			All	52	1.08 (0.81–1.41)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Kidney, incidence	Duration of employment, full-time firefighters (RIR):			Age, calendar period	
			> 3 mo to 10 yr	1	1		
			10–20 yr	7	6.95 (0.85–56.81)		
			≥ 20 yr	25	8.19 (1.01–66.62)		
			Trend-test *P* value, 0.05				
		Kidney, incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	3	1		
			10–20 yr	8	5.34 (1.31–21.76)		
			≥ 20 yr	8	3.97 (0.83–19.02)		
			Trend-test *P* value, 0.13				
		Kidney, incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	4	1		
			10–20 yr	15	4.81 (1.57–14.72)		
			≥ 20 yr	33	4.29 (1.37–13.50)		
			Trend-test *P* value, 0.03				
		Kidney, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	2	1		
			Tertile 2	5	2.73 (0.53–14.11)		
			Tertile 3	5	1.68 (0.32–8.75)		
			Trend-test *P* value, 0.65				
		Kidney, incidence	No. of fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	2	1		
			Tertile 2	4	2.3 (0.42–12.61)		
			Tertile 3	6	1.96 (0.39–9.87)		
			Trend-test *P* value, 0.47				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Kidney, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	3	1		
			Tertile 2	6	2.23 (0.56–8.94)		
			Tertile 3	3	0.65 (0.13–3.26)		
			Trend-test *P* value, 0.55				
		Kidney, incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	2	1		
			Tertile 2	3	1.60 (0.27–9.60)		
			Tertile 3	7	2.47 (0.51–12.03)		
			Trend-test *P* value, 0.24				
		Kidney, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	2	1		
			Tertile 2	2	1.17 (0.16–8.34)		
			Tertile 3	8	2.97 (0.62–14.15)		
			Trend-test *P* value, 0.13				
		Kidney, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	1	0.24 (0.01–1.35)		
			10–20 yr	7	1.07 (0.43–2.21)		
			≥ 20 yr	25	1.08 (0.70–1.60)		
		Kidney, incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	3	0.63 (0.13–1.83)		
			10–20 yr	8	2.28 (0.98–4.49)		
			≥ 20 yr	8	1.39 (0.60–2.73)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Kidney, incidence	Era of first employment, full-time firefighters (SIR):			Age, calendar period	
			Pre-1970	17	1.26 (0.73–2.01)		
			1970–1994	15	0.86 (0.48–1.41)		
			1995 or after	1	0.33 (0.01–1.82)		
		Kidney, incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	4	1.77 (0.48–4.52)		
			1970–1994	13	1.51 (0.81–2.59)		
			1995 or after	2	0.61 (0.07–2.21)		
		Urinary bladder, incidence	Firefighter status (SIR):				
			Full-time	23	0.85 (0.54–1.27)		
			Part-time	5	0.57 (0.19–1.34)		
			All	28	0.78 (0.52–1.13)		
		Urinary bladder, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	1	0.52 (0.01–2.88)		
			10–20 yr	4	1.14 (0.31–2.91)		
			≥ 20 yr	18	0.84 (0.50–1.32)		
		Urinary bladder, incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	1	0.55 (0.01–3.07)		
			10–20 yr	1	0.54 (0.01–3.02)		
			≥ 20 yr	3	0.60 (0.12–1.75)		
		Urinary bladder, incidence	Era of first employment, full-time firefighters(SIR):				
			Pre-1970	11	0.65 (0.33–1.17)		
			1970–1994	12	1.31 (0.67–2.28)		
			1995 or after	0	0		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Urinary bladder, incidence	Era of first employment, part-time firefighters (SIR):			Age, calendar period	
			Pre-1970	2	0.81 (0.10–2.91)		
			1970–1994	3	0.58 (0.12–1.71)		
			1995 or after	0	0 (NR)		
Glass et al. (2016b) Victoria, Australia Enrolment, 1971–1999/follow-up, 1980–2011 (mortality), 1982–2012 (incidence) Cohort	614, all male (611) and female (3) employed and volunteer Country Fire Authority trainers and a group of paid [career] Country Fire Authority firefighters who trained at the Fiskville site between 1971 and 1999; all analyses limited to men since no deaths or cancers were observed among women Exposure assessment method: employed or volunteer firefighter trainers and paid [career] firefighters who trained at training facility for any period of time from human resources records, categorized into risk of low, medium, and high chronic exposure to smoke and other agents based on job assignment.	Male reproductive (ICD-10, C60–C63), incidence	Risk of chronic exposure (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Incorporated categorical level of exposure into assessment for each type of firefighter. Volunteers mainly rural, paid [career] firefighters were municipal. *Strengths*: included firefighter instructors with high potential exposure to smoke and other hazardous agents; assessed exposure based on job assignment. *Limitations*: low number of cases; young age at end of follow-up.
			Low	2	0.52 (0.06–1.87)		
			Medium	7	0.71 (0.29–1.47)		
			High	7	1.77 (0.71–3.65)		
		Prostate, incidence	Risk of chronic exposure (SIR):				
			Low	2	0.63 (0.08–2.28)		
			Medium	7	0.79 (0.32–1.62)		
			High	5	1.43 (0.46–3.34)		
		Testis, incidence	Risk of chronic exposure (SIR):				
			Low	0	0 (NR)		
			Medium	0	0 (NR)		
			High	2	11.9 (1.44–42.9)		
		Urinary tract (ICD-10, C64–C68), incidence	Risk of chronic exposure (SIR):				
			Low	0	0 (NR)		
			Medium	1	0.50 (0.01–2.81)		
			High	1	1.27 (0.03–7.07)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bates et al. (2001) New Zealand Enrolment, 1977 through June 1995/ follow-up, 1977–1995 (mortality), 1977–1996 (incidence) Cohort	4305; the cohort comprises all male (4221) and female (84) firefighters (paid [career] and volunteer) employed as a career firefighter for ≥ 1 yr and who also worked as a career firefighter for ≥ 1 day between 1977 and 1995; all analyses limited to men due to small numbers of women Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Prostate, incidence	Follow-up period (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job classification. May include urban [municipal] and rural firefighters. *Strengths*: ascertained both incidence and mortality outcomes. *Limitations:* little information on confounders; significant loss to follow-up.
			1977–1996	11	1.08 (0.5–1.9)		
			1990–1996	9	1.09 (0.5–2.1)		
		Prostate, incidence	Duration of paid service (SIR):				
			0–10 yr	3	1.46 (0.3–4.3)		
			11–20 yr	1	0.60 (0.0–3.3)		
			> 20 yr	1	0.29 (0.0–1.6)		
			Trend-test *P* value, 0.12				
		Prostate, incidence	Duration of paid and volunteer service (SIR):				
			0–10 yr	1	1.09 (0.0–6.1)		
			11–20 yr	2	1.90 (0.2–6.9)		
			> 20 yr	2	0.38 (0.0–1.4)		
			Trend-test *P* value, 0.21				
		Testis, incidence	Follow-up period (SIR):				
			1977–1996	11	1.55 (0.8–2.8)		
			1990–1996	8	2.97 (1.3–5.9)		
		Testis, incidence	Duration of paid service (SIR):				
			0–10 yr	3	1.55 (0.3–4.5)		
			11–20 yr	4	3.51 (1.0–9.0)		
			> 20 yr	2	4.14 (0.5–14.9)		
			Trend-test *P* value, 0.21				
		Testis, incidence	Duration of paid and volunteer service (SIR):				
			0–10 yr	2	1.39 (0.2–5.0)		
			11–20 yr	5	4.03 (1.3–9.4)		
			> 20 yr	2	2.65 (0.3–9.6)		
			Trend-test *P* value, 0.44				
		Kidney, incidence	Follow-up period (SIR):				
			1977–1996	2	0.57 (0.1–2.1)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bates et al. (2001) (cont.)		Urinary bladder, incidence	Follow-up period (SIR):			Age, calendar period	
			1977–1996	5	1.14 (0.4–2.7)		
			1990–1996	2	0.74 (0.1–2.7)		
		Urinary bladder, incidence	SMR:				
			Firefighters vs male New Zealand population	2	2.73 (0.3–9.8)		

9/11, World Trade Center disaster, 11 September 2001; BMI, body mass index; CFHS, Career Firefighter Health Study; CI, confidence interval; FDNY, Fire Department of the City of New York; HR, hazard ratio; HWSE, healthy-worker survivor effect; ICD, International Classification of Diseases; IDR, incidence density ratio; JEM, job-exposure matrix; LRT, likelihood ratio test; mo, month; NR, not reported; RCS, restricted cubic splines; RIR, relative incidence ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States; vs, versus; WTC, World Trade Center; yr, year.

information on the risk of cancers of the genitourinary system (prostate, testis, and kidney, excluding the renal pelvis) and cancers of the urinary tract (urinary bladder and renal pelvis) (Marjerrison et al., 2022a, b). The cohort included mostly full-time firefighters employed between 1950 and 2019 with past or present employment in positions entailing active firefighting duties. The follow-up period for both cancer incidence and mortality analyses was from 1960 through 2018. With the general male population of Norway as the referent, the SIR for prostate cancer was moderately elevated (SIR, 1.18; 95% CI, 1.03–1.35; 214 cases), but the SMR (SMR, 1.07; 95% CI, 0.80–1.39; 54 deaths) was not. The SIR for cancer of the testis was elevated (SIR, 1.39; 95% CI, 0.81–2.22; 17 cases), as was the SIR for kidney cancer (SIR, 1.28; 95% CI, 0.86–1.84; 29 cases); however, the kidney cancer mortality rate was not elevated (SMR, 0.97; 95% CI, 0.46–1.78; 10 deaths). Incidence (SIR, 1.25; 95% CI, 0.97–1.58; 69 cases) and mortality (SMR, 1.14; 95% CI, 0.64–1.88; 15 deaths) for cancer of the urinary tract appeared to be moderately elevated compared with that in the general population. The only findings of note in analyses stratified by employment characteristics were: a raised SIR for prostate cancer for follow-up from 1995 onwards and for cases diagnosed in firefighters aged 50–69 years; a raised SIR for kidney cancer for follow-up between 1985 and 1994 and for cases diagnosed in firefighters aged ≥ 70 years; and a raised SIR for urinary tract cancer in firefighters first employed before 1950, in firefighters ≥ 40 years after first employment, and for cases diagnosed in firefighters aged ≥ 70 years.

A cancer incidence study in a cohort of 8136 male firefighters in Sweden provided information on the risk of cancers of the urogenital system (cancers of the prostate, testis, kidney, and urinary bladder) (Bigert et al., 2020). Employment information was ascertained from national decennial censuses from 1960 through 1990, and cancer incidence was ascertained from the national cancer registry with follow-up from 1961 through 2009. The SIRs for cancers of the prostate (SIR, 1.06; 95% CI, 0.96–1.16; 444 cases), kidney (SIR, 0.84; 95% CI, 0.61–1.14; 41 cases), and bladder (SIR, 1.08; 95% CI, 0.89–1.31; 109 cases) were all close to the null, whereas the SIR for testicular cancer was less than expected (SIR, 0.39; 95% CI, 0.11–1.01; 4 cases) but based on few cases. For prostate cancer, there was no apparent relation with duration of employment ($P = 0.13$) or period of follow-up (no results from test of linear trend were provided). Results for duration of employment were not reported for other urogenital cancers.

A cancer incidence study in a cohort of 1080 male firefighters in Stockholm, Sweden, provided information on the risk of cancers of the urogenital system (Kullberg et al., 2018). Firefighters were identified through annual enrolment records from 15 fire stations and worked for ≥ 1 year between 1931 and 1983. This was an update to a previous study (Tornling et al., 1994) and added 26 years of cancer incidence follow-up from 1958 through 2012 in the Swedish Cancer Registry. For cancer incidence, only the more recent study is discussed here. With the male general population of Stockholm County as the referent, the overall SIR was less than one for cancer of the prostate (SIR, 0.68; 95% CI, 0.52–0.87; 60 cases). The overall SIR also appeared to be decreased for cancer of the kidney (SIR, 0.57; 95% CI, 0.21–1.23; 6 cases) and cancer of the urinary organs (SIR, 0.72; 95% CI, 0.41–1.17; 16 cases), but results were imprecise. The SIR for prostate cancer did not increase with age or employment duration and showed a significant but inconsistent decreasing trend with starting year of employment ($P < 0.01$).

The earlier study in the same cohort also investigated mortality in a slightly larger population of 1116 male firefighters (with follow-up from 1951 through 1986) and provided information on the risk of cancers of the prostate and kidney (Tornling et al., 1994). The overall SMRs for prostate cancer (SMR, 1.21; 95% CI, 0.66–2.02;

14 deaths) and kidney cancer (SMR, 1.10; 95% CI, 0.30–2.81; 4 cases) suggested modest elevations, although confidence intervals were wide.

A cancer incidence study in a cohort of 9061 male full-time, part-time, and volunteer firefighters provided information on the risk of cancers of the urogenital system (Petersen et al., 2018a). Cohort members were employed as firefighters at some time between 1964 and 2004, and cancer incidence follow-up was conducted in the Danish Cancer Registry from 1968 through 2014. The SIR for prostate cancer was slightly raised when the referent used was a random sample of Danish employees (SIR, 1.15; 95% CI, 1.00–1.32; 202 cases) or the general population (SIR, 1.10; 95% CI, 0.95–1.26; 202 cases), but not when the referent was the Danish military (SIR, 1.02; 95% CI, 0.88–1.17; 202 cases). The SIRs for cancer of the renal pelvis (10 cases) were 1.46, 1.59, and 1.35 with the general population, employed, and military population, respectively, as referent, whereas the SIR for cancer of the testis (47 cases) was raised only with the general population as referent (SIR, 1.30; 95% CI, 0.97–1.73). The SIRs for urinary bladder cancer (88 cases) were similar regardless of the comparison group: 1.09 (95% CI, 0.89–1.35) with the general population; 1.11 (95% CI, 0.90–1.37) with a sample of employees; and 1.05 (95% CI, 0.86–1.30) with the military population. For incidence of cancers of the prostate, testis, and urinary bladder, there was no association with employment type, era of first employment, job function (e.g. regular, specialized), age at first employment, or employment duration, apart from a raised SIR for cancer of the urinary bladder when the age at first employment was < 25 years.

Cancer mortality was investigated in the same cohort of Danish firefighters as described above (Petersen et al., 2018b). An expanded study population of 11 775 male firefighters was followed for mortality in the Danish national death registry from 1970 through 2014. With the military as the referent, the SMR for prostate cancer was raised for part-time and volunteer firefighters (SMR, 1.89; 95% CI, 1.22–2.93; 20 deaths), but not for full-time firefighters (SMR, 0.66; 95% CI, 0.40–1.07; 16 deaths), and there was no relation between prostate cancer mortality and duration of employment for full-time firefighters. [The Working Group noted that the relatively strong association in part-time and volunteer firefighters, but not full-time firefighters, suggested the possibility of medical surveillance bias.]

A cancer incidence study in a cohort of 10 786 male firefighters from the FDNY exposed to the WTC disaster site and 8813 firefighters in the CFHS (which included firefighters from fire departments in Philadelphia, Chicago, and San Francisco) provided information on the risk of cancers of the prostate and kidney (Webber et al., 2021). Cancer incidence follow-up was conducted in several state cancer registries selected on the basis of residential history information and began on 11 September 2001 and ended in 2016. With the US male general population as the referent, overall SIRs for prostate cancer were increased in both the FDNY (SIR, 1.70; 95% CI, 1.53–1.88; 332 cases) and CFHS (SIR, 1.22; 95% CI, 1.11–1.35; 358 cases) cohorts. Because WTC-exposed FDNY firefighters undergo free and routine health-monitoring examinations, the authors noted concern about medical surveillance bias attributable to earlier detection since such screening is not widely available to the general population. After adjusting for potential medical surveillance bias by adding a 2-year lag to diagnosis dates for cases diagnosed within 6 months of a routine blood test, the SIR for prostate cancer in the FDNY cohort remained elevated (SIR, 1.55; 95% CI, 1.39–1.73). In internal comparison analyses, the risk of prostate cancer was increased in FDNY firefighters compared with CFHS firefighters (RR, 1.39; 95% CI, 1.19–1.63). This was also the case after adjustment for surveillance bias (RR, 1.28; 95% CI, 1.09–1.51). For kidney cancer, SIRs were close to one for the FDNY cohort (SIR, 0.93; 95% CI, 0.67–1.28; 39 cases) and slightly raised in the

CFHS cohort (SIR, 1.19; 95% CI, 0.90–1.56; 55 cases). After the adjustment for medical surveillance bias (for cases diagnosed within 6 months of a chest CT scan), the estimated SIR for kidney cancer for the FDNY cohort remained below one (SIR, 0.85; 95% CI, 0.61–1.19). The risk of kidney cancer appeared decreased in FDNY firefighters compared with CFHS firefighters in internal comparison analyses (RR, 0.82; 95% CI, 0.52–1.30). This was also the case after the adjustment for medical surveillance bias (RR, 0.75; 95% CI, 0.47–1.20). [The Working Group noted that this study was limited by a possible incompletely controlled effect of greater medical surveillance bias in FDNY firefighters than in CFHS firefighters or the US general population. This bias may be particularly influential for prostate cancer.]

An earlier study of cancer incidence in an overlapping cohort of 9853 FDNY male firefighters investigated the risk of cancers of the prostate, testis, kidney, and urinary bladder associated with exposure to the WTC disaster site. (Zeig-Owens et al., 2011). Cancer incidence follow-up was conducted in state cancer registries from 1996 through 2008. With the US male general population as the referent, the SIR for prostate cancer (adjusted for increased cancer surveillance) was raised when restricted to exposed person-time in firefighters (SIR, 1.21; 95% CI, 0.96–1.52; 73 cases) and was also raised when restricted to unexposed person-time in firefighters (SIR, 1.35; 95% CI, 1.01–1.81; 45 cases). The SIR restricted to exposed person-time was not raised for testicular cancer, kidney cancer, or bladder cancer. The equivalent SIR for unexposed person-time was 1.54 (95% CI, 0.85–2.78; 11 cases) for testicular cancer, 0.30 (95% CI, 0.07–1.18; ≤ 5 cases) for kidney cancer, and 0.79 (95% CI, 0.36–1.76; 6 cases) for bladder cancer. The estimated SIR ratios (SIR for exposed person-time divided by the SIR for unexposed person-time) for kidney cancer and for bladder cancer were raised but imprecise. The estimated SIR ratios for prostate cancer (SIR ratio, 0.90; 95% CI, 0.62–1.30) and testicular cancer (SIR ratio, 0.56; 95% CI, 0.19–1.60) were less than one but also imprecise. [The Working Group noted that the SIR ratio is not a standard epidemiological effect measure. The results for prostate cancer may be influenced by medical surveillance bias in this cohort.]

A mortality study was conducted in a cohort of 29 992 male and female municipal career firefighters in the USA. The CFHS from San Francisco, Chicago, and Philadelphia provided information on the risk of cancers of the prostate, kidney, and bladder (Pinkerton et al., 2020). Mortality follow-up was conducted from 1950 through 2016. With the US general population as the referent, the SMR for prostate cancer was raised for the Chicago subcohort (SMR, 1.23; 95% CI, 1.05–1.42; 176 deaths), but not for the other subcohorts or the cohort overall. Also, the SMR for kidney cancer was raised for the whole cohort (SMR, 1.22; 95% CI, 1.00–1.47; 108 deaths) and for the Chicago subcohort (SMR, 1.57; 95% CI, 1.22–2.00; 66 deaths), but not for the other subcohorts. However, in internal regression analyses using fully adjusted models, there was no evidence of a positive association between number of exposed days, fire-runs, or fire-hours and kidney cancer or prostate cancer. However, for bladder cancer, the hazard ratio estimate for number of exposed days was elevated (HR, 1.23; 95% CI, 0.50–3.41) and crossed the null after adjustment for employment duration. [The Working Group noted that this may reflect healthy-worker survivor bias in the unadjusted point estimates for the number of exposed days.] In external comparison analyses, the SMRs for bladder cancer were not raised, either overall (SMR, 0.98; 95% CI, 0.80–1.18; 104 deaths) or for any of the municipal subcohorts. There were too few cases of cancer of other male genital organs to provide informative information for this cancer type.

An earlier study of a subset of 19 309 firefighters from the same CFHS cohort examined internal exposure–response associations for both mortality and incidence of cancer, with follow-up to the end of 2009 (Daniels et al., 2015). The methods were similar to those used in Pinkerton et al. (2020); however, the results of the present study were not adjusted for employment duration. There was no evidence of increasing incidence of bladder or prostate cancer with measures of exposure in any regression model, nor was there evidence of prostate cancer risk heterogeneity by time since exposure, age at exposure, or exposure period. [The Working Group noted that confounding by employment duration was evident for bladder cancer mortality in Pinkerton et al. (2020), shifting the association from negative to positive when controlling for duration.]

An additional study in the CFHS cohort investigated cancer incidence in 29 993 municipal career firefighters and reported external and internal comparison analyses with follow-up to the end of 2009 (Daniels et al., 2014). The methods were similar to those used in the study by Pinkerton et al. (2020). Cancer incidence follow-up was conducted in state cancer registries relevant to each fire department to the end of 2009, with start years varying between 1985 and 1988. Residential history information was used to select state registries for follow-up. With the US general population as the referent, the SIR for prostate cancer (including all primary cancers) among firefighters was not elevated (SIR, 1.03; 95% CI, 0.98–1.09; 1261 cases), and this was consistent for Caucasian [White] firefighters (SIR, 1.02; 95% CI, 0.96–1.08; 1167 cases), but not for "Other" race groups (SIR, 1.26; 95% CI, 1.02–1.54; 94 cases). For kidney cancer, the overall SIR was elevated (SIR, 1.27; 95% CI, 1.09–1.48; 166 cases). For bladder cancer, the overall SIR was modestly elevated (SIR, 1.12; 95% CI, 1.00–1.25; 316 cases). There was no excess incidence of testicular or other male genital cancers.

There was no strong evidence of heterogeneity among the elevated SIRs for the three fire departments for any of the cancers of the urogenital system (prostate cancer, $P = 0.078$; kidney cancer, $P = 1.00$; bladder cancer, $P = 1.00$). However, there was evidence of heterogeneity among results in different age groups for prostate cancer ($P < 0.001$) and bladder cancer ($P = 0.002$). The excess prostate and bladder cancer incidence was mostly among firefighters in younger age groups (17–64 years). The authors noted that the excess in prostate cancer incidence was limited to those aged 45–59 years, whereas for bladder cancer the pattern was less clear. [The Working Group noted that some evidence of risk heterogeneity by fire department suggested that differences in exposures or other risk factors (e.g. smoking habits) across departments may not have been adequately addressed. There was also a lack of data on many important potential confounders, particularly smoking. Heterogeneity by age at onset of prostate cancer may indicate a medical surveillance bias related to screening.]

A cancer incidence study in a cohort of 2447 male municipal firefighters from Seattle and Tacoma, USA, provided information on the risk of cancer of the prostate, bladder and kidney in comparison with the local male general population or with a cohort of male police officers from Washington state (Demers et al., 1994). Firefighters were employed for ≥ 1 year between 1944 and 1979, and cancer incidence follow-up was conducted from 1974 through 1989 in the regional SEER cancer registry using residential history information to reduce loss to follow-up. Duration of active-duty employment in direct firefighting positions was ascertained from employment records in the Seattle subcohort. With the general population as the referent, the SIR was raised for prostate cancer (SIR, 1.4; 95% CI, 1.1–1.7; 66 cases) and, more moderately, for bladder cancer (SIR, 1.2; 95% CI, 0.7–1.9; 18 cases), but not for kidney cancer (SIR, 0.5; 95% CI, 0.1–1.6; 3 cases). The SIR for prostate cancer

was raised among firefighters with 20–29 years of employment (SIR, 1.5; 95% CI, 1.1–2.0; 47 cases), but not for those with a shorter or longer duration of employment, although the number of cases in the other groups was small (all less than 10). The SIR for prostate cancer was also increased for the longest time since first employment group (SIR for ≥ 30 years since first employment, 1.3; 95% CI, 1.0–1.7; 60 cases). The SIR for bladder cancer was not related to years of exposure or time since first employment. In internal comparisons using the police officers as the reference group, the IDR was not increased for prostate cancer or kidney cancer, but was increased for bladder cancer (IDR, 1.7; 95% CI, 0.7–4.3; 18 cases), although the result was imprecise.

An earlier study of 4401 male municipal firefighters, including firefighters from Portland, Oregon, and Seattle and Tacoma, Washington, reported findings for the risk of mortality from cancers of the prostate, kidney, bladder, and other organs of the urinary tract (Demers et al., 1992a). The mortality follow-up period was from 1945 to the end of 1989. Comparison of mortality rates was made with US White males in the general population and with a cohort of local male police officers. With the general population as the referent, the SMR for cancer of the prostate was elevated (SMR, 1.34; 95% CI; 0.90–1.91; 30 deaths). There were only two cases each of cancers of the kidney, bladder, and other urinary organs. Similar results were found when using police officers as the referent. There was no apparent relation between mortality risk and duration of exposed employment for prostate cancer; however, the SMR for prostate cancer was raised in firefighters with ≥ 30 years since first employment (SMR, 1.42; 95% CI, 1.0–2.0; 30 deaths) and in those aged ≥ 65 years (SMR, 1.46; 95% CI, 1.0–2.1; 26 deaths).

A mortality study in a cohort of 1867 White male municipal firefighters who worked for the City of Buffalo, USA, provided information on the risk of cancers of the prostate, kidney, and urinary bladder (Vena & Fiedler, 1987). Firefighters had been employed for ≥ 1 year between 1950 and 1979, and mortality follow-up was from 1950 through 1979. With the US White male general population as the referent, the mortality rate for bladder cancer was raised (SMR, 2.86; 95% CI, 1.30–5.40; 9 deaths), as was the mortality rate for kidney cancer (SMR, 1.30; 95% CI, 0.26–3.80; 3 deaths), although both estimates were imprecise. The mortality rate for prostate cancer (SMR, 0.71; 95% CI, 0.23–1.65; 5 deaths) was not raised. The SMR for bladder cancer was particularly elevated in firefighters with a long duration of employment (SMR for ≥ 40 years duration, 5.71; 95% CI, [1.8–13.8]; 4 deaths) and latency period (SMR for 40–49 years latency, 4.53; 95% CI, [1.7–10.3]; 5 deaths; and SMR for ≥ 50 years latency, 6.38; 95% CI, [1.5–16.3]; 3 deaths).

A mortality study in a cohort of 5414 male career firefighters in Toronto, Canada, who had worked for ≥ 6 months between 1950 and 1989 provided information on the risk of cancers of the prostate, testis, kidney and ureter, and bladder (Aronson et al., 1994). Mortality follow-up was conducted in a national mortality database from 1950 through 1989. Compared with the male general population of Ontario, the cohort exhibited an excess of cancers of the prostate (SMR, 1.32; 95% CI, 0.76–2.15; 16 cases), testis (SMR, 2.52; 95% CI, 0.52–7.37; 3 cases), and bladder (SMR, 1.28; 95% CI, 0.51–2.63; 7 cases), although estimates were somewhat imprecise. There was a deficit in mortality from cancer of the kidney and ureter, but this result was based on only two cases. There was little evidence of a relation between the SMR and duration of employment, time since first employment, or age for cancers of the prostate and testis.

A mortality study of 3328 municipal firefighters in two cohorts from Calgary and Edmonton, Canada, provided information on the risk of cancers of the prostate, kidney and ureter, and urinary bladder (Guidotti, 1993). Firefighters were employed between 1927 and

1987, and mortality follow-up was conducted in both provincial and national sources from 1927 through 1987. Compared with the male general population of Alberta, firefighters had elevations in overall SMR for cancers of the kidney and ureter (SMR, 4.14; 95% CI, 1.66–8.53), prostate (SMR, 1.46; 95% CI, 0.63–2.88), and bladder (SMR, 3.16; 95% CI, 0.86–8.08), but estimates were based on few cases and were imprecise. The SMR for cancer of the kidney and ureter was raised for firefighters who entered the cohort before 1920 and for latencies of 40–49 years, but not for other years of entry or other latencies. The SMR for bladder cancer was raised for firefighters who entered the cohort before 1920 and for latencies of 40–49 years, although results were based on few cases. Other SMRs for cancer of the bladder and for cancer of the kidney and ureter for different cohort entry years and different latencies were not raised. [The Working Group noted that this study was limited by the low number of deaths for genitourinary system cancers, and confidence intervals were wide.]

A cancer incidence study in an entirely female cohort of 37 962 volunteer firefighters in Australia provided information on the risk of cancer of the kidney, urinary tract, cervix/uterus, and reproductive system (Glass et al., 2019). Cancer incidence follow-up was conducted in a national cancer registry from 1982 through 2010. Work history information describing the number and type of incidents attended was ascertained from fire agency personnel records. With the female general population of Australia as the referent, SIRs for all volunteer firefighters were equal to or below one for cancers of the urinary tract (SIR, 0.78; 95% CI, 0.49–1.17; 23 cases), kidney (SIR, 0.98; 95% CI, 0.59–1.53; 19 cases), and reproductive system, including cervix (SIR, 0.80; 95% CI, 0.64–0.98). Results were similar for volunteers who had attended incidents. Results from internal regression analyses were statistically imprecise for cancers of the urinary tract and kidney but indicated elevated rates of reproductive system cancers among firefighters in the highest tertile of number of incidents attended compared with those who had never attended incidents. Trend tests across tertile categories did not suggest a relation between risk of any of these cancers and the total number of incidents attended overall, or all fire incidents, structure fire incidents, landscape fire incidents, or vehicle fire incidents.

Using the same methods as in the study of female firefighters, cancer incidence was also investigated in a parallel cohort of 163 094 male volunteer firefighters in Australia (Glass et al., 2017). With the male general population of Australia as the referent, SIRs among all volunteer firefighters were increased for male reproductive cancers combined (SIR, 1.08; 95% CI, 1.04–1.12; 2763 cases) and for prostate cancer (SIR, 1.12; 95% CI, 1.08–1.16; 2655 cases). In contrast, SIRs for urinary tract cancers combined, kidney cancer, and bladder cancer were all decreased (SIR for urinary tract cancers combined, 0.72; 95% CI, 0.65–0.81; 334 cases; SIR for kidney cancer, 0.82; 95% CI, 0.71–0.94, 196 cases; and SIR for bladder cancer, 0.60; 95% CI, 0.50–0.72, 117 cases). The results for volunteers who had attended incidents were similar to those for all volunteers. The SIRs for male reproductive cancers combined, prostate cancer, and testicular cancer decreased with period of first employment from before 1970 to more recent years, but there was no formal test for trend. In internal regression analyses, there was a trend of increasing incidence of male reproductive cancers combined and increasing duration of service among both volunteer firefighters ($P = 0.01$) and volunteer firefighters who attended incidents ($P = 0.01$). This trend was also observed for prostate and testicular cancers, but not for cancers of the urinary tract or kidney. The RIRs [equivalent to rate ratios] from the analysis of number and type of incidents attended indicated positive associations for cancers of the urinary tract and exposure to structure fire incidents, including kidney cancer and exposure to several incident types, although estimates were

imprecise. For prostate and testicular cancers, there was no apparent association between the number and type of incidents attended and risk.

Using similar methods as those in the two studies of volunteer firefighters, a cancer incidence study in a cohort of 30 057 paid full-time and part-time male firefighters in Australia provided information on the risk of cancers of the reproductive system, prostate, testis, kidney, urinary bladder, and urinary tract (Glass et al., 2016a). Included firefighters had worked between 1976 and 2003 and were primarily municipal or semi-metropolitan firefighters. Cancer incidence follow-up was conducted in a national registry to the end of 2010. With the Australian male general population as the referent, SIRs were increased for male reproductive cancers combined and prostate cancer in all firefighters (SIR for male reproductive cancers combined, 1.26; 95% CI, 1.15–1.37; 524 cases; and SIR for prostate cancer, 1.31; 95% CI, 1.19–1.43; 478 cases). The excess persisted with stratification among both full-time (SIR for male reproductive cancers combined, 1.20; 95% CI, 1.08–1.33; 357 cases; and SIR for prostate cancer, 1.23; 95% CI, 1.10–1.37; 325 cases) and part-time firefighters (SIR for male reproductive cancers combined, 1.41; 95% CI, 1.20–1.64; 167 cases; and SIR for prostate cancer, 1.51; 95% CI, 1.28–1.77; 153 cases). The SIR for cancer of the testis among full-time firefighters was also increased (SIR, 1.44; 95% CI, 0.98–2.05; 31 cases), but otherwise there was no increase in SIRs for cancers of the testis, urinary tract, kidney, or urinary bladder. In internal regression analyses, there was evidence of increasing risk of prostate cancer with increasing duration of employment. Duration results for cancer of the urinary tract and kidney cancer were too imprecise to make inferences. As for the duration of employment results, there was evidence of increasing risk of prostate cancer with an increasing number of total incidents attended among full-time firefighters. This association persisted for all types of attended incidents (all fire, structure fire, landscape fire, and vehicle fire). There was little evidence of positive associations for cancers of the testis, urinary tract, or kidney, although the analyses were based on few cases. [The apparent increased risk of prostate cancer could be partly because of increased medical surveillance of firefighters, although the authors reported that the fire agencies employing the firefighters did not offer screening for prostate cancer.]

A study of cancer incidence was conducted in a cohort of 614 firefighters and trainers who attended a firefighter-training facility in Australia (Glass et al., 2016b). Three female firefighters were excluded from the analysis. Cancer incidence follow-up was conducted from 1982 through 2012. Participants were grouped into risk categories of low, medium, and high chronic exposure (to smoke and other hazardous agents) on the basis of job assignment. The male general population of Victoria was the reference group in external comparison analyses. None of the SIRs for male reproductive cancers, prostate cancer, or cancer of the urinary tract were raised for any of the assessed exposure categories (low, medium, and high chronic exposure risk based on job assignment), although estimates were imprecise because of low numbers of cases. The SIR for testicular cancer was raised among those with high chronic exposure risk, although the estimate was based on only two cases.

A mortality and cancer incidence study in a cohort of 4305 paid [career] and volunteer firefighters in New Zealand provided information on the risk of cancer of the prostate, testis, kidney, and urinary bladder (Bates et al., 2001). The cohort included 84 female firefighters who were excluded from the analysis. Included firefighters had worked for ≥ 1 year as a career firefighter and were employed for ≥ 1 day between 1977 and 1995. Follow-up for cancer mortality and incidence was conducted in a national data source to the end of 1995 (for mortality) or 1996 (for incidence). With the male general population of New Zealand as the referent, none of the SIRs for

cancer of the prostate (SIR, 1.08; 95% CI, 0.5–1.9; 11 cases), testis (SIR, 1.55; 95% CI, 0.8–2.8; 11 cases), kidney (SIR, 0.57; 95% CI, 0.1–2.1; 2 cases) or bladder (SIR, 1.14; 95% CI, 0.4–2.7; 5 cases) appeared raised, but results were generally based on few cases and were imprecise. Results were similar when restricted to recent calendar years (1990–1996) of diagnosis, except for testicular cancer, for which the SIR was raised (SIR, 2.97; 95% CI, 1.3–5.9; 8 cases). There was little evidence of a positive relation between the incidence of prostate or testicular cancer and either duration of career service or duration of total (career and volunteer) service, and estimates were based on few cases. Overall excess risk of bladder cancer incidence and mortality was suggested, but results were similarly imprecise.

2.2.2 Studies only reporting having ever worked as a firefighter

(a) Occupational cohort studies

Studies first described in Section 2.1.2(a) are described in less detail in the present section.

See Table S2.4 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Between 1978 and 2021, eight occupational cohort studies were published that reported on the risk of cancers of the urogenital system among firefighters compared with non-firefighting populations, using employment status as proxy for exposure (Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Giles et al., 1993; Deschamps et al., 1995; Ma et al., 2005, 2006; Amadeo et al., 2015). This section includes a description of the relevant findings of these studies on cancers of the reproductive and urinary systems. Most studies were longitudinal (cohort) designs reporting SMRs or SIRs; however, two early studies reported PMRs (Eliopulos et al., 1984; Grimes et al., 1991). [The Working Group noted that many of the strengths and limitations described in Section 2.1.2(a) also apply to outcomes in the present section. In addition, cancers of the urogenital system as a group have favourable survival; therefore, mortality studies may largely underestimate cancer risk. The Working Group also noted a potential for upward bias in prostate cancer incidence studies (and downward bias in mortality studies) because of increased cancer screening among firefighters compared with the general population (e.g. Sritharan et al., 2018; Jakobsen et al., 2021). Risk estimates for cervical cancer may be similarly susceptible to surveillance bias. Finally, the Working Group noted that PMR studies rely on strong assumptions that may not be valid for firefighter cohorts.]

The mortality study of 10 829 male career firefighters in France (1979–2008) examined cancers of the kidney, bladder, and prostate in firefighters compared with the French general population (Amadeo et al., 2015). The study found no evidence of increased mortality from cancers of the urinary bladder (SMR, 0.73; 95% CI, 0.41–1.21; 15 deaths) or kidney (SMR, 0.63; 95% CI, 0.30–1.16; 10 deaths). Prostate cancer mortality was substantially below the expected rate (SMR, 0.54; 95% CI, 0.31–0.86; 17 deaths). [The Working Group noted that all-cause mortality was also below that expected, which implied a potential for strong bias from healthy-worker selection.]

The mortality study of male career firefighters (n = 830) employed by the *Brigade des sapeurs-pompiers de Paris* (Paris Fire Brigade), France (1977–1990) examined all cancers of the urogenital system combined (ICD-9, 180–189) (Deschamps et al., 1995). Urogenital cancer mortality was above the expected rate (SMR, 3.29; 95% CI, 0.40–11.88); however, only two deaths were observed (one from bladder cancer and one from testicular cancer). [Findings based on two deaths from cancers of the urogenital system merit cautious interpretation because of small numbers. The Working Group noted

that less than 4% of the cohort was deceased, and that deaths from all causes were about half that expected using reference population rates. Also, all deaths occurred at young ages (range, 31–63 years) indicating a relatively young cohort. Together, these findings implied a strong potential for downward bias in risk estimates from healthy-worker selection.]

The longitudinal studies of cancer mortality (Ma et al., 2005) and incidence (Ma et al., 2006) among career firefighters in Florida, USA, examined several cancers of the urogenital system in analyses stratified by sex. Among male firefighters, there were increased rates of bladder cancer incidence (SIR, 1.29; 95% CI, 1.01–1.62; 73 cases) and mortality (SMR, 1.79; 95% CI, 0.98–3.00; 14 cases) relative to state population rates. There was also an increased incidence of testicular cancer (SIR, 1.60; 95% CI, 1.20–2.09; 54 cases). In contrast, there was no evidence of increased risk for cancers of the kidney or prostate. Among female firefighters, there was evidence of a substantial excess incidence of cervical cancer (SIR, 5.24; 95% CI, 2.93–8.65; 15 cases). There was only one incident event each for bladder and kidney cancer among women; therefore, estimates were unstable. [The large study size and stratification by sex were notable strengths; however, risk estimates among female firefighters were substantively limited by small numbers for most types of cancer. Given improved access to health care among firefighters, differences in cancer screening may have contributed to excess cervical cancer among female firefighters compared with women in the reference group.]

Cancers of the urogenital system (ICD-9, 179–189) were analysed in the PMR study of firefighters in Honolulu, Hawaii, USA (1969–1988) (Grimes et al., 1991). The proportion of urogenital cancers combined was substantially greater than that in the state reference population (PMR, 2.28; 95% CI, 1.28–4.06; [11] deaths). The excess was attributable to prostate cancer (ICD-9, 185) (PMR, 2.61; 95% CI, 1.38–4.97; [9] deaths). The PMR for prostate cancer was elevated in both Caucasian [White] (PMR, 3.70; 95% CI, 1.71–8.02; [6] deaths) and Hawaiian firefighters (PMR, 3.35; 95% CI, 1.07–10.45; [3] deaths); however, few firefighter deaths were observed. The risk among other racial groups was not investigated. [Stratification by race was a notable study strength. The Working Group also noted the lack of standardization of PMRs by age or calendar period as a limitation.]

Cancers of the urogenital system (ICD-7, 177–181) were analysed as a group in a study in Boston, USA, in career firefighters ($n = 5655$) with ≥ 3 years of service between 1915 and 1975 (Musk et al., 1978). The SMR for urogenital cancers was below the expected rate (SMR, 0.92; 95% CI, [0.71–1.17]; 64 deaths) when the state population was used as the referent. [The long follow-up and large study sizes were notable strengths. The Working Group also noted that all-cause mortality was modestly below the expected rate (SMR, 0.91; 95% CI, [0.87–0.94]), implying that there was a small potential for a strong downward bias from healthy-worker selection. Among study limitations, findings were available only for urogenital cancers combined, although numbers appeared to have been sufficient for stable estimates of risk by cancer type.]

The cohort study of cancer incidence in male career firefighters from Melbourne, Australia, (1980–1989) examined cancers of the urinary tract, prostate, and testis (Giles et al., 1993). Prostate cancer incidence was greater than expected, although few cases were observed (SIR, 2.09; 95% CI, 0.67–4.88; 5 cases). There was no evidence of increased risk of urinary tract or testicular cancers, with only four and two cases observed, respectively. [The Working Group noted the study had limited statistical power, given its small size and short observation period.]

The cohort study of male career firefighters (n = 990) employed by the Western Australian Fire Brigade between 1939 and 1978 examined proportionate mortality for cancers of the

urogenital system (Eliopulos et al., 1984). That study calculated an age- and calendar period-standardized PMR for urogenital cancers combined, with deaths among Western Australian men as the reference group. The PMR was not notably elevated (PMR, 1.08; 95% CI, 0.29–2.76); however, only four deaths were observed. [The average follow-up of 17 years was a notable strength of this study. The Working Group also noted that risk estimation was limited to a PMR for all urogenital cancers combined. All-cause mortality was below the expected rate (SMR, 0.80; 95% CI, 0.67–0.96; 116 deaths), implying strong downward bias from healthy-worker selection. The study had limited statistical power given its small size.]

(b) Population-based studies

With one exception (Stang et al., 2003), all studies were previously described in Section 2.1.2(b) and are described in less detail in the present section.

See Table S2.4 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Between 1990 and 2021, four population-based cohort studies were published that reported on the risk of cancers of the urogenital system among firefighters compared with non-firefighters, using employment status as a proxy for exposure (Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020; Sritharan et al., 2022), and ten case–control or mortality surveillance studies reported risk estimates for cancers of the urogenital system and employment as a firefighter (Sama et al., 1990; Burnett et al., 1994; Ma et al., 1998; Stang et al., 2003; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Muegge et al., 2018; Lee et al., 2020; McClure et al., 2021).

Three cohort studies had designs that used national census data to describe the study group (Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020). Another study cohort was enumerated using information from an occupational injury and disease claims database and linked to person and cancer registries (Sritharan et al., 2022).

One case–control study on testicular cancer in Germany assessed exposure information, including work history from questionnaires, and used population-based controls obtained from residence registers (Stang et al., 2003). Another eight case–control studies were event-only designs where cancer cases and controls with other cancers were extracted from the same cancer registry (Sama et al., 1990; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Lee et al., 2020; McClure et al., 2021) or death certificate database (Ma et al., 1998; Muegge et al., 2018). The remaining study estimated PMRs using information from death certificates obtained from a national occupational mortality surveillance database (Burnett et al., 1994). [The Working Group noted that cancer diagnoses from death certificates may be less accurate than those from cancer registries and cover a smaller fraction of cases than cancer registries if the cancer does not have a high fatality rate.] Job titles in these case–control studies were extracted from the source registries from which study participants had been retrieved. [The Working Group noted that job titles were available for different proportions of cases than controls. Risk estimates may be biased if control cancers are also associated with firefighting or if the rates of the control cancers differ across occupations.] Two partly overlapping case–control studies were based on record linkage from firefighter employment records with incident cancer registry data (Lee et al., 2020; McClure et al., 2021). [The Working Group noted that the study strengths and limitations pertaining to design that were previously described for cancers of the respiratory system in Section 2.1.2(b) also apply to outcomes in the present section. Also, the limitations associated with cancer survival and surveillance bias for studies on cancers of the urogenital system, as

described in Section 2.2.2(a), also apply to these studies.]

Zhao et al. (2020) examined mortality patterns by occupation in a census-based cohort study in the male population of Spain (2001–2011). Age-adjusted MRRs were calculated to compare rates in firefighters with rates in all other occupations. There was elevated but imprecise mortality from cancers of the prostate (MRR, 1.26; 95% CI, 0.67–2.36; 10 deaths) and kidney (MRR, 1.18; 95% CI, 0.57–2.44; 8 deaths), and no evidence of increased mortality from bladder cancer (MRR, 0.62; 95% CI, 0.32–1.17; 10 deaths). The rate ratio for cancer of the renal pelvis was unstable given that there was only one observed death. [The Working Group noted limited statistical power because of few deaths from urogenital cancers among firefighters over the relatively short observation period (10 years).]

Testicular or extra-gonadal germ cell tumour cases (n = 269), histologically confirmed and diagnosed between 1995 and 1997 in participants aged 15–69 years, were examined in a population-based cancer registry study in five regions in Germany (Stang et al., 2003). Control participants from the same regions were randomly selected from residence registries. For ages 15–34 years, each case was matched with two potential controls on 5-year age groups. Similarly, for ages 35–69 years, each case was matched with four potential controls. The overall response proportions were 78% for cases and 57% for controls [The Working Group noted the difference in response proportions for cases and controls, which could have led to selection bias if case firefighters were more willing to participate than control firefighters.] Information on exposures, including detailed work history, was collected primarily by personal interview. Based on four cases, the overall OR (adjusted for history of cryptorchidism) was 4.5 (95% CI, 0.7–31.9). Inclusion of a 5-year lag period or a minimum of 10 years work history as a firefighter decreased the ORs marginally. [The Working Group noted that this study was based on few cases (1.5%) and controls (0.4%) classified as firefighters. There was potential for selection and recall bias, and exposure assessment quality was rated as minimal.]

The large, census-based cohort study (NOCCA) of cancer incidence in Nordic male career firefighters (1961–2005) reported a modest but relatively precise excess incidence of prostate cancer in the full cohort (SIR, 1.13; 95% CI, 1.05–1.22; 660 cases) (Pukkala et al., 2014). Excess prostate cancer was observed in multiple countries, primarily those with the largest case numbers (SIR for Finland, 1.21, 143 cases; SIR for Norway, 1.16, 137 cases; and SIR for Sweden, 1.11, 347 cases; compared with SIR for Denmark, 1.03, 27 cases; and SIR for Iceland, 0.90, 6 cases). Prostate cancer risk compared with that in the general population was greatest in the youngest age group (SIR for age 30–49 years, 2.59; 95% CI, 1.34–4.52; 12 cases) and within the most recent follow-up period (SIR for 1991–2005, 1.15; 95% CI, 1.05–1.26, 495 cases). The study yielded little evidence of increased risk of cancers of the kidney, bladder, or testis. [The Working Group noted that the pattern of excess prostate cancer risk at younger ages and later periods of observation implied a potential for surveillance bias from improved medical screening. For example, prostate cancer risk was greatest in the period 1991–2005, which coincides with the onset of prostate-specific antigen testing. The Working Group also noted that risk evaluations by country, age, or calendar-period were limited to a select group of cancer sites, precluding detailed evaluation of other urogenital cancers.]

A cohort study of worker compensation claimants in Ontario, Canada, compared site-specific cancer incidence in firefighters (n = 13 642) to that in police and all other occupations, using Cox proportional hazards regression models controlling for age at start of follow-up, birth year, and sex (Sritharan et al., 2022). Elevated risk was observed for cancers of the prostate (HR, 1.43; 95% CI, 1.31–1.57; 492 cases), testis (HR, 2.56;

95% CI, 1.78–3.68; 30 cases), and kidney (HR, 1.52; 95% CI, 1.24–1.87; 94 cases) among firefighters compared with all other workers. Higher risk of cancer of the testis was also observed in firefighters compared with police (HR, 1.96; 95% CI, 1.19–3.23). With police as the referent, firefighters had an elevated incidence of kidney cancer (HR, 1.31; 95% CI, 0.98–1.75). There was no evidence of increased risk of prostate cancer in firefighters compared with police (HR, 0.99; 95% CI, 0.88–1.12). There was no evidence of increased risk of cancer of the bladder in either comparison. [The Working Group noted as study strengths the large study size, access to tumour incidence information, and use of other workers and police as referents. Risk estimates might be biased in either direction given that the type of claims used to identify the cohort may differ by occupation.]

The census-based incidence study of male firefighters (n = 4535) in the CanCHEC (1991–2010) cohort found a higher prostate cancer risk in firefighters than in other male workers (HR, 1.18; 95% CI, 1.01–1.37; 170 cases) in a model adjusting for age group, region, and education level (Harris et al., 2018). Restricting to prostate cancer diagnosed before age 50 years resulted in a comparable estimate (HR, 1.18; 95% CI, 0.38–3.67; 10 cases). There was also evidence of excess testicular and kidney cancer, although the confidence intervals were wide (HR for testicular cancer, 1.80; 95% CI, 0.85–3.78; 10 cases; HR for kidney cancer, 1.14; 95% CI, 0.74–1.74; 25 cases). No excess incidence was observed for bladder cancer (HR, 0.89; 95% CI, 0.60–1.33; 25 cases). [The Working Group noted in this study the absence of higher risk of early-onset prostate cancer among firefighters, in contrast to findings in other studies (e.g. Pukkala et al., 2014; Barry et al., 2017). This provided some evidence against a strong surveillance bias in prostate cancer risks. Still, given only weak effects, the Working Group could not rule out cancer screening as a plausible explanation for the observed excess in prostate cancer.]

Site-specific ORs for various incident cancers of both male and female firefighters from Florida, USA, were reported (Lee et al., 2020). Firefighter state certification records were linked with the state cancer registry database. ORs for cancer in female firefighters were reported for cervix uteri (0.41; 95% CI, 0.15–1.12), urinary bladder (1.88; 95% CI, 0.47–7.59) and kidney and renal pelvis (0.59; 95% CI, 0.15–2.36). For the male firefighters, the ORs for cancers of the prostate and testis were increased: OR for prostate, 1.36 (95% CI, 1.27–1.46); and OR for testis, 1.66 (95% CI, 1.34–2.07). This was not the case for cancer of the penis: 0.79 (95% CI, 0.33–1.90). The ORs for cancers of the urinary bladder (OR, 0.91; 95% CI, 0.75–1.10) and for kidney and renal pelvis (OR, 1.06; 95% CI, 0.90–1.24) were close to the null. Cancers were stratified by stage at diagnosis for men. Risk was somewhat higher for late-stage cancer than for early-stage cancer of the prostate (OR, 1.42; 95% CI, 1.19–1.68; and OR, 1.13; 95% CI, 1.03–1.23; respectively) and for the testis (OR, 1.69; 95% CI, 1.12–2.54; and OR, 1.39; 95% CI, 1.07–1.82; respectively). Finally, ORs for men were stratified by age at diagnosis. The most notable differences were seen for cancers of the prostate – OR for those aged < 50 years, 1.88 (95% CI, 1.49–2.36) versus OR for those aged ≥ 50 years, 1.36 (95% CI, 1.26–1.47) – and the urinary bladder – OR for those aged < 50 years, 1.13 (95% CI, 0.72–1.79) versus OR for those aged ≥ 50 years, 0.87; 95% CI, 0.71–1.08). [The Working Group noted small numbers for female firefighters and, in particular, the potential for surveillance bias for prostate cancer if firefighters were screened more often for prostate cancer than were the reference occupations.]

McClure et al. (2021) extended the Florida cancer registry-based case–control study of Lee et al. (2020) to assess whether results differed between two different methods of identifying firefighter status. For cancers of the urinary

system [not defined], the OR based on state certification records (OR, 1.00; 95% CI, 0.88–1.13; 267 cases) was similar to that based on cancer registry records (OR, 1.01; 95% CI, 0.85–1.20; 138 cases). For cancers of the genital system, the OR was 1.37 (95% CI, 1.28–1.47) based on 1228 state certification cases and 1.10 (95% CI, 0.99–1.22) based on 534 cases from cancer registry job records. [The Working Group noted that the number of available firefighters was different for the two data sources, but results differed only slightly for genital tumours in this example. The cancer groupings were broad and of minimal utility in examining risks for individual genitourinary tumour types.]

Cancer mortality was examined in firefighters compared with non-firefighters in Indiana, USA, for the period 1985–2013 (Muegge et al., 2018). An increased OR for kidney cancer (1.84; 95% CI, 1.17–2.83) was observed. [The Working Group noted as limitations the lack of information on exposure and potential confounders, as well as the event-only death certificate approach, which includes normally less-accurate cancer diagnoses.]

Risk of incident cancer in male firefighters was evaluated by race, using the California Cancer Registry, USA, in 1988–2007 (Tsai et al., 2015). For prostate cancer, the ORs were increased for both White and non-White firefighters: 1.40 (95% CI, 1.19–1.64) and 2.42 (95% CI, 1.53–3.84), respectively. For cancers of testis, urinary bladder, and kidney, the ORs were notably increased only for non-White firefighters: 3.73 (95% CI, 1.26–11.02), 2.37 (95% CI, 1.05–5.33), and 2.59 (95% CI, 1.44–4.80), respectively. Bates (2007) conducted a similar study with the California Cancer Registry, 1988–2003, but these data were included in the study conducted later by Tsai et al. (2015) with data from 1988–2007. [The Working Group noted the high proportion of cancer cases lacking information on occupation in the registry as a limitation.]

Data from the cancer registry-based case–control study in Massachusetts, USA, for the period 1982 to 1986 (Sama et al., 1990) were investigated over an extended period between 1987 and 2003 for White men employed as a firefighter, a police officer, or other occupation (Kang et al., 2008). Using police as the reference group, the SMBORs (adjusted for age and smoking) for cancers of the prostate, testis, kidney, and urinary bladder were 0.98 (95% CI, 0.78–1.23), 1.53 (95% CI, 0.75–3.14), 1.34 (95% CI, 0.90–2.01), and 1.22 (95% CI, 0.89–1.69), respectively. Results using all other occupations as the referent were not notably changed, except for kidney cancer (SMBOR, 1.01 (95% CI, 0.74–1.38). [The Working Group noted that a large proportion of the study population lacked occupational information.]

A registry-based case–control study (1982–1986) in Massachusetts, USA, compared risks in men with an occupation as firefighter to other occupations, including police (Sama et al., 1990). Increased SMBOR (adjusted for age alone) for urinary bladder cancer was observed both when police were used as the referent (SMBOR, 2.11; 95% CI, 1.07–1.14; 26 cases) and when the reference group was any non-firefighting job title (SMBOR, 1.59; 95% CI, 1.02–2.50). Stratified by age group [18–54, 55–74, and ≥ 75 years] the SMBORs were 1.25 (95% CI, 0.26–5.88), 2.19 (95% CI, 0.99–4.84), and 4.40 (95% CI, 0.42–46.26). [The Working Group noted as a key limitation of this study the absence of occupational information for about the half of the cancer registry population.]

A death certificate-based study of firefighters from 24 US states reported MORs for Black and White men (Ma et al., 1998). For Black firefighters, the MORs for cancers of the prostate and urinary bladder were 1.9 (95% CI, 1.2–3.2; 16 cases) and 1.3 (95% CI, NR; 1 case), respectively. For White firefighters, the MORs for cancers of the prostate and urinary bladder were 1.2 (95% CI, 1.0–1.3; 189 cases) and 1.2 (95% CI, 0.9–1.6; 48 cases), respectively. In addition, White men

had MORs for cancers of the testis, kidney, and ureter of 0.6 (95% CI, NR; 1 case), 1.3 (95% CI, 1.0–1.7; 49 cases) and 1.0 (95% CI, NR; 1 case), respectively. [The Working Group noted limited numbers of site-specific cancers, which made results imprecise.]

Burnett et al. (1994) investigated proportionate mortality in White male firefighters compared with the general population in the USA (1984–1990). Mortality for kidney cancer (ICD-9, 189.0–189.2) was above the expected rate for all firefighter deaths (PMR, 1.44; 95% CI, 1.08–1.89; 53 deaths) and for deaths before age 65 years (PMR, 1.41; 95% CI, 0.90–2.10; 24 deaths). Mortality for bladder cancer (ICD-9, 188) was at the expected rate for all firefighters and deaths before age 65 years. [The Working Group noted that in the absence of rate denominator data, PMRs rely on strong assumptions that may not be valid for firefighter cohorts; therefore, little weight was generally given to these studies for causal inference.]

2.3 Cancers of lymphatic and haematopoietic tissues

2.3.1 Studies reporting occupational characteristics of firefighters

See Table 2.5.

Studies first described in Section 2.1.1 are described in less detail in the present section.

The Working Group identified 24 occupational and population-based cohort studies that had investigated the relationship between occupational exposure as a firefighter and cancers of lymphatic and haematopoietic tissues (Feuer & Rosenman, 1986; Demers et al., 1992a, 1994; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014, 2015; Ahn & Jeong, 2015; Glass et al., 2016a, b, 2017, 2019; Moir et al., 2016; Kullberg et al., 2018; Petersen et al., 2018a, b; Bigert et al., 2020; Pinkerton et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a, b). Of these studies, two were from Asia, seven were from Europe, four were from Oceania, and eleven were from North America. Three other studies are not described in detail as they largely represent earlier follow-up periods of included studies (Heyer et al., 1990; Beaumont et al., 1991; Baris et al., 2001).

The grouping of cancers of the lymphatic and haematopoietic tissues includes the following cancer sites: NHL, Hodgkin lymphoma, leukaemia, multiple myeloma, other lymphatic or haematopoietic cancer, and, less commonly, lymphosarcoma/reticulosarcoma and myelodysplastic syndrome. A challenge of evaluating evidence for this group of cancers is that cancer site classifications, particularly for NHL, have changed over time. For that reason, the relevant ICD revision and codes have been provided, when available. [Myelodysplastic syndrome was reportable only in more recent years.]

In the Republic of Korea, a mortality study in a cohort of 33 442 male professional [career] emergency responders, of whom 29 453 (88%) were firefighters, provided information on the risk of cancers of lymphatic and haematopoietic tissues (Ahn & Jeong, 2015). Emergency responders had been employed between 1980 and 2007, and mortality follow-up occurred between 1992 to 2007. During follow-up, there were 15 deaths from all lymphatic and haematopoietic malignancies and 6 deaths from leukaemia among firefighters [ICD codes were not provided in the 2015 publication but, assuming the same coding as the 2012 paper from the same cohort, and on the basis of ICD-10, all lymphatic and haematopoietic malignancies were coded as C81–C96, and leukaemia as C91–C95]. The SMR for all lymphatic and haematopoietic malignancies was 0.91 (95% CI, 0.51–1.50) with the male population of the Republic of Korea as the referent. The SMRs for < 10 years, 10 to < 20 years, and ≥ 20 years of employment were 0.80 (95% CI, 0.21–2.04), 0.96 (95% CI, 0.35–2.08) and 0.96 (95% CI, 0.31–2.23),

Table 2.5 Cohort studies reporting occupational characteristics of firefighters and cancers of lymphatic and haematopoietic tissues

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn & Jeong (2015) Republic of Korea Enrolment, 1980–2007/ follow-up, 1992–2007 Cohort	33 442 men employed as emergency responders for ≥ 1 mo in 1980–2007 with (29 453) and without (3989) firefighting experience and not deceased in 1991 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighters and non-firefighters from employment records	Lymphatic and haematopoietic, mortality	Duration of firefighting employment, 1-yr lag (SMR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include both municipal and rural firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: small number of deaths from lymphatic and haematopoietic cancers; no information on personal characteristics or confounders; follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	4	0.80 (0.21–2.04)		
			10 to < 20 yr	6	0.96 (0.35–2.08)		
			≥ 20 yr	5	0.96 (0.31–2.23)		
			Total	15	0.91 (0.51–1.50)		
		Lymphatic and haematopoietic, mortality	Duration of firefighting employment, 1-yr lag (RR):				
			< 10 yr (including non-firefighters)	5	1		
			10 to < 20 yr	6	1.22 (0.36–4.11)		
			≥ 20 yr	5	3.26 (0.67–15.8)		
		Leukaemia, mortality	Duration of firefighting employment, 1-yr lag (SMR):				
			1 mo to < 10 yr	1	0.33 (0.00–1.86)		
			10 to < 20 yr	3	0.83 (0.17–2.42)		
			≥ 20 yr	2	0.81 (0.09–2.91)		
			Total	6	0.66 (0.24–1.44)		
		Leukaemia, mortality	Duration of firefighting employment, 1-yr lag (RR):				
			< 10 yr (including non-firefighters)	1	1		
			10 to < 20 yr	3	6.54 (0.50–85.12)		
			≥ 20 yr	2	83.65 (2.21–3166.29)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) Republic of Korea Enrolment, 1980–2007/ follow-up, 1996–2007 Cohort	33 416 men employed as emergency responders for ≥ 1 mo between 1980 and 2007 with (29 438) and without (3978) firefighting experience and not deceased in 1995 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Lymphatic and haematopoietic (ICD-10, C81–C96), incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include rural and municipal firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: no information on personal characteristics or confounders (except the firefighter cohort had a lower BMI and smoked less than the comparison population for the SIR analysis); follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	13	1.59 (0.84–2.71)		
			≥ 10 yr	19	1.19 (0.72–1.86)		
			Total	32	1.33 (0.91–1.87)		
		Lymphatic and haematopoietic (ICD-10, C81–C96), incidence	SRR:				
			Non-firefighters	4	1		
			Ever employed as a firefighter	32	0.81 (0.28–2.33)		
		NHL (ICD-10, C82–C85), incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	6	1.68 (0.62–3.67)		
			≥ 10 yr	12	1.69 (0.87–2.96)		
			Total	18	1.69 (1.01–2.67)		
		NHL (ICD-10, C82–C85), incidence	SRR:				
			Non-firefighters	3	1		
			Ever employed as a firefighter	18	0.52 (0.15–1.78)		
		Leukaemia (ICD-10, C91–C95), incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	7	1.60 (0.64–3.31)		
			≥ 10 yr	6	0.75 (0.27–1.62)		
			Total	13	1.05 (0.56–1.79)		
		Leukaemia (ICD-10, C91-C95), incidence	SRR:				
			Non-firefighters	1	1		
			Ever employed as a firefighter	13	1.68 (0.22–13.06)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) Norway Enrolment, 1950–2019/ follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Hodgkin lymphoma (ICD-10, C81), incidence	SIR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions. May include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; low number of cases for some cancer sites; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	2	0.53 (0.06–1.91)		
		Hodgkin lymphoma (ICD-10, C81), incidence	Year of first employment (SIR):				
			Pre-1950	0	0 (0.00–3.75)		
			1950–1969	2	2.29 (0.28–8.28)		
			1970 or after	0	0 (0.00–1.42)		
		Hodgkin lymphoma (ICD-10, C81), incidence	Time since first employment (SIR):				
			< 20 yr	0	0 (0.00–1.70)		
			20–39 yr	0	0 (0.00–2.19)		
			≥ 40 yr	2	3.05 (0.37–11.0)		
		Hodgkin lymphoma (ICD-10, C81), incidence	Duration of employment (SIR):				
			< 10 yr	0	0 (0.00–2.46)		
			10–19 yr	0	0 (0.00–3.63)		
			20–29 yr	0	0 (0.00–3.64)		
			≥ 30 yr	2	2.17 (0.26–7.85)		
		NHL (ICD-10, C82–C86, C96), incidence	SIR:				
			Firefighters	26	1.17 (0.76–1.71)		
		NHL (ICD-10, C82–C86, C96), incidence	Year of first employment (SIR):				
			Pre-1950	6	1.14 (0.42–2.47)		
			1950–1969	9	1.20 (0.55–2.27)		
			1970 or after	11	1.17 (0.58–2.09)		
		NHL (ICD-10, C82–C86, C96), incidence	Time since first employment (SIR):				
			< 20 yr	4	1.30 (0.35–3.32)		
			20–39 yr	14	1.50 (0.82–2.52)		
			≥ 40 yr	8	0.81 (0.35–1.61)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) (cont.)		NHL (ICD-10, C82–C86, C96), incidence	Duration of employment (SIR):			Age, calendar year	
			< 10 yr	2	0.72 (0.09–2.61)		
			10–19 yr	4	1.28 (0.35–3.27)		
			20–29 yr	10	1.68 (0.81–3.10)		
			≥ 30 yr	10	0.96 (0.46–1.77)		
		Multiple myeloma (ICD-10, C90), incidence	SIR:				
			Firefighters	9	0.79 (0.36–1.51)		
		Multiple myeloma (ICD-10, C90), incidence	Year of first employment (SIR):				
			Pre-1950	5	1.21 (0.39–2.82)		
			1950–1969	1	0.25 (0.01–1.40)		
			1970 or after	3	0.93 (0.19–2.71)		
		Multiple myeloma (ICD-10, C90), incidence	Time since first employment (SIR):				
			< 20 yr	0	0 (0.00–4.31)		
			20–39 yr	4	0.88 (0.24–2.26)		
			≥ 40 yr	5	0.82 (0.27–1.91)		
		Multiple myeloma (ICD-10, C90), incidence	Duration of employment (SIR):				
			< 10 yr	1	1.07 (0.03–5.97)		
			10–19 yr	0	0 (0.00–2.47)		
			20–29 yr	4	1.32 (0.36–3.39)		
			≥ 30 yr	4	0.65 (0.18–1.66)		
		Leukaemia (ICD-10, C91–C95), incidence	SIR:				
			Firefighters	14	0.83 (0.46–1.40)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) (cont.)		Leukaemia (ICD-10, C91–C95), incidence	Year of first employment (SIR):			Age, calendar year	
			Pre-1950	5	0.91 (0.29–2.11)		
			1950–1969	4	0.72 (0.20–1.84)		
			1970 or after	5	0.88 (0.29–2.05)		
		Leukaemia (ICD-10, C91–C95), incidence	Time since first employment (SIR):				
			< 20 yr	1	0.48 (0.01–2.70)		
			20–39 yr	6	0.92 (0.34–1.99)		
			≥ 40 yr	7	0.86 (0.34–1.77)		
		Leukaemia (ICD-10, C91–C95), incidence	Duration of employment (SIR):				
			< 10 yr	2	1.02 (0.12–3.70)		
			10–19 yr	2	0.94 (0.11–3.38)		
			20–29 yr	0	0 (0.00–0.69)		
			≥ 30 yr	10	1.20 (0.57–2.20)		
Marjerrison et al. (2022b) Norway Enrolment, 1950–2019/ follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Hodgkin lymphoma (ICD-10, C81), mortality	SMR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions. May include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment.
			Firefighters	0	0 (0.00–2.31)		
		Hodgkin lymphoma (ICD-10, C81), incidence	Period of follow-up (SIR):				
			1984 or before	0	0 (0.00–2.40)		
			1985–1994	0	0 (0.00–5.32)		
			1995 or after	< 5	1.01 (0.12–3.67)		
		Hodgkin lymphoma (ICD-10, C81), mortality	Period of follow-up (SMR):				
			1984 or before	0	0 (0.00–3.80)		
			1985–1994	0	0 (0.00–15.7)		
			1995 or after	0	0 (0.00–9.40)		
		Hodgkin lymphoma (ICD-10, C81), incidence	Age at diagnosis (SIR):				
			≤ 49 yr	0	0 (0.00–1.51)		
			50–69 yr	< 5	1.49 (0.18–5.37)		
			≥ 70 yr	0	0 (0.00–7.98)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Hodgkin lymphoma (ICD-10, C81), mortality	Age at diagnosis (SMR):			Age, calendar year	*Limitations*: probable healthy-worker effect; low number of cases for some cancer sites; no data on potential confounders apart from age, sex, and calendar time.
			≤ 49 yr	0	0 (0.00–6.39)		
			50–69 yr	0	0 (0.00–5.70)		
			≥ 70 yr	0	0 (0.00–9.89)		
		NHL (ICD-10, C82–C86, C96), mortality	SMR:				
			Firefighters	9	0.96 (0.44–1.83)		
		NHL (ICD-10, C82–C86, C96), incidence	Period of follow-up (SIR):				
			1984 or before	< 5	1.03 (0.21–3.01)		
			1985–1994	7	2.00 (0.81–4.13)		
			1995 or after	16	1.01 (0.58–1.64)		
		NHL (ICD-10, C82–C86, C96), incidence	Period of follow-up (SMR):				
			1984 or before	< 5	0.59 (0.02–3.31)		
			1985–1994	< 5	1.01 (0.12–3.66)		
			1995 or after	6	1.05 (0.39–2.29)		
		NHL (ICD-10, C82–C86, C96), incidence	Age at diagnosis (SIR):				
			≤ 49 yr	6	1.60 (0.59–3.48)		
			50–69 yr	13	1.22 (0.65–2.09)		
			≥ 70 yr	7	0.89 (0.36–1.84)		
		NHL (ICD-10, C82–C86, C96), mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–2.92)		
			50–69 yr	5	1.35 (0.44–3.14)		
			≥ 70 yr	< 5	0.87 (0.24–2.22)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Multiple myeloma (ICD-10, C90), mortality	SMR:			Age, calendar year	
			Firefighters	7	0.97 (0.39–2.00)		
		Multiple myeloma (ICD-10, C90), incidence	Period of follow-up (SIR):				
			1984 or before	< 5	1.39 (0.29–4.07)		
			1985–1994	< 5	1.03 (0.12–3.72)		
			1995 or after	< 5	0.55 (0.15–1.42)		
		Multiple myeloma (ICD-10, C90), mortality	Period of follow-up (SMR):				
			1984 or before	< 5	1.36 (0.17–4.93)		
			1985–1994	< 5	2.05 (0.42–5.99)		
			1995 or after	< 5	0.47 (0.06–1.69)		
		Multiple myeloma (ICD-10, C90), incidence	Age at diagnosis (SIR):				
			≤ 49 yr	0	0 (0.00–3.81)		
			50–69 yr	5	0.93 (0.30–2.16)		
			≥ 70 yr	< 5	0.78 (0.21–1.99)		
		Multiple myeloma (ICD-10, C90), mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–11.2)		
			50–69 yr	< 5	0.70 (0.09–2.55)		
			≥ 70 yr	5	1.22 (0.40–2.85)		
		Leukaemia (ICD-10, C91–C95), mortality	SMR:				
			Firefighters	10	1.00 (0.48–1.84)		
		Leukaemia (ICD-10, C91–C95), incidence	Period of follow-up (SIR):				
			1984 or before	< 5	1.18 (0.32–3.03)		
			1985–1994	< 5	0.38 (0.01–2.12)		
			1995 or after	9	0.84 (0.38–1.59)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Leukaemia (ICD-10, C91–C95), mortality	Period of follow-up (SMR):			Age, calendar year	
			1984 or before	< 5	1.09 (0.22–3.18)		
			1985–1994	< 5	0.57 (0.01–3.15)		
			1995 or after	6	1.10 (0.40–2.39)		
		Leukaemia (ICD-10, C91–C95), incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	0.42 (0.01–2.37)		
			50–69 yr	8	1.05 (0.45–2.07)		
			≥ 70 yr	5	0.73 (0.24–1.71)		
		Leukaemia (ICD-10, C91–C95), mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–2.62)		
			50–69 yr	< 5	1.09 (0.30–2.79)		
			≥ 70 yr	6	1.16 (0.43–2.52)		
Bigert et al. (2020) Sweden Enrolment 1960–1990/follow-up 1961–2009 Cohort	8136 firefighters; male firefighters identified from national censuses in 1960, 1970, 1980, and 1990 Exposure assessment method: ever employed and categorical duration of employment (years) as firefighter from census surveys	NHL (ICD-10, C83, C85), incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighter for whole employment. May include full-time, part-time, municipal, and rural firefighters. *Strengths*: near complete ascertainment of cancer incidence; long length of follow-up (mean, 28 yr); analyses stratified by calendar period of employment.
			Firefighters	42	1.05 (0.75–1.41)		
		NHL (ICD-10, C83, C85), incidence	Duration of employment (SIR):				
			1–9 yr	1	0.88 (0.02–4.89)		
			10–19 yr	12	1.10 (0.57–1.93)		
			20–29 yr	17	1.17 (0.68–1.87)		
			≥ 30 yr	12	0.88 (0.45–1.53)		
			Trend-test *P* value, 0.90				
		NHL (ICD-10, C83, C85), incidence	Time period (SIR):				
			1961–1975	1	0.35 (0.01–1.97)		
			1976–1990	10	0.84 (0.40–1.54)		
			1991–2009	31	1.22 (0.83–1.73)		
		Multiple myeloma (ICD-10, C90), incidence	SIR:				
			Firefighters	26	1.25 (0.82–1.83)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2020) (cont.)		Multiple myeloma (ICD-10, C90), incidence	Duration of employment (SIR):			Age, calendar period	*Limitations*: no data on job duties, employment type, or potential confounders (aside from age, sex, and calendar year); probable healthy-worker hire bias; potential non-differential misclassification of employment duration.
			1–9 yr	0	0 (0.00–7.24)		
			10–19 yr	4	0.77 (0.21–1.96)		
			20–29 yr	8	1.17 (0.51–2.31)		
			≥ 30 yr	14	1.70 (0.93–2.85)		
			Trend-test *P* value, 0.11				
		Multiple myeloma (ICD-10, C90), incidence	Time period (SIR):				
			1961–1975	2	1.17 (0.14–4.21)		
			1976–1990	6	1.07 (0.39–2.32)		
			1991–2009	18	1.34 (0.79–2.11)		
		Leukaemia (ICD-10, C91–C95), incidence	SIR:				
			Firefighters	33	0.94 (0.65–1.33)		
		Chronic lymphatic leukaemia, incidence	SIR:				
			Firefighters	14	0.85 (0.47–1.43)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1958–2012 Cohort	1080 men who worked ≥ 1 yr as a firefighter in Stockholm in 1931–1983 Exposure assessment method: ever employed and categorical duration of employment (years) as an urban [municipal] firefighter from annual enrolment records	Lymphatic and haematopoietic (ICD-7, 200–209), incidence	Follow-up period (SIR):			Birth year, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence; analyses of duration and era of employment. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year); lack of exposure assessment based on job tasks or fire responses.
			Full: 1958–2012	18	0.73 (0.43–1.16)		
			Former: 1958–1986	3	0.31 (0.06–0.90)		
			Extended: 1987–2012	15	1.01 (0.56–1.66)		
		NHL (ICD-7, 200), incidence	Follow-up period (SIR):				
			Full: 1958–2012	6	0.68 (0.25–1.48)		
			Former: 1958–1986	1	0.35 (0.01–1.97)		
			Extended: 1987–2012	5	0.83 (0.27–1.94)		
		Hodgkin lymphoma (ICD-7, 206), incidence	Follow-up period (SIR):				
			Full: 1958–2012	2	1.39 (0.17–5.00)		
			Former: 1958–1986	1	0.97 (0.02–5.42)		
			Extended: 1987–2012	1	2.41 (0.06–13.4)		
		Multiple myeloma (ICD-7, 203), incidence	Follow-up period (SIR):				
			Full: 1958–2012	5	1.18 (0.38–2.75)		
			Former: 1958–1986	0	0 (0.00–2.15)		
			Extended: 1987–2012	5	1.96 (0.64–4.57)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) (cont.)		Leukaemia (ICD-7, 204–207), incidence	Follow-up period (SIR): Full: 1958–2012 Former: 1958–1986 Extended: 1987–2012	 3 1 2	 0.38 (0.08–1.10) 0.29 (0.01–1.62) 0.43 (0.05–1.59)	Birth year, calendar period	
Tornling et al. (1994) Stockholm, Sweden Enrolment, 1931–1983/ follow-up, 1951–1986 (mortality), 1958–1986 (incidence) Cohort	1116 for mortality/1091 for incidence; male firefighters employed for ≥ 1 yr by the City of Stockholm between 1931 and 1983 identified from annual enrolment records Exposure assessment method: ever firefighter and duration (years) of firefighting employment from annual enrolment records; number of fires fought ascertained from exposure index developed from fire reports	Lymphatic and haematopoietic (ICD-8, 200–209), mortality Lymphatic and haematopoietic (ICD-8, 200–209), incidence	SMR: Firefighters SIR: Firefighters	 3 3	 0.44 (0.09–1.27) 0.32 (0.06–0.92)	Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Enhanced exposure assessment (but based on 10% sample of reports) to differentiate exposure based on number of fires fought accounting for job position, station, and year of exposure. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence and mortality; assessed exposure to fire responses for some outcomes. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year); low number of cases.

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) Denmark Enrolment, 1964–2004/ follow-up, 1968–2014 Cohort	9061 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born on 2 April 1928 or later, employed before age 60 yr and 31 December 2004, no cancer diagnosis before employment as a firefighter, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years), as well as employment type, job title/function, and work history, ascertained from civil registration, pension, employer personnel, and trade union membership records	Hodgkin lymphoma (ICD-10, C81), incidence	Reference group (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; near-complete ascertainment of cancer incidence; use of three reference groups to evaluate healthy-worker bias; analyses by proxies of exposure including job task. *Limitations*: little information on potential confounders.
			Firefighters vs general population	13	1.64 (0.95–2.82)		
			Firefighters vs sample of employees	13	1.35 (0.78–2.32)		
			Firefighters vs military	13	1.42 (0.82–2.44)		
		Hodgkin lymphoma (ICD-10, C81), incidence	Employment type (SIR):				
			Full-time	NR	NR		
			Part-time or volunteer	NR	2.29 (1.15–4.58)		
		NHL (ICD-10, C82–C85, C88.3–C88.9), incidence	SIR:				
			General population referent	37	0.96 (0.69–1.32)		
			Sample of working population referent	37	0.97 (0.70–1.33)		
			Military employees referent	37	0.97 (0.70–1.34)		
		NHL (ICD-10, C82–C85, C88.3–C88.9), incidence	Employment type (SIR):				
			Full-time	23	1.02 (0.68–1.53)		
			Part-time or volunteer	14	0.87 (0.52–1.47)		
		NHL (ICD-10, C82–C85, C88.3–C88.9), incidence	Era of first employment (SIR):				
			Pre-1970	13	0.90 (0.52–1.55)		
			1970–1994	18	0.89 (0.56–1.42)		
			1995 or after	6	1.46 (0.65–3.24)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		NHL (ICD-10, C82–C85, C88.3–C88.9), incidence	Job function (SIR):			Age, calendar period	
			Regular	33	0.91 (0.65–1.29)		
			Specialized	4	1.53 (0.57–4.08)		
		NHL (ICD-10, C82–C85, C88.3–C88.9), incidence	Age at first employment (SIR):				
			< 25 yr	15	0.83 (0.50–1.37)		
			25–34 yr	15	1.21 (0.73–2.00)		
			≥ 35 yr	7	0.86 (0.41–1.80)		
		NHL (ICD-10, C82–C85, C88.3–C88.9), incidence	Duration of employment (SIR):				
			< 1 yr	8	0.86 (0.43–1.73)		
			≥ 1 yr	29	0.98 (0.68–1.42)		
			≥ 10 yr	23	0.93 (0.62–1.40)		
			≥ 20 yr	16	0.88 (0.54–1.43)		
		Multiple myeloma (ICD-10, C90, C88.0–C88.2), incidence	Reference group (SIR):				
			Firefighters vs general population	8	0.62 (0.31–1.24)		
			Firefighters vs sample of employees	8	0.66 (0.33–1.32)		
			Firefighters vs military	8	0.65 (0.33–1.31)		
		Leukaemia (lymphoid) (ICD-10, C91), incidence	Reference group (SIR):				
			Firefighters vs general population	15	0.91 (0.55–1.51)		
			Firefighters vs sample of employees	15	0.97 (0.59–1.61)		
			Firefighters vs military	15	0.88 (0.53–1.47)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Leukaemia (myeloid) (ICD-10, C92), incidence	Reference group (SIR):			Age, calendar period	
			Firefighters vs general population	9	0.76 (0.40–1.46)		
			Firefighters vs sample of employees	9	0.73 (0.38–1.40)		
			Firefighters vs military	9	0.83 (0.43–1.60)		
Petersen et al. (2018b) Denmark Enrolment, 1964–2014/ follow-up, 1970–2014 Cohort	11 775 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born in 1928 or later, employed before age 60 yr and 31 December 2004, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years) as a firefighter ascertained from civil registration, pension, employer personnel, and trade union membership records	Lymphatic and blood forming tissues (ICD-10, C81–C96), mortality Lymphatic and blood forming tissues (ICD-10, C81–C96), mortality	Employment type (SMR, military reference group):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; use of military reference group to evaluate healthy-worker bias; analyses by duration of employment. *Limitations*: little information on potential confounders.
			Full-time	17	0.89 (0.56–1.44)		
			Part-time/ volunteer	5	0.47 (0.20–1.13)		
			Duration of employment (SMR, military reference group):				
			< 1 yr	4	0.46 (0.17–1.23)		
			≥ 1 yr	13	1.25 (0.73–2.16)		
			≥ 10 yr	12	1.30 (0.74–2.29)		
			≥ 20 yr	7	0.88 (0.42–1.85)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Webber et al. (2021) New York City, Chicago, Philadelphia, San Francisco, USA 2001–2016 Cohort	10 786 FDNY, 8813 CFHS; FDNY and CFHS cohorts; male firefighters who were active on 11 September 2001; FDNY cohort included men who worked at the WTC site any time between 11 September 2001 and 25 July 2002; CFHS cohort included men who were actively employed on 11 September 2001 and assumed not to be working at the WTC site Exposure assessment method: presence at WTC site from employment records and duty rosters	NHL, incidence	Group (SIR, US reference rates):			Age, calendar year, race/ ethnicity	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. Qualitative assessment based on presence at the WTC site, exposures complex and probably unique to 9/11 disaster. Municipal firefighters. *Strengths*: ascertainment of cancer incidence; comparison of two firefighter cohorts to evaluate bias; adjustment for smoking. *Limitations*: medical surveillance bias; young age of cohort; relatively short length of follow-up.
			CFHS firefighters	43	1.04 (0.77–1.41)		
			FDNY WTC firefighters	55	1.39 (1.06–1.83)		
		NHL, incidence	SIR (2-year adjustment for potential surveillance bias):				
			FDNY WTC firefighters	NR	1.29 (0.97–1.71)		
		NHL, incidence	Group (RR):			Age on 11 September 2001, race/ ethnicity	
			CFHS firefighters	43	1		
			FDNY WTC firefighters	55	1.26 (0.80–2.00)		
		NHL, incidence	Group (RR, 2-year adjustment for potential surveillance bias):				
			CFHS firefighters	NR	1		
			FDNY WTC firefighters	NR	1.21 (0.75–1.94)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Moir et al. (2016) USA Follow-up, 11 September 2001 through 2009 Cohort	11 457 WTC-exposed firefighters; 8220 non-WTC firefighters; White male WTC-exposed firefighters who were employed at FDNY on or after 1 January 1996, actively employed for ≥ 1.5 yr before end of follow-up (31 December 2009), whose identifying information was sent to state cancer registries; contributing person-years at risk at ages 30–70 yr from 11 September 2001 to study end; referent group included firefighters from San Francisco, Chicago, and Philadelphia Exposure assessment method: presence at WTC site from employment records and duty rosters	Haematological, incidence	Group (RR):			Age	*Exposure assessment critique*: Satisfactory quality. Exposure at WTC captured but did not consider previous firefighter work. Only measure of exposure was being a firefighter at WTC. Exposures complex and probably unique to 9/11 disaster. Urban [municipal] firefighters. *Strengths*: cancer incidence; comparison with other firefighter cohorts to establish effect of WTC exposures. *Limitations*: short follow-up period.
			Referent group	41	1		
			WTC-exposed FDNY firefighters	40	1.04 (0.64–1.71)		
		Haematological, incidence	Group (RR, early time period (11 September 2001 to 31 December 2004) diagnoses only)				
			Referent group	12	1		
			WTC-exposed FDNY firefighters	13	1.16 (0.45–3.02)		
		Haematological, incidence	Group (RR, late time period (1 January 2005 to 31 December 2009) diagnoses only)				
			Referent group	29	1		
			WTC-exposed FDNY firefighters	27	0.97 (0.53–1.76)		
		Haematological, incidence	Group (RR, 2-year adjustment for potential surveillance bias)				
			Referent group	41	1		
			WTC-exposed FDNY firefighters	37	0.97 (0.58–1.60)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeig-Owens et al. (2011) New York City, USA Enrolment, 1996/follow-up, 1996–2008 Cohort	9853 male FDNY firefighters employed for ≥ 18 mo, were active firefighters on 1 January 1996, with no prior cancer, and, if alive on 12 September 2001, also had known WTC exposure status Exposure assessment method: WTC-exposed and non-exposed firefighter from employment records and questionnaires	Hodgkin lymphoma, incidence	WTC-exposure status (SIR):			Age, race, ethnic origin, calendar year	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. WTC exposure self-reported using three methods. WTC site exposures complex and probably unique to 9/11 disaster. *Strengths*: evaluation of medical surveillance bias. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Non-exposed	≤ 5	0.82 (0.20–3.27)		
			Exposed	0	0 (NR)		
		NHL, incidence	WTC-exposure status (SIR, 2-year adjustment for potential surveillance bias):				
			Non-exposed	9	0.83 (0.43–1.60)		
			Exposed	20	1.50 (0.97–2.33)		
			SIR ratio (exposed vs non-exposed)	NR	1.81 (0.82–3.97)		
		Multiple myeloma, incidence	WTC-exposure status (SIR):				
			Non-exposed	0	0 (NR)		
			Exposed	≤ 5	1.49 (0.56–3.97)		
		Leukaemia, incidence	WTC-exposure status (SIR):				
			Non-exposed	7	1.47 (0.63–3.40)		
			Exposed	9	1.40 (0.73–2.70)		
			SIR ratio (exposed vs non-exposed)	NR	0.98 (0.33–2.77)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) San Francisco, Chicago, and Philadelphia, USA Enrolment, 1950–2009/ follow-up, 1950–2016 Cohort	29 992 municipal career firefighters in the CFHS cohort employed by the fire departments of San Francisco, Chicago, or Philadelphia for ≥ 1 day between 1950 and 2009; exposure–response analyses limited to 19 287 male firefighters of known race hired in 1950 or later and employed for ≥ 1 yr Exposure assessment method: ever-employed as a firefighter, and number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, C96), mortality	Fire department (SMR):			Gender, race, age, calendar period	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices; adjustment for HWSE. *Limitations*: healthy-worker selection bias in external comparison analyses; little information on potential confounders.
			San Francisco	30	1.19 (0.80–1.70)		
			Chicago	66	1.11 (0.86–1.41)		
			Philadelphia	55	1.37 (1.03–1.78)		
			Overall	151	1.21 (1.03–1.42)		
			Heterogeneity *P* value, 0.51				
		NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, C96), mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	76	0.94 (0.60–1.50)		
			RCS without HWSE adjustment	76	0.96 (0.54–1.82)		
			Fully adjusted loglinear	76	1.10 (0.60–2.11)		
			Fully adjusted RCS	76	1.08 (0.49–2.64)		
		NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, C96), mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	65	0.70 (0.47–1.01)		
			RCS without HWSE adjustment	65	0.71 (0.45–1.11)		
			Fully adjusted loglinear	65	0.74 (0.47–1.12)		
			Fully adjusted RCS	65	0.76 (0.45–1.29)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, C96), mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	40	0.61 (0.35–1.04)		
			RCS without HWSE adjustment	40	0.79 (0.39–1.68)		
			Fully adjusted loglinear	40	0.64 (0.34–1.17)		
			Fully adjusted RCS	40	0.83 (0.38–1.93)		
		Multiple myeloma (ICD-10, C88.7, C88.9, C90), mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	12	1.03 (0.53–1.79)		
			Chicago	24	0.86 (0.55–1.27)		
			Philadelphia	18	0.97 (0.58–1.54)		
			Overall	54	0.93 (0.70–1.21)		
			Heterogeneity *P* value, 0.85				
		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), mortality	Fire department (SMR):				
			San Francisco	26	0.94 (0.62–1.38)		
			Chicago	75	1.18 (0.93–1.48)		
			Philadelphia	49	1.12 (0.83–1.48)		
			Overall	150	1.11 (0.94–1.31)		
			Heterogeneity *P* value, 0.61				

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), mortality	Exposure-days model (HR at 8700 exposed-days vs 2500 exposed-days, 5-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	72	1.26 (0.77–2.11)		
			RCS without HWSE adjustment	72	1.12 (0.61–2.19)		
			Fully adjusted loglinear	72	2.32 (1.13–5.19)		
			Fully adjusted RCS	72	2.39 (0.91–7.37)		
		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 5-yr lag):				
			Loglinear without HWSE adjustment	64	1.07 (0.74–1.52)		
			RCS without HWSE adjustment	64	1.46 (0.90–2.43)		
			Fully adjusted loglinear	64	1.15 (0.77–1.67)		
			Fully adjusted RCS	64	1.89 (1.06–3.48)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92-C95), mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 5-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	41	1.07 (0.63–1.77)		
			RCS without HWSE adjustment	41	1.41 (0.71–2.97)		
			Fully adjusted loglinear	41	1.17 (0.65–2.05)		
			Fully adjusted RCS	41	1.74 (0.78–4.15)		
		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), mortality	Time since first exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Lag to < 20 yr	NR	2.56 (1.04–5.75)		
			20 to < 30 yr	NR	0.58 (0.19–1.58)		
			≥ 30 yr	NR	1.12 (0.57–2.08)		
			LRT *P* value, 0.15				
		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), mortality	Age at exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):				
			< 40 yr	NR	1.42 (0.72–2.63)		
			≥ 40 yr	NR	0.96 (0.51–1.73)		
			LRT *P* value, 0.44				

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Leukaemia (ICD-10, C91.0–C91.3, C91.5-C91.9, C92–C95), mortality	Period of exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Pre-1970	NR	0.97 (0.42–2.06)		
			1970 or after	NR	1.24 (0.75–2.01)		
			LRT *P* value, 0.63				
Daniels et al. (2015) San Francisco, Chicago, Philadelphia, USA Enrolment, 1950–2009/ follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	19 309; all male career firefighters in the CFHS cohort of known race who were on active duty ≥ 1 day in 1950–2009 in the fire departments of Chicago, Philadelphia, or San Francisco, with ≥ 1 yr of employment Exposure assessment method: number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	NHL, incidence	Exposed-days model (HR, power model, 5-yr lag):			Age, race, fire department, birth cohort	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices. *Limitations*: little information on potential confounders.
			8700 days vs 2500 days	92	1.07 (0.92–1.28)		
		NHL, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, linear model, 5-yr lag):			Age, race, fire department, birth cohort	
			8800 runs vs 2100 runs	79	0.79 (0.64–1.10)		
		NHL, incidence	Fire-hours (Chicago only) model (HR, power model, 5-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	45	1.12 (0.89–1.50)		
		Leukaemia, incidence	Exposed-days model (HR, RCS model, 5-yr lag):			Age, race, fire department, birth cohort	
			8700 days vs 2500 days	58	0.99 (0.56–1.89)		
		Leukaemia, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, linear model, 5-year lag):			Age, race, fire department, birth cohort	
			8800 runs vs 2100 runs	49	1.08 (0.75–1.84)		
		Leukaemia, incidence	Fire-hours (Chicago only) model (HR, power model, 5-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	33	0.90 (0.68–1.30)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2015) (cont.)		Leukaemia, incidence	Time since first exposure in piecewise loglinear fire-runs (Chicago and Philadelphia only) model (HR at 4600 runs, 5-yr lag):			Age, race, fire department, birth cohort	
			5–15 yr	NR	1.51 (0.65–3.21)		
			15–25 yr	NR	1.52 (0.71–2.93)		
			> 25 yr	NR	0.70 (0.38–1.19)		
			LRT *P* value, 0.123				
		Leukaemia, incidence	Age at exposure in piecewise loglinear fire-runs (Chicago and Philadelphia only) model (HR at 4600 runs, 5-yr lag):				
			< 40 yr	NR	0.95 (0.52–1.62)		
			≥ 40 yr	NR	1.19 (0.73–1.85)		
			LRT *P* value, 0.598				
		Leukaemia, incidence	Exposure period in piecewise loglinear fire-runs (Chicago and Philadelphia only) model (HR at 4600 runs, 5-yr lag):				
			Pre-1970	NR	0.95 (0.48–1.72)		
			1970 or after	NR	1.14 (0.76–1.66)		
			LRT *P* value, 0.652				
Daniels et al. (2014) Chicago, San Francisco, and Philadelphia, USA Enrolment, 1950–2009/ follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	29 993 (24 453 for incidence analyses) male and female career firefighters in the CFHS cohort employed for ≥ 1 day in Chicago, San Francisco, or Philadelphia fire departments between 1950 and 2009 Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, C96), incidence	SIR:			Gender, race, age, calendar period	*Exposure assessment critique*: Satisfactory quality. Minimum exposure is 1 day of work as a municipal firefighter. *Strengths*: long period of follow-up; ascertained incidence outcomes; included female firefighters. *Limitations*: healthy-worker hire bias in external comparisons; little information on potential confounders.
			All cancers	170	0.99 (0.85–1.15)		
			First primary cancer	145	0.99 (0.83–1.16)		
		NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, C96), incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men: Caucasian [White]	161	1.02 (0.87–1.19)		
			Other	7	0.56 (0.23–1.16)		
		Multiple myeloma (ICD-10, C88.7, C88.9, C90), incidence	SIR:			Gender, race, age, calendar period	
			All cancers	36	0.72 (0.50–0.99)		
			First primary cancer	33	0.75 (0.52–1.06)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Multiple myeloma (ICD-10, C88.7, C88.9, C90), incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men: Caucasian [White]	35	0.76 (0.53–1.06)		
			Other	NR	0.24 (0.01–1.32)		
		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), incidence	SIR:			Gender, race, age, calendar period	
			All cancers	100	0.94 (0.77–1.15)		
			First primary cancer	85	0.93 (0.74–1.15)		
		Leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, C92–C95), incidence	Race, men (SIR, all cancers):			Age, calendar period	
			Caucasian [White]	88	0.88 (0.71–1.09)		
			Other	11	1.90 (0.95–3.40)		
Demers et al. (1994) Seattle and Tacoma, USA Enrolment, 1944–1979/ follow-up, 1974–1989 Cohort	2447 male firefighters employed for ≥ 1 yr between 1944 and 1979, alive as of 1 January 1974 and known to be a resident of one of 13 counties in the catchment area of the tumour registry for ≥ 1 mo; reference group included 1878 local male police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration of employment (years) in direct firefighting positions from employment records	Hodgkin lymphoma (ICD-9, 201), incidence	SIR (local county rates):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Duration (years) involved in direct firefighting (surrogate for fire smoke) was not measured equally in the two study populations. Municipal firefighters. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders; small number of cases.
			Firefighters	1	0.7 (0.0–4.1)		
		NHL (ICD-9, 200–202), incidence	SIR (local county rates):				
			Firefighters	7	0.9 (0.4–1.9)		
		NHL (ICD-9, 200–202), incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	1	0.9 (0.0–4.9)		
			10–19 yr	1	0.6 (0.0–3.5)		
			20–29 yr	5	1.2 (0.4–2.7)		
			≥ 30 yr	0	0 (0.0–5.8)		
		NHL (ICD-9, 200–202), incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	2	1.9 (0.2–6.7)		
			20–29 yr	1	0.7 (0.0–3.7)		
			≥ 30 yr	4	0.8 (0.2–2.0)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		NHL (ICD-9, 200–202), incidence	IDR:			Age, calendar period	
			Local police	2	1		
			Firefighters	7	1.8 (0.4–13)		
		Multiple myeloma (ICD-9, 203), incidence	SIR (local county rates):				
			Firefighters	2	0.7 (0.1–2.6)		
		Leukaemia (ICD-9, 204–208), incidence	SIR (local county rates):				
			Firefighters	6	1.0 (0.4–2.1)		
		Leukaemia (ICD-9, 204–208), incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	0	0 (0.0–4.4)		
			10–19 yr	2	1.9 (0.2–6.8)		
			20–29 yr	4	1.1 (0.3–2.8)		
			≥ 30 yr	0	0 (0.0–5.4)		
		Leukaemia (ICD-9, 204–208), incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	1	1.6 (0.0–8.9)		
			20–29 yr	1	1.0 (0.0–5.6)		
			≥ 30 yr	4	0.9 (0.2–2.2)		
		Leukaemia (ICD-9, 204–208), incidence	IDR:				
			Local police	4	1		
			Firefighters	6	0.8 (0.2–3.5)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1992a) Seattle and Tacoma, Washington; Portland, Oregon, USA Enrolment, 1944–1979/ follow-up, 1945–1989 Cohort	4401 male firefighters employed for ≥ 1 yr between 1944 and 1979 in Seattle, Tacoma, or Portland, USA; reference group included 3676 local police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration (years) of exposure to fire combat from employment records	Lymphatic and haematopoietic (ICD-9, 200–208), mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Duration (years) involved in fire combat (surrogate for fire smoke) was not measured equally in the three municipal firefighter populations. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: information on potential confounders; ascertained mortality outcomes only.
			Firefighters	37	1.31 (0.92–1.81)		
		Lymphatic and haematopoietic (ICD-9, 200–208), mortality	Duration of exposed employment (SMR):				
			< 10 yr	4	0.91 (0.2–2.3)		
			10–19 yr	7	1.46 (0.06–3.0)		
			20–29 yr	14	1.06 (0.6–1.8)		
			≥ 30 yr	12	2.05 (1.1–3.6)		
		Lymphatic and haematopoietic (ICD-9, 200–208), mortality	Years since first employment (SMR):				
			< 20 yr	8	1.65 (0.7–3.2)		
			20–29 yr	2	0.39 (0.1–1.4)		
			≥ 30 yr	27	1.48 (1.0–2.2)		
		Lymphatic and haematopoietic (ICD-9, 200–208), mortality	Age at risk (SMR):				
			18–39 yr	5	1.74 (0.6–4.1)		
			40–64 yr	13	0.96 (0.5–1.6)		
			≥ 65 yr	19	1.61 (1.0–2.5)		
		Lymphatic and haematopoietic (ICD-9, 200–208), mortality	IDR:				
			Local police	21	1		
			Firefighters	37	1.03 (0.62–1.73)		
		Lymphosarcoma-reticulosarcoma (ICD-9, 200), mortality	SMR:				
			Firefighters	7	1.42 (0.57–2.93)		
		Lymphosarcoma-reticulosarcoma (ICD-9, 200), mortality	IDR:				
			Local police	5	1		
			Firefighters	7	0.81 (0.30–2.22)		
		Hodgkin lymphoma (ICD-9, 201), mortality	SMR:				
			Firefighters	3	1.05 (0.22–3.08)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1992a) (cont.)		Leukaemia (ICD-9, 204–208), mortality	SMR:			Age, calendar period	
			Firefighters	15	1.27 (0.71–2.09)		
		Leukaemia (ICD-9, 204–208), mortality	Duration of exposed employment (SMR):				
			< 10 yr	2	1.13 (0.1–4.1)		
			10–19 yr	2	1.04 (0.1–3.7)		
			20–29 yr	4	0.73 (0.2–1.9)		
			≥ 30 yr	7	2.60 (1.0–5.4)		
		Leukaemia (ICD-9, 204–208), mortality	Years since first employment (SMR):				
			< 20 yr	3	1.50 (0.3–4.4)		
			20–29 yr	1	0.50 (0.1–2.8)		
			≥ 30 yr	11	1.40 (0.7–2.5)		
		Leukaemia (ICD-9, 204–208), mortality	Age at risk (SMR):				
			18–39 yr	1	0.82 (0.1–4.6)		
			40–64 yr	5	0.95 (0.3–2.2)		
			≥ 65 yr	9	1.67 (0.8–3.2)		
		Leukaemia (ICD-9, 204–208), mortality	IDR:				
			Local police	11	1		
			Firefighters	15	0.80 (0.38–1.70)		
		Other lymphatic and haematopoietic (ICD-9, 202, 203), mortality	SMR:				
			Firefighters	12	1.40 (0.72–2.44)		
		Other lymphatic and haematopoietic (ICD-9, 202, 203), mortality	IDR:				
			Local police	5	1		
			Firefighters	12	1.40 (0.48–4.07)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Feuer & Rosenman (1986) New Jersey (NJ), USA 1974–1980 Cohort	263 deceased White male firefighters in the New Jersey Police and Firemen Retirement System (firefighters vested with ≥ 10 yr of service, or firefighters who died while on payroll regardless of employment duration); one reference group included 567 White male police deaths Exposure assessment method: ever employed, and categorical duration of employment (years), as a career firefighter from retirement system records	Leukaemia (ICD-8, 204–207), mortality	Reference population (PMR): Firefighters vs US White men Firefighters vs NJ White men Firefighters vs White male NJ police	 4 4 4	 [1.86 (0.59–4.49)] [1.77 (0.56–4.27)] [2.76 (0.88–6.65)]	Age, race	*Exposure assessment critique*: Satisfactory quality. Assessment provides duration of employment categories. May include municipal and rural firefighters. *Strengths*: comparison with other uniformed service occupation. *Limitations*: PMR study design lacks event-free follow-up time; short observation period; little information on potential confounders; small number of cases.
Aronson et al. (1994) Toronto, Canada 1950–1989 Cohort	5414 male firefighters employed for ≥ 6 mo at one of six fire departments in Metropolitan Toronto any time between 1950 and 1989 Exposure assessment method: ever employed and categorical duration of employment (years) as municipal firefighter from employment records	Lymphatic and haematopoietic (ICD-9, 200–208), mortality Lymphosarcoma-reticulosarcoma (ICD-9, 200), mortality Lymphosarcoma-reticulosarcoma (ICD-9, 200), mortality Hodgkin lymphoma (ICD-9, 201), mortality	SMR: Any employment SMR: Any employment SMR: 10–14 yr of employment SMR: Any employment	18 3 NR 1	0.98 (0.58–1.56) 2.04 (0.42–5.96) 8.33 (1.01–30.1) 0.47 (0.01–2.59)	Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Probably municipal firefighters. *Strengths*: long period of follow-up; analysis of employment duration. *Limitations*: healthy-worker hire bias; little information on confounders or exposure; ascertained mortality outcomes only.

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aronson et al. (1994) (cont.)		Multiple myeloma (ICD-9, 203), mortality	SMR:			Age, calendar period	
			Any employment	1	0.39 (0.01–2.15)		
		Leukaemia (lymphoid) (ICD-9, 204), mortality	SMR:				
			Any employment	4	1.90 (0.52–4.88)		
		Leukaemia (lymphoid) (ICD-9, 204), mortality	Years since first exposure (SMR):				
			< 20 yr	0	0 (0–10.25)		
			20–29 yr	0	0 (0–9.97)		
			≥ 30 yr	4	2.92 (0.80–7.48)		
		Leukaemia (lymphoid) (ICD-9, 204), mortality	Years of employment (SMR):				
			< 15 yr	0	0 (0–10.54)		
			15–29 yr	0	0 (0–6.25)		
			≥ 30 yr	4	3.51 (0.96–8.98)		
		Leukaemia (lymphoid) (ICD-9, 204), mortality	Age (SMR):				
			< 60 yr	0	0 (0–4.01)		
			≥ 60 yr	4	3.36 (0.92–8.60)		
		Leukaemia (myeloid) (ICD-9, 205), mortality	SMR:				
			Any employment	4	1.20 (0.33–3.09)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) Edmonton and Calgary, Canada 1927–1987 Cohort	3328; all firefighters employed between 1927 and 1987 by either fire departments of Edmonton or Calgary Exposure assessment method: ever employed and categorical duration of employment (years) from employment records; exposure index of years of employment weighted by time spent in proximity to fires based on job classification	Lymphatic and haematopoietic (ICD-9, 200–208), mortality Lymphatic and haematopoietic (ICD-9, 200–208), mortality	SMR: Any employment Year of cohort entry (SMR): Pre-1920 1920–1929 1930–1939 1940–1949 1950–1959 1960–1969 1970–1979	10 3 0 2 2 1 2 0	1.26 (0.61–2.32) [2.27 (0.58–6.18)] 0 (NR) [3.23 (0.54–10.66)] [1.33 (0.22–4.40)] [0.43 (0.02–2.12)] [1.85 (0.31–6.12)] 0 (NR)	Age, calendar period	*Exposure assessment critique*: Good quality. Good approach to differentiate exposure between ranks. Urban [municipal] firefighters. *Strengths*: long length of follow-up; analyses by duration of employment and exposure index. *Limitations*: little information on potential confounders; ascertained mortality outcomes only; low number of cases for stratified analyses.
Glass et al. (2019) Australia Enrolment, varied by agency/ follow-up, 1980–2011 (mortality); 1982–2010 (incidence) Cohort	39 644 female firefighters, both paid [career] (1682) and volunteer (37 962), from nine fire agencies in Australia Exposure assessment method: ever career or volunteer firefighter, ever attended an incident, tertiles of cumulative number of incidents and type of incidents attended from personnel records	Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence NHL (ICD-10, C82–C85), incidence	SIR: All volunteer firefighters Volunteers who attended incidents SIR: All volunteer firefighters Volunteers who attended incidents	90 37 38 18	0.99 (0.80–1.22) 1.02 (0.72–1.41) 1.00 (0.71–1.38) 1.19 (0.71–1.88)	Age, calendar year	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents for volunteer firefighters. Included specific incident types, but early exposure was extrapolated from more recent data. Volunteers mainly rural. *Strengths*: study of female firefighters; includes predominantly rural firefighters; ascertained exposure to number and type of incidents.

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Multiple myeloma (ICD-10, C90), incidence	SIR:			Age, calendar year	*Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			All volunteer firefighters	13	1.27 (0.68–2.17)		
			Volunteers who attended incidents	4	1.04 (0.28–2.67)		
		Leukaemia (ICD-10, C91–C95), incidence	SIR:				
			All volunteer firefighters	23	1.10 (0.70–1.65)		
			Volunteers who attended incidents	6	0.71 (0.26–1.55)		
Glass et al. (2017) Australia Enrolment, date varied by agency (1998–2000)/ follow-up to 30 November 2011 (mortality) and 31 December 2010 (cancer incidence) Cohort	163 094; all male volunteer firefighters from five fire agencies, enrolled on or after the date on which the agency's roll was complete and who had ever held an active firefighting role Exposure assessment method: ever volunteer firefighter, categorical volunteer duration (years) and era from service records; ever volunteer firefighter who attended an incident, tertiles of cumulative emergency incidents from contemporary incident data	Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents. Included specific incident types, but early exposure was extrapolated from more recent data. Firefighters from rural or peri-urban areas. *Strengths*: includes predominantly rural firefighters; ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			All volunteers	663	0.81 (0.75–0.88)		
			Volunteers who attended incidents	426	0.81 (0.74–0.89)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	Duration of service, all volunteers (RIR) [equivalent to rate ratios]:				
			> 3 mo to < 10 yr	239	1		
			10–20 yr	126	0.91 (0.73–1.12)		
			≥ 20 yr	296	0.84 (0.70–1.01)		
			Trend-test *P* value, 0.06				
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45-D46, D47.1, D47.3), incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	113	1		
			10–20 yr	83	1.04 (0.78–1.38)		
			≥ 20 yr	237	0.94 (0.74–1.20)		
			Trend-test *P* value, 0.55				

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	391	1		
			Group 2	24	1.36 (0.90–2.05)		
			Group 3	11	1.32 (0.72–2.40)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	392	1		
			Group 2	24	1.32 (0.87–1.99)		
			Group 3	10	1.38 (0.74–2.58)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	400	1		
			Group 2	18	1.65 (1.03–2.64)		
			Group 3	8	1.45 (0.72–2.92)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	336	1		
			Group 2	63	1.08 (0.82–1.41)		
			Group 3	27	1.29 (0.87–1.91)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	393	1		
			Group 2	22	1.17 (0.76–1.80)		
			Group 3	11	1.55 (0.85–2.83)		
		Hodgkin lymphoma (ICD-10, C81), incidence	SIR:				
			All volunteers	33	0.85 (0.59–1.20)		
			Volunteers who attended incidents	23	0.89 (0.56–1.33)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		NHL (ICD-10, C82–C85), incidence	SIR:			Age, calendar period	
			All volunteers	267	0.83 (0.73–0.94)		
			Volunteers who attended incidents	181	0.87 (0.75–1.00)		
		NHL (ICD-10, C82–C85), incidence	Duration of service, all volunteers (RIR):				
			> 3 mo to < 10 yr	100	1		
			10–20 yr	48	0.82 (0.58–1.20)		
			≥ 20 yr	118	0.82 (0.62–1.08)		
			Trend-test *P* value, 0.16				
		NHL (ICD-10, C82–C85), incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to < 10 yr	54	1		
			10–20 yr	32	0.81 (0.52–1.25)		
			≥ 20 yr	98	0.79 (0.56–1.13)		
			Trend-test *P* value, 0.22				
		NHL (ICD-10, C82–C85), incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	168	1		
			Group 2	10	1.30 (0.69–2.47)		
			Group 3	3	0.82 (0.26–2.58)		
		NHL (ICD-10, C82–C85), incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	69	1		
			Group 2	11	1.39 (0.75–2.56)		
			Group 3	1	0.32 (0.04–2.25)		
		NHL (ICD-10, C82–C85), incidence	No. of structure fire incidents attended by volunteers (RIR):				
			Baseline	172	1		
			Group 2	8	1.67 (0.82–3.40)		
			Group 3	1	0.42 (0.06–2.97)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		NHL (ICD-10, C82–C85) incidence	No. of landscape fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	144	1		
			Group 2	28	1.09 (0.73–1.64)		
			Group 3	9	1.00 (0.51–1.96)		
		NHL (ICD-10, C82–C85), incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	169	1		
			Group 2	9	1.10 (0.56–2.16)		
			Group 3	3	0.96 (0.31–3.02)		
		NHL (follicular) (ICD-10, C82), incidence	SIR:				
			All volunteers	74	0.94 (0.73–1.17)		
			Volunteers who attended incidents	56	1.08 (0.81–1.40)		
		NHL (DLBCL) (ICD-10, C83.3), incidence	SIR:				
			All volunteers	126	0.82 (0.69–0.98)		
			Volunteers who attended incidents	82	0.83 (0.66–1.03)		
		Multiple myeloma (ICD-10, C90), incidence	SIR:				
			All volunteers	74	0.75 (0.59–0.94)		
			Volunteers who attended incidents	48	0.76 (0.56–1.01)		
		Leukaemia (ICD-10, C91–C95), incidence	SIR:				
			All volunteers	194	0.90 (0.77–1.03)		
			Volunteers who attended incidents	1.08	0.78 (0.64–0.94)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Myelodysplastic syndrome (ICD-10, D46), incidence	SIR: All volunteers Volunteers who attended incidents	 42 31	 0.81 (0.59–1.10) 1.01 (0.69–1.44)	Age, calendar period	
Glass et al. (2016a) Australia Enrolment, 1976–2003/ follow-up, 1976–2011 (mortality), 1982–2010 (incidence, except two states, 2009) Cohort	30 057; full- (17 394) or part-time (12 663) paid male firefighters employed at one of eight Australian fire agencies for ≥ 3 mo from start of personnel records (1976–2003, depending on agency). Exposure assessment method: employed as a part- or full-time firefighter for ≥ 3 mo, categorical employment duration (years) and era from employment records; tertiles of cumulative emergency incidents and type of incident attended from contemporary incident data	Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	Firefighter status (SIR): Full-time Part-time All	 109 43 152	 0.95 (0.78–1.15) 0.91 (0.66–1.23) 0.94 (0.80–1.10)	Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents, including specific incident types. Included specific incident types, but early exposure was extrapolated from more recent data. Municipal firefighters. *Strengths*: internal analysis by exposure to number and type of incidents; ascertained cancer incidence. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	Duration of employment, full-time firefighters (RIR) [equivalent to rate ratios]: > 3 mo to 10 yr 10–20 yr ≥ 20 yr Trend-test *P* value, 0.01	 10 22 75	 1 2.38 (1.08–5.26) 3.08 (2.32–7.20)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	Duration of employment, part-time firefighters (RIR): > 3 mo to 10 yr 10–20 yr ≥ 20 yr Trend-test *P* value, 0.92	 18 7 18	 1 0.83 (0.32–2.11) 1.07 (0.40–2.88)		
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	Duration of employment (RIR): > 3 mo to 10 yr 10–20 yr ≥ 20 yr Trend-test *P* value, 0.09	 28 29 93	 1 1.25 (0.72–2.18) 1.61 (0.92–2.82)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of all incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	12	1		
			Tertile 2	11	0.95 (0.42–2.16)		
			Tertile 3	19	1.06 (0.50–2.24)		
			Trend-test *P* value, 0.90				
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	14	1		
			Tertile 2	12	0.92 (0.42–2.01)		
			Tertile 3	16	0.76 (0.36–1.60)		
			Trend-test *P* value, 0.46				
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	15	1		
			Tertile 2	17	1.19 (0.59–2.40)		
			Tertile 3	10	0.46 (0.20–1.05)		
			Trend-test *P* value, 0.07				
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	12	1		
			Tertile 2	15	1.22 (0.57–2.63)		
			Tertile 3	15	0.86 (0.40–1.87)		
			Trend-test *P* value, 0.66				
		Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	13	1		
			Tertile 2	16	1.40 (0.65–2.86)		
			Tertile 3	13	0.72 (0.33–1.60)		
			Trend-test *P* value, 0.4				

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Hodgkin lymphoma (ICD-10, C81), incidence	Firefighter status (SIR):			Age, calendar period	
			Full-time	6	0.91 (0.34–1.99)		
			Part-time	4	1.14 (0.31–2.91)		
			All	10	0.99 (0.48–1.82)		
		NHL (ICD-10, C82–C85), incidence	Firefighter status (SIR):				
			Full-time	47	0.98 (0.72–1.30)		
			Part-time	19	0.95 (0.57–1.49)		
			All	66	0.97 (0.75–1.24)		
		NHL (ICD-10, C82–C85), incidence	Duration of employment, full-time firefighters (RIR):				
			> 3 mo to 10 yr	5	1		
			10–20 yr	9	2.12 (0.71–6.34)		
			≥ 20 yr	31	3.67 (1.28–10.54)		
			Trend-test *P* value, 0.01				
		NHL (ICD-10, C82–C85), incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	6	1		
			10–20 yr	3	0.95 (0.22–4.18)		
			≥ 20 yr	10	2.27 (0.59–8.71)		
			Trend-test *P* value, 0.20				
		NHL (ICD-10, C82–C85), incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	11	1		
			10–20 yr	12	1.69 (0.74–3.88)		
			≥ 20 yr	41	3.14 (1.42–6.95)		
			Trend-test *P* value, < 0.01				
		NHL (ICD-10, C82–C85), incidence	No. of all incidents attended by full-time firefighters (RIR):				
			Tertile 1	6	1		
			Tertile 2	5	0.88 (0.27–2.89)		
			Tertile 3	7	0.91 (0.30–2.73)		
			Trend-test *P* value, 0.86				

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		NHL (ICD-10, C82–C85), incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	7	1		
			Tertile 2	5	0.78 (0.25–2.45)		
			Tertile 3	6	0.70 (0.23–2.12)		
			Trend-test *P* value, 0.52				
		NHL (ICD-10, C82–C85), incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	8	1		
			Tertile 2	7	0.95 (0.34–2.61)		
			Tertile 3	3	0.32 (0.08–1.23)		
			Trend-test *P* value, 0.11				
		NHL (ICD-10, C82–C85), incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	6	1		
			Tertile 2	7	1.17 (0.4–3.48)		
			Tertile 3	5	0.65 (0.20–2.16)		
			Trend-test *P* value, 0.49				
		NHL (ICD-10, C82–C85), incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):			5-year-interval age groups	
			Tertile 1	5	1		
			Tertile 2	8	1.76 (0.57–5.40)		
			Tertile 3	5	0.85 (0.24–2.98)		
			Trend-test *P* value, 0.81				

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Multiple myeloma (ICD-10, C90), incidence	Firefighter status (SIR):			Age, calendar period	
			Full-time	15	1.14 (0.64–1.89)		
			Part-time	3	0.61 (0.13–1.78)		
			All	18	1.00 (0.59–1.58)		
		Leukaemia (ICD-10, C91–C95), incidence	Firefighter status (SIR):				
			Full-time	28	0.92 (0.61–1.33)		
			Part-time	15	1.21 (0.68–2.00)		
			All	43	1.00 (0.73–1.35)		
		Myelodysplastic syndrome (ICD-10, D46), incidence	Firefighter status (SIR):				
			Full-time	4	0.91 (0.25–2.33)		
			Part-time	0	0 (NR)		
			All	4	0.67 (0.18–1.71)		

Table 2.5 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016b) Victoria, Australia Enrolment, 1971–1999/ follow-up, 1980–2011 (mortality), 1982–2012 (incidence) Cohort	614; all male (611) and female (3) employed and volunteer Country Fire Authority trainers and a group of paid [career] Country Fire Authority firefighters who trained at the Fiskville site between 1971 and 1999; all analyses limited to men as no deaths or cancers were observed among women Exposure assessment method: employed or volunteer firefighter trainers and career firefighters who trained at training facility for any period of time, from human resources records, categorized into risk of low, medium, and high chronic exposure to smoke and other agents based on job assignment	Lymphatic and haematopoietic (ICD-10, C81–C96, D45–D46, D47.1, D47.3), incidence	Risk of chronic exposure (SIR): Low Medium High	 0 4 4	 0 (NR) 1.12 (0.30–2.86) 2.83 (0.77–7.24)	Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Incorporated categorical level of exposure into assessment for each type of firefighter. Volunteers mainly rural, career firefighters were municipal. *Strengths*: included firefighter instructors with high potential exposure to smoke and other hazardous agents; assessed exposure based on job assignment. *Limitations*: low number of cases; young age at end of follow-up; reported only on the grouping of all lymphatic and haematopoietic cancers.

9/11, World Trade Center disaster, 11 September 2001; BMI, body mass index; CFHS, Career Firefighter Health Study; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; Fire Department of the City of New York; HR, hazard ratio; HWSE, healthy-worker survivor effect; ICD, International Classification of Diseases; IDR, incidence density ratio; JEM, job-exposure matrix; LRT, likelihood ratio test; mo, month; NHL, non-Hodgkin lymphoma; NJ, New Jersey; NR, not reported; PMR, proportionate mortality ratio; RCS, restricted cubic splines; RIR, relative incidence ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; US, United States; vs, versus; WTC, World Trade Center; yr, year.

respectively. The SMR for leukaemia was 0.66 (95% CI, 0.24–1.44) overall, with SMRs of 0.33 (95% CI, 0–1.86), 0.83 (0.17–2.42) and 0.81 (95% CI, 0.09–2.91) for < 10 years, 10 to < 20 years, and ≥ 20 years, respectively. ARRs [adjusted rate ratios] were also calculated in internal analyses using a reference group of firefighters with < 10 years of employment and non-firefighters within the cohort. For lymphatic and haematopoietic malignancies, the age and calendar year ARRs were 1.22 (95% CI, 0.36–4.11) for those with 10 to < 20 years of employment and 3.26 (95% CI, 0.67–15.80) for those with ≥ 20 years of employment. For leukaemia, the ARRs were 6.54 (95% CI, 0.50–85.12; 3 cases) for those with 10 to < 20 years of employment and 83.65 (95% CI, 2.21–3166.29; 2 cases) for those with ≥ 20 years of employment (Ahn & Jeong, 2015). [Although there were no apparent differences in risk with longer employment, the number of cases in each stratum was small, limiting the ability to draw inferences. Although there was increased risk of leukaemia in those with the longest duration in internal analyses, the estimates were not stable because of small numbers of cases. The young age of the cohort (mean age at end of follow-up, 41.3 years) was a limitation, being much younger than the median age at diagnosis for these cancers typically seen in the general population.]

An earlier study in the same cohort (33 416 professional [career] emergency responders; 29 438 firefighters) investigated cancer incidence rather than mortality (Ahn et al., 2012). With cancer incidence follow-up between 1996 and 2007, those ever employed as a firefighter had an age- and calendar year-adjusted SIR of 1.33 (95% CI, 0.91–1.87; 32 cases) for all lymphatic and haematopoietic malignancies [ICD-10, C81–C96] with the national male population of the Republic of Korea as the referent. Stratification by duration of employment (< 10 and ≥ 10 years) did not reveal a higher estimate for those employed for a longer duration. For NHL [ICD-10, C82–C85], the overall SIR was 1.69 (95% CI, 1.01–2.67; 18 cases), with similar results for those employed for < 10 years and for ≥ 10 years. For leukaemia [ICD-10, C91–C95], the SIR for any employment was 1.05 (95% CI, 0.56–1.79; 13 cases). Although estimates for leukaemia and NHL were elevated for shorter employment duration (< 10 years), they were not stable because of small numbers of cases, and risks did not increase with longer duration (≥ 10 years). An internal analysis comparing firefighters with non-firefighters in the cohort showed that the age- and calendar year-adjusted SRRs were 0.81 (95% CI, 0.28–2.33) for lymphatic and haematopoietic malignancies, 0.52 (95% CI, 0.15–1.78) for NHL, and 1.68 (95% CI, 0.22–13.06) for leukaemia. [The relatively short follow-up (10 years) and young age of the cohort (mean age at the end of follow-up, 41.3 years) were limitations of this study. The elevated risks in the SIR analyses for all cancers of lymphatic and haematopoietic tissues combined and NHL were not observed in the internal analyses, whereas the opposite pattern was seen for leukaemia.]

Two reports from a study in Norway were published in 2022 (Marjerrison et al., 2022a, b); both included 3881 male professional [career] firefighters employed at one of fifteen fire departments around the country. The cohort included mostly full-time firefighters employed between 1950 and 2019, with past or present employment in positions entailing active firefighting duties. Cancer incidence was ascertained through linkage with the national cancer registry, whereas mortality was ascertained from the Cause of Death Registry with follow-up from 1960 through 2018 in both sources. Investigators calculated age- and calendar year-standardized SIRs and SMRs for firefighters compared with the general male population of Norway. For Hodgkin lymphoma (ICD-10, C81), the SIR for ever-employment was 0.53 (95% CI, 0.06–1.91; 2 cases); there were no deaths. The two cases both occurred in the same category of duration, time since first employment, and calendar follow-up period (first employed 1950–1969;

≥ 40 years since first employment; ≥ 30 years for duration of employment; follow-up period, 1995 or after). Both cases were diagnosed at age 50–59 years (SIR, 1.49; 95% CI, 0.18–5.37). For NHL (ICD-10, C82–C86, C96), the SIR was 1.17 (95% CI, 0.76–1.71; 26 cases), whereas the SMR was 0.96 (95% CI, 0.44–1.83; 9 cases). The risks were comparable across categories of year of first employment (before 1950, 1950–1969 and 1970 or after), whereas risks were elevated for time since first employment in the first two categories (< 20 years and 20–39 years), but not for the longest time (≥ 40 years). For time of follow-up, the SIR was elevated in the follow-up period 1985–1994 (SIR, 2.00; 95% CI, 0.81–4.13; 7 cases), but not in any category for mortality. Both the SIR and SMR were elevated in those diagnosed at age 50–69 years (SIR, 1.22; 95% CI, 0.65–2.09; 13 cases; and SMR, 1.35 (95% CI, 0.44–3.14; 5 deaths). For multiple myeloma (ICD-10, C90), neither the SIR nor the SMR showed evidence of association. In stratified analyses, the estimates in most categories were below 1.0 for year of first employment and time since first employment, the exception being an elevated risk (SIR, 1.21; 95% CI, 0.39–2.82) for those first employed before 1950, although the estimate was based on only five cases. The SIR was 1.32 (95% CI, 0.36–3.39; 4 cases) for an employment duration of 20–29 years. For calendar follow-up period, the SIR and SMR for follow-up to the end of 1984 were each elevated but imprecise, and the SMR for follow-up in 1985–1994 was elevated. The SMR, but not the SIR, was elevated for those diagnosed at age ≥ 70 years. [The Working Group noted the small number of cases in these categories.] For leukaemia, the SIR was 0.83 (95% CI, 0.46–1.40; 14 cases) and the SMR was 1.00 (95% CI, 0.48–1.84; 10 deaths) for ever-employment, and the SIR was near or above one for an employment duration of < 10 years (SIR, 1.02; 95% CI, 0.12–3.7; 2 cases) and ≥ 30 years (SIR, 1.2; 95% CI, 0.57–2.2; 10 cases). There did not appear to be differences by follow-up period or age at diagnosis for either incidence or mortality. In general, the results were similar for incidence and mortality, with the exceptions noted above. [The analysis of multiple specific subtypes of cancer of lymphatic and haematopoietic tissues was a strength; however, the sample sizes were often small for stratified analyses.]

In a cohort study of 8136 male firefighters in Sweden, firefighters were identified from employment information in the national decennial censuses between 1960 and 1990 (Bigert et al., 2020). Incident cancer diagnoses were ascertained in the Swedish Cancer Registry, with follow-up from 1961 through 2009. Age- and calendar time-standardized SIRs were calculated with the male general population of Sweden as the referent. In addition to analysis of ever-employment, external comparison analyses were also stratified by duration of employment and calendar time period. There were 42 cases of NHL (ICD-10, C83, C85) diagnosed, with an overall SIR for ever-employment of 1.05 (95% CI, 0.75–1.41). By duration of employment, the SIR in firefighters with ≥ 30 years of employment was 0.88 (95% CI, 0.45–1.53; *P* for trend, 0.90) and the SIR was highest in the most recent time period (1991–2009) at 1.22 (95% CI, 0.83–1.73; 31 cases). There were 26 cases of multiple myeloma (ICD-10, C90), with an overall SIR of 1.25 (95% CI, 0.82–1.83), and an SIR for ≥ 30 years of employment of 1.70 (95% CI, 0.93–2.85; 14 cases; $P = 0.11$). For leukaemia (ICD-10, C91–C95), the overall SIR was 0.94 (95% CI, 0.65–1.33; 33 cases) and for chronic lymphatic leukaemia (ICD-10 code not provided) it was 0.85 (95% CI, 0.47–1.43; 14 cases). Stratified analyses were not conducted for leukaemia.

A cancer incidence study in a cohort of 1080 male firefighters in Stockholm, Sweden, provided information on the risk of cancer of lymphatic and haematopoietic tissues (Kullberg et al., 2018). Firefighters were identified through annual enrolment records from 15 fire stations and worked for ≥ 1 year between 1931 and 1983.

As an update to a previous study (Tornling et al., 1994), this study added 26 years of cancer incidence follow-up from 1958 through 2012 in the Swedish Cancer Registry. The previous study reported three deaths from all haematopoietic cancers. For cancer incidence results, only the more recent study is discussed here. With the male general population of Stockholm County as the referent, the overall SIR for lymphatic and haematopoietic malignancies (ICD-7, 200–209) during the full follow-up period (1958–2012) was 0.73 (95% CI, 0.43–1.16; 18 cases), whereas for the latest follow-up period (1987–2012) the SIR was 1.01 (95% CI, 0.56–1.66; 15 cases). For NHL (ICD-7, 200), the overall SIR was 0.68 (95% CI, 0.25–1.48; 6 cases), whereas for the later time period the SIR was 0.83 (95% CI, 0.27–1.94; 5 cases). For Hodgkin lymphoma (ICD-7, 201), the overall SIR was 1.39 (95% CI, 0.17–5.00; 2 cases) and the SIR for the later follow-up was 2.41 (95% CI, 0.06–13.40; 1 case), whereas for multiple myeloma the SIR for the later follow-up was 1.96 (95% CI, 0.64–4.57; 5 cases). For leukaemia (ICD-7, 204–207), the overall SIR was 0.38 (95% CI, 0.08–1.10; 3 cases) and the SIR for the recent follow-up period was 0.43 (95% CI, 0.05–1.59; 2 cases). Overall, the results for the later time period were similar to those for the full-time period because most cancers occurred in the later time period. [Analyses of employment duration, latency, and number of fires fought were conducted in the earlier study by Tornling et al. (1994), but results were not reported for cancers of lymphatic and haematopoietic tissues.]

A cohort study of 9061 male firefighters in Denmark compared cancer incidence to that in three different reference groups: (i) the general population of men in Denmark; (ii) a sample of the male working population of Denmark; and (iii) male employees of the Danish military (Petersen et al., 2018a). Cohort members had been employed as firefighters at some time between 1964 and 2004, and cancer incidence follow-up was conducted in the Danish Cancer Registry from 1968 through 2014. With the military employees as the referent, the SIR for Hodgkin lymphoma (ICD-10, C81) was 1.42 (95% CI, 0.82–2.44; 13 cases) and the SIR for NHL (ICD-10, C82–85, C88.3–88.9) was 0.97 (95% CI, 0.70–1.34; 37 cases). With each reference group, the SIR was below one for multiple myeloma (ICD-10, C90, C88.0–C88.2; 8 cases), myeloid leukaemia (ICD-10, C92; 9 cases), and lymphoid leukaemia (ICD-10, C91; 15 cases). With the general population as the referent, the SIR for Hodgkin lymphoma was 2.29 (95% CI, 1.15–4.58) for part-time and volunteer firefighters. The results for Hodgkin lymphoma were not reported for the full-time workers and the number of cases was also not reported. The results for NHL were reported with stratification by employment type, era of first employment, job function (e.g. regular, specialized), age at first employment, and employment duration. The risks were elevated in those employed in or after 1995 (SIR, 1.46; 95% CI, 0.65–3.24; 6 cases), in those with a specialized job function, such as smoke divers, (SIR, 1.53; 95% CI, 0.57–4.08; 4 cases), and in those first employed at age 25–34 years (SIR, 1.21; 95% CI, 0.73–2.00; 15 cases). [The inclusion of three comparison groups allowed for the evaluation of healthy-worker bias. With the exception of Hodgkin lymphoma, for which the estimate was higher when using the general population as the referent, the estimates were very similar regardless of the reference group chosen, indicating that healthy-worker bias did not substantially influence results.]

Cancer mortality was investigated in the same cohort of Danish firefighters described above (Petersen et al., 2018b). An expanded study population of 11 775 male firefighters was followed for mortality in the Danish national death registry from 1970 through 2014. External comparisons were made with the military population as the referent [results with the working population as the referent were not reported for cancers of haematopoietic tissue]. SMRs were calculated

for lymphatic and blood forming tissue cancers (ICD-10, C81–C96) for full-time firefighters (17 deaths) and part-time/volunteer firefighters (5 deaths). For both categories, the SMR was below 1.0, although the SMR for part-time/volunteer firefighters was smaller in magnitude. Analyses were also conducted by duration of employment, with modestly elevated risk in the categories of ≥ 1 and ≥ 10 years of employment. [Results were only reported for the larger grouping of all cancers of lymphatic and haematopoietic tissues combined, limiting the ability to make etiological inferences.]

A cancer incidence study in a cohort of 10 786 male firefighters from the FDNY who were exposed to the WTC disaster site and 8813 firefighters in the CFHS, which included firefighters from Philadelphia, Chicago, and San Francisco Fire Departments, provided information on the risk of NHL (Webber et al., 2021). Cancer incidence follow-up was conducted using several state cancer registries selected on the basis of residential history information and began on 11 September 2001 and ended in 2016. There were 55 cases of NHL [ICD-O-3 was used, but codes were not provided to identify NHL] identified in the FDNY cohort and 43 in the CFHS cohort, resulting in SIRs of 1.39 (95% CI, 1.06–1.83) and 1.04 (95% CI, 0.77–1.41), respectively, with the US male general population as the referent. Because WTC-exposed FDNY firefighters undergo free routine health-monitoring examinations, the authors noted concern about medical surveillance bias because of earlier detection of certain cancers. The authors also noted that the median age at diagnosis of NHL in the FDNY cohort was 53.6 years compared with 60.1 years in the CFHS cohort ($P < 0.05$), indicating the possibility of screening-detected cases of NHL. Therefore, a sensitivity analysis was undertaken, reclassifying the diagnosis dates of any NHL case that was diagnosed ≤ 6 months after routine blood tests by delaying the diagnosis dates by 2 years. [The authors stated that 204 cancers were reclassified overall, but do not mention the number of cases of NHL affected.] In this surveillance bias-adjusted analysis, the SIR for NHL was 1.29 (95% CI, 0.97–1.71). In addition, the authors calculated RRs adjusted for age and race/ethnicity in the FDNY cohort compared with the CFHS cohort. The RR for NHL was 1.26 (95% CI, 0.80–2.00) and the surveillance bias-adjusted RR was 1.21 (95% CI, 0.75–1.94). [The elevated SIR in the WTC-exposed FDNY cohort, but not the CFHS cohort, could indicate either the presence of an exposure unique to the WTC cohort that increased risk or the presence of surveillance bias. Although attenuated, both the SIR and RR remained elevated after the surveillance bias adjustment, suggesting that the WTC exposures may be more likely than bias to be the reason for the elevation.]

An earlier study by Moir et al. (2016) investigated cancer incidence in an overlapping cohort of 11 457 WTC-exposed firefighters in the FDNY compared with a reference pooled cohort of 8220 municipal firefighters from the CFHS cohort. Cancer incidence follow-up was conducted in state cancer registries from 2001 through 2009. Both cohorts were restricted to White men aged 30–70 years who had been employed for ≥ 1.5 years before the end of the study, employed on or after 1 January 1996, and employed on 1 September 2001. From 11 September 2001 to 2009, 40 cases of haematological cancers were diagnosed among the WTC-exposed firefighters. [The paper noted "hematologic cancers" with no further description, but presumably this included all cancers of lymphatic and haematopoietic tissues.] With the pooled cohort of other firefighters as the referent, the age-adjusted RR for haematological cancers was 1.04 (95% CI, 0.64–1.71). To account for potential medical surveillance bias in the specialized cohort of WTC-exposed firefighters, the researchers also conducted analyses lagging the diagnosis date by 2 years for cases of Hodgkin lymphoma or NHL diagnosed < 6 months after a surveillance chest

CT scan, and all cases of haematological cancers diagnosed < 6 months after a routine blood test. The RR for all haematological malignancies after this correction remained similar at 0.97 (95% CI, 0.58–1.60). Previous follow-up of this cohort to the end of 2008 did not provide evidence of an excess incidence of specific subtypes of haematological cancers, including Hodgkin lymphoma, multiple myeloma, and leukaemia, in WTC-exposed firefighters compared with the general population. However, an elevated rate of NHL was observed with the surveillance bias correction (SIR, 1.50; 95% CI, 0.97–2.33; 20 cases) (Zeig-Owens et al., 2011). [Limitations of this study included the reliance on a one-time assessment of being a firefighter at the WTC disaster site, the grouping of all cancers of lymphatic and haematopoietic tissues together, and the very short follow-up period. Strengths of the study included the ascertainment of cancer incidence and the comparison of two firefighter groups.]

Investigators from NIOSH conducted a mortality study in a cohort of 29 992 male and female municipal career firefighters in the CFHS from San Francisco, Chicago, and Philadelphia (Pinkerton et al., 2020). Mortality follow-up was conducted from 1950 to 2016. With the US general population as the referent, there was an elevated SMR for NHL (ICD-10, C46.3, C82–C85, C88.0, C88.3, C91.4, and C96) (SMR, 1.21; 95% CI, 1.03–1.42; 151 deaths) among firefighters. In internal regression analyses by cumulative exposure to fire responses for NHL, with the referent of 2500 exposed days, the hazard ratio at 8700 exposed days was 1.10 (95% CI, 0.60–2.11; 76 deaths) based on the fully adjusted model (including adjustment for employment duration). There were no associations apparent for number of fire-runs or fire-hours. For leukaemia, the overall SMR among firefighters was modestly elevated (SMR, 1.11; 95% CI, 0.94–1.31; 150 deaths). For the internal exposure–response analyses, the preferred model for this site was based on restricted cubic splines applying a 5-year lag [The authors reported preferring this model for leukaemia based on the nonmonotonic response with increasing risk at low exposures followed by attenuated risk at higher exposure. This pattern required a more flexible exposure–response function. However, the cause of this attenuation was unclear.] The hazard ratio for the number of exposed days was elevated (HR, 2.39; 95% CI, 0.91–7.37; 72 deaths), as was the analysis based on 8800 fire-runs compared with 2100 fire-runs (HR, 1.89; 95% CI, 1.06–3.48; 64 deaths), and 2300 fire-hours compared with 600 fire-hours (HR, 1.74; 95% CI, 0.78–4.15; 41 deaths). [The Working Group noted that this study was among the most informative studies that evaluated cancers of lymphatic and haematopoietic tissues. A limitation of this study was the use of cancer mortality outcomes rather than incidence.]

An earlier study of a subset of firefighters from the same CFHS cohort examined internal exposure–response associations with both cancer mortality and incidence, with follow-up to the end of 2009 (Daniels et al., 2015). The study included 19 309 firefighters of known race hired in 1950 or later and employed for ≥ 1 year. Models were adjusted for the same covariates as in Pinkerton et al. (2020), with the exception of employment duration, and only the results for cancer incidence are reviewed here. Overall, there was little evidence of positive associations between exposure to fire responses and incidence of any cancers of lymphatic and haematopoietic tissues in the fully adjusted models. For NHL, there was a modest positive association with 2300 versus 600 fire-hours (HR, 1.12; 95% CI, 0.89–1.50, 45 cases). For leukaemia, the hazard ratio for 8800 versus 2100 fire-runs was 1.08 (95% CI, 0.75–1.84). For leukaemia, hazard ratios based on loglinear models that divided cumulative exposure into time windows were elevated for time since exposure of 5–15 years and 15–25 years, but not for > 25 years and age at exposure < 40 years. [Pinkerton et al. (2020) and Daniels et al. (2015) conducted more formal

adjustments for potential biases than did other studies, including the attempt to adjust for a healthy-worker survivor effect in Pinkerton et al. (2020). After these adjustments and based on internal analyses, the mortality and incidence results were relatively comparable. Together, these studies were considered informative for the evaluation of cancers of lymphatic and haematopoietic tissues.]

An additional study in the CFHS cohort investigated cancer incidence among 29 993 municipal career firefighters and reported external and internal comparison analyses with follow-up to the end of 2009 (Daniels et al., 2014). The methods were similar to those in the study by Pinkerton et al. (2020). Cancer incidence follow-up was conducted in state cancer registries relevant to each fire department to the end of 2009, with start years varying from 1985 to 1988. Residential history information was used to select state registries for follow-up. With the US general population as the referent, there were no elevations in the incidence rate of NHL (ICD-10, C46.3, C82–85, C88.0, C88.3, C91.4, and C96), leukaemia (ICD-10, C91.0–C91.3, C91.5–C91.9, and C92–C95), or multiple myeloma (ICD-10, C88.7, C88.9, and C90) among firefighters. In race-stratified analyses, there was an elevated SIR for leukaemia (SIR, 1.90; 95% CI, 0.95–3.40; 11 cases) among non-Caucasian [non-White] firefighters. No other associations by race were apparent.

In a cohort study of 2447 male municipal firefighters from Seattle and Tacoma, USA, cancer incidence was compared with that in the local male general population and in a cohort of male police officers from Washington state (Demers et al., 1994). Participants had been employed for ≥ 1 year between 1944 and 1979. Cancer incidence follow-up was conducted from 1974 through 1989 in the regional SEER cancer registry, using residential history information to reduce loss to follow-up. Duration of active-duty employment in direct firefighting positions was ascertained from employment records in the Seattle subcohort. For NHL (ICD-9, 200–202), the overall SIR was 0.9 (95% CI, 0.4–1.9; 7 cases) with the local county population as the referent. The SIR was modestly elevated, although imprecise, for firefighters with 20–29 years of employment (SIR, 1.2; 95% CI, 0.4–2.7), but no elevations were observed for other duration categories. Compared with incidence rates among police, the IDR for NHL was elevated among firefighters but was highly imprecise (IDR, 1.8; 95% CI, 0.4–13). For leukaemia (ICD-9, 204–208), the overall SIR was 1.0 (95% CI, 0.4–2.1; 6 cases) for firefighters compared with the local general population. In analyses of employment duration, the SIR for firefighters with 10–19 years of employment was elevated, but results were highly imprecise (SIR, 1.9; 95% CI, 0.2–6.8; 2 cases). No positive associations were observed for leukaemia in the comparison with police. [This study was limited by a low number of cases of cancer of lymphatic and haematopoietic tissues.]

A previous cohort study of 4401 male municipal firefighters from Seattle, Tacoma, Washington, and Portland, Oregon, USA, investigated the risk of mortality outcomes (Demers et al., 1992a). Firefighters included in this cohort had been employed between 1944 and 1979, and the mortality follow-up period was from 1945 to the end of 1989. In addition to US population rates for the White male general population, a cohort of police from the same cities was also used as a comparison group. With the general population as the referent, SMRs were elevated for lymphatic and haematopoietic malignancies (ICD-9, 200–208), lymphosarcoma-reticulosarcoma (ICD-9, 200), leukaemia (ICD-9, 204–208), and other lymphatic or haematopoietic malignancies (ICD-9, 202, 203), but not for Hodgkin lymphoma. With police as the referent, the mortality IDR was elevated only for other lymphatic or haematopoietic malignancies. SMRs were also calculated evaluating duration of employment (in active firefighting positions for

Seattle and Portland firefighters, or any employment as a firefighter for Tacoma firefighters), time since first employment, and age. For lymphatic and haematopoietic malignancies overall, the SMR was elevated in those with 10–19 years and ≥ 30 years duration of employment (SMR, 1.46; 95% CI, 0.06–3.0, 7 cases; and SMR 2.05; 95% CI, 1.1–3.6, 12 cases; respectively). SMRs were also elevated for those with < 20 or ≥ 30 years since first employment. For leukaemia, the SMR was elevated in those with ≥ 30 years duration of employment (SMR, 2.6; 95% CI, 1.0–5.4), ≥ 30 years since first employment (SMR, 1.4; 95% CI, 0.7–2.5), and age ≥ 65 years (SMR, 1.67; 95% CI, 0.8–3.2, 9 deaths). [For several stratified analyses, the number of cases was small.]

A proportionate mortality study of police and firefighters was conducted in New Jersey, USA (Feuer & Rosenman, 1986). Analyses were based on 263 deaths in White male firefighters reported to the state comprehensive retirement system for police and firefighters in 1974–1980. Three reference populations were used to compare mortality proportions among firefighters, including the US general population, the New Jersey general population, and police officers identified in the same data source. [Although duration of employment and latency-based analyses were reported for some outcomes, these were not reported for any cancers of lymphatic and haematopoietic tissues.] For leukaemia (ICD-8, 204–207), the PMR for firefighters was elevated using each of the three reference groups, although estimates were based on only four deaths. The greatest elevation was observed when using the police officers as the referent (PMR, 2.76; 95% CI, [0.88–6.65]).

A mortality study in a cohort of 5414 male career firefighters was conducted in Toronto, Canada (Aronson et al., 1994). Firefighters had been employed between 1950 and 1989 and mortality follow-up was conducted in a national mortality database from 1950 through 1989. Overall, there were 18 deaths from lymphatic and haematopoietic malignancies (ICD-9, 200–208). With the male general population of Ontario as the referent, the overall SMR for lymphatic and haematopoietic malignancies among firefighters was 0.98 (95% CI, 0.58–1.56). For lymphosarcoma/reticulosarcoma (ICD-9, 200), the SMR was elevated, but the estimate was highly imprecise (SMR, 2.40; 95% CI, 0.42–5.96; 3 deaths). There was an increase in the SMR for firefighters employed for 10–14 years, although the estimate was also highly imprecise. [No additional information was provided for this cancer site for duration, time since first employment, or age.] There was one case each of Hodgkin lymphoma and multiple myeloma, with SMR estimates below 1.0 and wide confidence intervals. For lymphoid leukaemia (ICD-9, 204), the SMR was elevated for ever-employment as a firefighter (SMR, 1.90; 95% CI, 0.52–4.88; 4 deaths). All cases of lymphoid leukaemia occurred in firefighters with ≥ 30 years since first exposure, ≥ 30 years of employment duration, and age ≥ 60 years, resulting in elevated, but imprecise, SMRs for these categories. For myeloid leukaemia, the SMR for ever-employment was elevated (SMR, 1.20; 95% CI, 0.33–3.09), although the estimate was based on only four cases. Results stratified by duration, age, and time since employment were not reported for this site. [This study was limited by a low number of deaths from cancers of lymphatic and haematopoietic tissues.]

A mortality study of 3328 municipal firefighters in two cohorts from Calgary and Edmonton, Canada, provided information on the risk of all cancers of lymphatic and haematopoietic tissues combined (Guidotti, 1993). Firefighters had been employed between 1927 and 1987, and mortality follow-up was conducted in both provincial and national sources from 1927 through 1987. Overall, there were 10 deaths from lymphatic and haematopoietic malignancies (ICD-9, 200–208) among the firefighters, resulting in an elevated SMR of 1.26 (95% CI, 0.61–2.32) with the male general

population of Alberta as the referent. Year at entry into the cohort was evaluated, and SMRs were elevated for those who entered before 1920 and in 1930–1939, 1940–1949, and 1960–1969. [The reporting of results only for all cancers of lymphatic and haematopoietic tissues combined limited the informativeness of this study.]

A cancer incidence study in an entirely female cohort of 37 962 volunteer firefighters was conducted in Australia (Glass et al., 2019). Cancer incidence follow-up was conducted in a national cancer registry from 1982 through 2010. Work history information describing the number and type of incidents attended was ascertained from fire agency personnel records. With the female general population of Australia as the referent, the SIR for lymphatic and haematopoietic neoplasms (ICD-10, C81–C96, D45–D46, D47.1, and D47.3) among all volunteer firefighters was 0.99 (95% CI, 0.80–1.22; 90 cases), and among those who had attended incidents it was 1.02 (95% CI, 0.72–1.41; 37 cases). For NHL (ICD-10, C82–C85), the SIR for those who had attended incidents was modestly elevated (SIR, 1.19; 95% CI, 0.71–1.88; 18 cases). For multiple myeloma (ICD-10, C90), the SIR was higher for all volunteers (13 cases) than for those who attended incidents (4 cases). A similar pattern was seen for leukaemia (ICD-10, C91–C95) based on 23 and 6 cases, respectively. Results from internal regression analyses by tertile of number of incidents attended were imprecise and did not indicate positive associations for either all lymphatic and haematopoietic malignancies combined or NHL. [In external analyses, the magnitude of reported effect estimates was smaller for volunteers who attended fire incidents than for volunteers overall for multiple myeloma and leukaemia, making it less likely that any increase was attributable to firefighting activities. For NHL, the increase was only seen in those who had attended incidents.]

Two studies of male firefighters in Australia were similar to that focused on female firefighters. The first was a cohort study of cancer incidence among 163 094 male volunteer firefighters from five fire agencies (Glass et al., 2017). A total of 663 cases of lymphohaematopoietic neoplasms (ICD-10, C81–C96, D45–D46, D47.1, and D47.3) were identified among all volunteer firefighters and 426 among the subset of those who had attended fire incidents. With the male general population of Australia as the referent, the SIR for all volunteer firefighters (SIR, 0.81; 95% CI, 0.75–0.88) was the same as that for volunteers who attended incidents (SIR, 0.81; 95% CI, 0.74–0.89). In internal regression analyses, the RIRs [equivalent to rate ratios] for all lymphohaematopoietic neoplasms indicated no elevated risks for any category of duration of service among either the full cohort or those who attended incidents. The rate of all lymphohaematopoietic neoplasms decreased with increasing duration of service among all volunteer firefighters. In contrast, the RIRs were elevated in all categories of exposure based on the number of incidents attended overall, as well as the number of structure fire, landscape fire, and vehicle fire incidents. For NHL (ICD-10, C82–C85), the SIR analyses indicated no evidence of excess risk in all volunteers or in volunteers who attended incidents. The RIRs were elevated for the middle tertile only of the total number of incidents attended (RIR, 1.30; 95% CI, 0.69–2.47; 10 cases), and for the number of fire incidents (RIR, 1.39; 95% CI, 0.75–2.56; 11 cases) and structure fire incidents (RIR, 1.67; 95% CI, 0.82–3.40; 8 cases), although confidence intervals were wide. There was no elevated risk in the higher tertiles of cumulative incidents, or in any category of duration of service. The authors also reported SIRs for volunteers who had attended incidents for some NHL subtypes, including follicular lymphoma (ICD-10, C82) (SIR, 1.08; 95% CI, 0.81–1.40; 56 cases) and diffuse large B-cell lymphoma (ICD-10, C83.3) (SIR, 0.83; 95% CI, 0.66–1.03; 82 cases). Internal analyses were not conducted for the subtypes. SIRs were also reported for Hodgkin lymphoma (ICD-10, C81), multiple myeloma (ICD-10, C90), leukaemia (ICD-10, C91–C95),

and myelodysplastic syndrome (ICD-10, D46), but none were elevated for either the cohort as a whole or for the subset of those who attended incidents. [The analysis of specific NHL subtypes was a strength of this study.]

The second study of male firefighters in Australia was conducted in a cohort of 30 057 paid full-time and part-time firefighters (Glass et al., 2016a). The cohort was enumerated and analysed using similar methods as those used in the studies of volunteer firefighters. Included firefighters had worked between 1976 and 2003 and were primarily municipal or semi-metropolitan firefighters. Cancer incidence follow-up was conducted in a national registry to the end of 2010. With the general male population of Australia as the referent, there was no excess risk of all lymphatic and haematological neoplasms (ICD-10, C81–C96, D45–D46, D47.1, and D47.3) among either full-time or part-time firefighters. In internal regression analyses, the RIRs [equivalent to rate ratios] for duration of employment and all lymphatic and haematological neoplasms combined were elevated for both 10–20 years and ≥ 20 years employment for full-time firefighters (RIR, 2.38; 95% CI, 1.08–5.26; 22 cases; and RIR, 3.08; 95% CI, 2.32–7.20; 75 cases; respectively; *P* for trend, 0.01), but not for part-time firefighters. There were few elevations in the RIRs for all lymphatic and haematological neoplasms across categories of number of any type of fire incident attended, except for tertile 2 for landscape and vehicle fires. For NHL (ICD-10, C82–C85), the SIRs were not elevated for full-time or part-time firefighters in external analyses. In internal analyses, the RIRs were elevated for both 10–20 years and ≥ 20 years of employment among full-time firefighters (RIR, 2.12; 95% CI, 0.71–6.34; and RIR, 3.67; 95% CI, 1.28–10.54; respectively; $P = 0.01$). For part-time firefighters, the RIR was elevated in the ≥ 20 years duration category only. For analyses of NHL based on the number and type of incidents attended, there were no apparent positive associations for any type of incident. For other cancer types, external comparison analyses indicated no excess risk of Hodgkin lymphoma, multiple myeloma, leukaemia, or myelodysplastic syndrome among firefighters compared with the male population of Australia.

A study of cancer incidence was conducted in a cohort of 614 firefighters and trainers who attended a firefighter-training facility in Australia (Glass et al., 2016b). Three female firefighters were excluded from the analysis. Cancer incidence follow-up was conducted from 1982 through 2012. Participants were grouped into risk categories of low, medium, and high chronic exposure (to smoke and other hazardous agents) on the basis of job assignment. Eight cases of lymphohaematopoietic neoplasms (ICD-10, C81–C96, D45–D46, D47.1, and D47.3) were identified during follow-up. Compared with the general male population of Victoria, participants with an estimated medium risk of chronic exposure had an SIR of 1.12 (95% CI, 0.30–2.86; 4 cases), and those with high risk of chronic exposure had an SIR of 2.83 (95% CI, 0.77–7.24; 4 cases). [This study was limited by the low number of cases in each exposure group and the reporting of risks only by the grouping of all neoplasms of lymphatic and haematopoietic tissues combined.]

2.3.2 Studies only reporting having ever worked as a firefighter

(a) Occupational cohort studies

Studies first described in Section 2.1.2(a) are described in less detail in the present section.

See Table S2.6 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Occupational cohort studies that described incidence or mortality for cancers of lymphatic and haematopoietic tissues in firefighters are included in this section. Cancer sites included

in this classification include lymphoma (non-Hodgkin and Hodgkin), lymphosarcoma-reticulosarcoma, multiple myeloma, and leukaemia. Eight studies were included (Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Giles et al., 1993; Bates et al., 2001; Ma et al., 2005; 2006; Amadeo et al., 2015). All cohorts assessed in this section were enumerated through record linkage of employment records or certifications. [The grouping of all cancers of lymphatic and haematopoietic tissues together was a limitation of most studies in this section. Furthermore, changes in the classification of these cancers over time made it particularly difficult to compare findings across studies.]

A cohort of all male French firefighters employed on 1 January 1979 was assembled (Amadeo et al., 2015). With follow-up to the end of 2008, there were 42 deaths from lymphohaematopoietic malignancies [ICD codes not given] with an age- and calendar year-adjusted SMR of 0.89 (95% CI, 0.64–1.20) for the 10 829 cohort members compared with the male general population of France.

Two studies were conducted in a cohort of firefighters certified between 1972 and 1999 in Florida, USA; one study assessed cancer incidence (Ma et al., 2006), and the other assessed mortality (Ma et al., 2005). The overall cohort size for both studies was 36 813, including 34 796 men and 2017 women. For cancer incidence, cases were identified through linkage with the Florida Cancer Data System (the Florida cancer registry), and age- and calendar-year adjusted SIRs were calculated separately for men and women with the population of Florida as the referent (Ma et al., 2006). Risks were reported only separately for each sex. [The ICD codes used were not provided; only the ICD-O-3 morphology codes for exclusion were included in the manuscript.] For men, the SIRs were 0.68 (95% CI, 0.54–0.85; 78 cases) for cancers of lymphatic and haematopoietic tissues overall, 1.09 (95% CI, 0.61–1.80; 15 cases) for NHL, 0.77 (95% CI, 0.38–1.38; 11 cases) for Hodgkin lymphoma, and 0.77 (95% CI, 0.47–1.19; 20 cases) for leukaemia. For women, the SIRs were 2.62 (95% CI, 0.96–5.70; 6 cases) for all cancers of lymphatic and haematopoietic tissues, 33.30 (95% CI, 0.44–185.00; 1 case) for NHL, and 6.25 (95% CI, 1.26–18.30; 3 cases) for Hodgkin lymphoma. There were no cases of leukaemia in women. [The Working Group noted that evaluation of specific types of cancer of lymphatic and haematopoietic tissues (NHL, leukaemia) was a strength of this study, but that subtypes within these categories (e.g. NHL subtypes) were not reported.] Mortality was assessed in the same cohort (Ma et al., 2005). With the general population of Florida as the referent, the SMR for men was 0.77 (95% CI, 0.56–1.05; 42 cases) for all lymphatic and haematopoietic malignancies (n = 42), 0.65 (95% CI, 0.13–1.90; 3 cases) for lymphosarcoma-reticulosarcoma, 0.23 (95% CI, 0.00–1.30; 1 case) for Hodgkin lymphoma, and 0.84 (95% CI, 0.46–1.42; 14 cases) for leukaemia. For women, the SMR for all lymphatic and haematopoietic malignancies was 1.25 (95% CI, 0.02–6.95; 1 case). There were no deaths among women for lymphosarcoma-reticulosarcoma, Hodgkin lymphoma, or leukaemia. [Codes used for classification were not provided for the mortality analysis but were based on ICD-9.] In men, the risks of lymphatic and haematopoietic malignancies and leukaemia on the basis of incidence and mortality were similar. In women, the risks of lymphatic and haematopoietic malignancies overall and NHL were elevated for cancer incidence, but not for mortality; however, the number of cases was small (6 cases of lymphatic and haematopoietic malignancies and 1 case of NHL), resulting in a wide confidence interval.

A study of 205 deaths among male firefighters in Honolulu, USA, reported a PMR for deaths from cancers of the lymphatic system [ICD-9, 200–209] of 0.95 (95% CI, 0.36–2.50; 4 deaths) (Grimes et al., 1991). [The Working Group noted the lack of standardization of PMRs by age and calendar year as an important limitation.]

A study in male firefighters employed for ≥ 3 years in Boston, USA, reported SMRs based on deaths from 1915 through 1975 (Musk et al., 1978). With the male general population of Massachusetts as the referent, the SMR for all lymphatic and haematopoietic malignancies [ICD-7, 200–205] among firefighters was 0.63 (95% CI, [0.41–0.94]; 22 deaths). [Confidence intervals were calculated by the Working Group.]

A study of 4221 male paid [career] and volunteer firefighters in New Zealand identified through a database evaluated both cancer incidence (1977–1996) and mortality (1977–1995) (Bates et al., 2001). [Although women were enumerated, only men were included in the analyses.] The SIR for myeloid leukaemia (ICD-9, 205) was 1.81 (95% CI, 0.5–4.6), adjusted for age and calendar year and with the male general population of New Zealand as the referent. There were four deaths from lymphatic or haematopoietic cancers (ICD-9, 200–208) with an SMR of 0.72 (95% CI, 0.2–1.8). [The inclusion of results for myeloid leukaemia was a strength. The reliance on the overall grouping of cancers of lymphatic and haematopoietic tissues for the mortality analysis was a limitation.]

A cohort of 2865 male firefighters in Melbourne, Australia, was followed from 1980 through 1989 for cancer incidence (Giles et al., 1993). Exposure assessment was based on employment records and included firefighters employed between 1917 and 1989. Age- and calendar period-adjusted SIRs were calculated with the general population of the state of Victoria as the referent. For NHL (ICD, 200, 202), the SIR was 1.85 (95% CI, 0.50–4.74; 4 cases). [The Working Group noted that the ICD revision was not specified in the publication.] No cases of leukaemia were diagnosed during this period.

A cohort of 990 male firefighters employed by the Western Australia Fire Brigade was followed from 1939 through 1978 for mortality (Eliopulos et al., 1984). Standardized PMRs were calculated for lymphohaematopoietic malignancies overall [ICD codes not given]. The age- and calendar year-standardized PMR was 1.88 (95% CI, 0.39–5.50; 3 deaths). [Although there were some analyses of duration and time of first employment, this was only applied to death overall and not specifically to cancers of lymphatic and haematopoietic tissues.]

(b) Population-based studies

Studies first described in Section 2.1.2(b) are described in less detail in the present section.

See Table S2.6 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

This section includes general population-based studies that evaluated the risks of cancer of lymphatic and haematopoietic tissues among people with the occupation of firefighter and includes four cohort studies derived from census or compensation claims data (Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020; Sritharan et al., 2022), two studies based on death certificate data (Burnett et al., 1994; Ma et al., 1998), and six event-only studies using US state cancer registry data (Sama et al., 1990; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Lee et al., 2020; McClure et al., 2021).

For the cohort studies, occupation as a firefighter was ascertained from census questionnaires, workers' compensation claims data, or death certificates. Comparisons were made with the rest of the enumerated group not employed as a firefighter. All except one study (Sritharan et al., 2022) included only men. The case–control [event-only] studies used patients with other types of cancer (or other causes of death) as controls.

The first census-based study was conducted in Spain (Zhao et al., 2020) and linked data from the 2001 census to the mortality registry to the end of 2011. Among 9 579 759 male cohort members aged 20–64 years and employed on the date of the 2001 census, there were 27 365 firefighters.

Among the firefighters, there were 11 deaths from lymphoma (ICD-10, C81–C83), including two from Hodgkin lymphoma (ICD-10, C81), and seven from leukaemia (ICD-10, C91–C95) for a total of 18 cases of cancers of lymphatic or haematopoietic tissue. Age-standardized MRRs were calculated using the European population as the standard. The MRR was 1.29 (95% CI, 0.69–2.34) for lymphoma, 1.41 (95% CI, 0.34–5.85) for Hodgkin lymphoma, and 0.90 (95% CI, 0.40–2.01) for leukaemia. [Although the overall study size was large, there were few cases of lymphoma and leukaemia among the firefighters because of the short follow-up and young age of the cohort members at the end of follow-up.]

Another census-based study was an analysis of the NOCCA pooled cohort based on census data from five Nordic countries (Denmark, 1970 census; Finland, 1970, 1980, and 1990 censuses; Iceland, 1981 census; Norway, 1970, 1970, and 1980 censuses; and Sweden, 1960, 1970, 1980, and 1990 censuses) that evaluated occupation as a firefighter (Pukkala et al., 2014). Among 15 million respondents to these censuses, 16 422 male firefighters were identified. Overall among those employed as firefighters, there were 82 cases of NHL (ICD-10, C82–C85, C96), 41 cases of multiple myeloma (ICD-10, C90), and 56 cases of leukaemia (ICD-10, C91–C95), including 21 cases of acute myeloid leukaemia. Analyses were conducted by country, with the country-specific rates for the male population used as the referent, by age at follow-up, and by 5-year category of calendar period of follow-up (1961–2005). The overall (all countries combined) SIR for NHL was 1.04 (95% CI, 0.83–1.29), for multiple myeloma it was 1.13 (95% CI, 0.81–1.53), and for leukaemia it was 0.94 (95% CI, 0.71–1.22). Within leukaemia subtypes, the SIR for acute myeloid leukaemia was 1.27 (95% CI, 0.79–1.94). The risk of multiple myeloma was elevated in those diagnosed at age ≥ 70 years, with an SIR of 1.69 (95% CI, 1.08–2.51). Other analyses stratified by country, age, and calendar time of follow-up did not reveal meaningful differences. [The Working Group noted that the large size of the cohort allowed for the evaluation of specific types of cancer of lymphatic and haematopoietic tissues; however, some strata were still limited by small numbers.]

Sritharan et al. (2022) evaluated the cancer experience of firefighters identified from the Occupational Disease Surveillance System (ODSS), a database created from workers' injury and disease claims in Ontario, Canada. The cohort comprising 2 368 226 workers, including 13 642 firefighters and 22 595 police, was linked to the Ontario Cancer Registry to identify cancers diagnosed from 1983 to 2020. Hazard ratios were calculated comparing firefighters to all other workers in the full cohort, as well as to the police identified in the cohort, and were adjusted for age at start of follow-up, birth year, and sex. The hazard ratio for firefighters compared with all other workers was 1.35 (95% CI, 1.11–1.64; 104 cases) for NHL (ICD-10, C82), 1.27 (95% CI, 0.68–2.37; 10 cases) for Hodgkin lymphoma (ICD-10, C81), 1.18 (95% CI, 0.82–1.70; 29 cases) for myeloma (ICD-10, C90), and 1.35 (95% CI, 1.05–1.73; 64 cases) for leukaemia (ICD-10, C91). The hazard ratio for firefighters compared with police was 1.21 (95% CI, 0.92–1.58) for NHL, 1.33 (95% CI, 0.57–3.12) for Hodgkin lymphoma, 0.94 (95% CI, 0.57–1.53) for multiple myeloma, and 1.15 (95% CI, 0.81–1.62) for leukaemia. [The Working Group noted that results were attenuated when comparing the firefighters with the police rather than with the full worker cohort for NHL, multiple myeloma, and leukaemia, suggesting that selection bias or healthy-worker bias may have influenced the results for the full cohort or, alternatively, that these groups may have shared exposures.]

The CanCHEC study of more than 1.1 million people was created by linking the 1991 census to the Canadian Cancer Registry (Harris et al., 2018). This study, which identified 4535 male firefighters aged 25–74 who were employed at the time of the

census in 1991, included follow-up to the end of 2010. Using all other members of the cohort as the referent, hazard ratios were calculated for Hodgkin lymphoma (5 cases), multiple myeloma (10 cases), NHL (30 cases) and leukaemia (15 cases) for employment as a firefighter adjusted for age group, region, and education level. [Classification was based on ICD-O-3, but codes were not provided for individual cancer sites.] The hazard ratio for Hodgkin lymphoma was 2.89 (95% CI, 1.29–6.46), for multiple myeloma was 1.52 (95% CI, 0.82–2.84), for NHL was 1.00 (95% CI, 0.71–1.41) and for leukaemia was 0.93 (95% CI, 0.55–1.58).

Lee et al. (2020) used linkage between employment records of the Florida State Fire Marshal, USA, and the Florida cancer registry to study associations between firefighter employment and cancers of lymphatic and haematopoietic tissues. Controls were cancer patients diagnosed with any other type of cancer, and ORs were adjusted for age and year of diagnosis. Among 3760 male firefighters, there was no evidence of higher risk of cancers of the lymphatic or haematopoietic tissues. Associations were inverse for all sites (e.g. OR for NHL, 0.88; 95% CI, 0.75–1.03; 168 cases; OR for multiple myeloma, 0.80; 95% CI, 0.59–1.10; 40 cases; and OR for acute myeloid leukaemia, 0.63; 95% CI, 0.41–0.96; 21 cases). There was no clear evidence of heterogeneity of these associations by stage (early versus late stage) or age at cancer diagnosis (age < 50 years, or > 50 years), although sample size limited the ability to assess this for most cancers of lymphatic or haematopoietic tissues other than NHL. Among 168 female firefighters, risk appeared elevated for Hodgkin lymphoma (OR, 1.68; 95% CI, 0.62–4.56; < 10 cases), multiple myeloma (OR, 1.32; 95% CI, 0.33–5.32; < 10 cases), and chronic lymphocytic leukaemia (OR, 2.33; 95% CI, 0.58–9.41; < 10 cases), but inverse for myeloid leukaemia (OR, 0.51; 95% CI, 0.07–3.57; < 10 cases) [The Working Group noted the substantial imprecision of all estimates.] Risk of NHL in female firefighters was similar to that in female non-firefighters (OR, 0.98; 95% CI, 0.43–2.21; < 10 cases). [The Working Group noted that case sample size among female firefighters was particularly small (< 10 cases for all cancers of lymphatic and haematopoietic tissues).] A subsequent paper (McClure et al., 2019) compared the firefighter occupation information used in Lee et al. (2020) (from employment records of the Florida State Fire Marshal) with that in occupation records in the Florida cancer registry (an approach used by previous studies). In this analysis, McClure et al. (2019) found that of 3928 firefighters studied by Lee et al., only 679 (17%) had a firefighting-related occupation code in the Florida cancer registry and that this information was differentially distributed by sociodemographic and diagnosis characteristics. McClure et al. (2021) then compared occupation as a firefighter and risk of cancers of lymphatic and haematopoietic tissues using these two different occupation ascertainment approaches. Data were available from the Florida cancer registry for 1981–2014 and from the office of the Florida State Fire Marshal for 1972–2012. Results for leukaemia were similar using the two different occupation information sources but were conflicting for lymphoma (employment as defined by the Florida State Fire Marshal, OR, 0.86; 95% CI, 0.75–0.99; 200 cases; cancer-registry-defined employment, OR, 1.10; 95% CI, 0.90–1.34; 109 cases).

Tsai et al. (2015) conducted a registry–based study using the California Cancer Registry, USA, in 1988–2007. Patients with cancers of the pharynx, stomach, liver, and pancreas were considered as controls. Occupation as a firefighter was associated with increased risk of most cancers of lymphatic and haematopoietic tissue, including multiple myeloma (OR, 1.35; 95% CI, 1.00–1.82; 55 cases), NHL (OR, 1.22; 95% CI, 1.00–1.50; 183 cases) and leukaemia (OR, 1.32; 95% CI, 1.05–1.66; 122 cases), particularly acute myeloid leukaemia (OR, 1.44; 95% CI, 1.02–2.02; 42 cases). Most associations were stronger for

non-White individuals. Among non-White cancer patients, firefighters were two to three times as likely as non-firefighters to be diagnosed with NHL (OR, 2.17; 95% CI, 1.20–3.92; 24 cases), multiple myeloma (OR, 3.77; 95% CI, 1.91–7.44; 13 cases), or leukaemia (OR, 3.64; 95% CI, 1.96–6.74; 20 cases). Bates (2007) conducted a similar study with the California Cancer Registry, 1988–2003, but these data were included in the study conducted later by Tsai et al. (2015) with data from 1988–2007.

In a cancer registry-based study in Massachusetts, USA (1987–2003), Kang et al. (2008) calculated SMBORs (adjusted for age and smoking) for cancers of lymphatic and haematopoietic tissues in firefighters compared with two occupation groups: police and all other occupations. Control cancers were those in the Massachusetts registry other than the 25 "cancers of concern" for which at least two previous studies had reported an observed association with firefighting. Compared with male police officers, male firefighters appeared to have lower risk of leukaemia (SMBOR, 0.72; 95% CI, 0.43–1.20; 46 cases), NHL (0.77; 95% CI, 0.31–1.92; 13 cases), and multiple myeloma (SMBOR, 0.76; 95% CI, 0.39–1.48; 29 cases), but the estimates were quite imprecise. Compared with men in other occupations, male firefighters had a similar risk of leukaemia (SMBOR, 0.98; 95% CI, 0.69–1.39), NHL (SMBOR, 1.10, 0.58–2.09), and multiple myeloma (SMBOR, 0.92; 95% CI, 0.58–1.47). Risk of Hodgkin lymphoma appeared to be higher for firefighters than for police (SMBOR, 1.81; 95% CI, 0.72–4.53) or for other occupations (SMBOR, 1.56; 95% CI, 0.71–3.43), although based on only 8 cases. [The Working Group noted that the Kang et al. analyses controlled for smoking status and age. Smoking is a suspected or known risk factor for some but not all types of cancer of lymphatic and haematopoietic tissues, including some types of leukaemia, NHL, and myeloma. Etiological heterogeneity may play a role in null and/or inconsistent results in Kang and other studies.] Sama et al. (1990) conducted a similar cancer registry-based study in Massachusetts, USA, but covering an earlier time period (1982–1986) and controlling only for age. In the earlier study, occupation as a firefighter was associated with increased odds of NHL and leukaemia with either group as referent, but associations were stronger with police as the referent – SMBOR for NHL, 3.27 (95% CI, 1.19–8.98; 14 cases); and SMBOR for leukaemia: 2.67 (95% CI, 0.62–11.54; 6 cases). With other occupations as the referent, the SMBORs for occupation as a firefighter were 1.59 (95% CI, 0.89–2.84) for NHL and 1.12 (95% CI, 0.48–2.59) for leukaemia. [The Working Group noted that stronger associations were observed when firefighters were compared with police in Sama et al. (1990) but not in Kang et al. (2008). Differences included the time period covered and control for smoking in Kang et al. Differences in the distribution of NHL and leukaemia subtypes may also account for differences in findings. Random variation may also have played a role in this inconsistency because of small sample size for most cancers of lymphatic and haematopoietic tissues in both studies.]

Ma et al. (1998) conducted a study of employment as a firefighter and risk of cancers of lymphatic and haematopoietic tissues using occupation codes on male death certificates in 24 US states (1984–1993). Analyses controlled for age and time of death and were stratified by race. Controls were non-cancer causes of death. Among White men, positive associations for occupation as a firefighter were observed both for Hodgkin lymphoma (MOR, 2.4; 95% CI, 1.4–4.1; 13 cases) and for NHL (MOR, 1.4; 95% CI, 1.1–1.7; 76 cases). Smaller associations were observed for multiple myeloma (MOR, 1.1; 95% CI, 0.8–1.6; 28 cases) and leukaemia (MOR, 1.1; 95% CI, 0.8–1.4; 60 cases). Only two cases of cancer of lymphatic and haematopoietic tissues were reported among Black firefighters. [The Working Group noted that etiology as well as survival varies by subtype of cancer of lymphatic and haematopoietic tissues,

and these differences may limit the conclusions that can be drawn from mortality studies.]

Another US mortality surveillance study calculated PMRs for individual causes of death, overall and by age at death, in 27 US states (Burnett et al., 1994). There were 169 deaths from lymphatic and haematopoietic malignancies (PMR, 1.30; 95% CI, 1.11–1.51), of which 85 occurred before age 65 years (PMR, 1.61; 95% CI, 1.29–1.99). For NHL (ICD-9, 200–202), there were 66 deaths overall, resulting in a PMR of 1.32 (95% CI, 1.02–1.67), with 35 deaths under age 65 years (PMR, 1.61; 95% CI, 1.12–2.24). For multiple myeloma (ICD-9, 203), there were 34 deaths overall, of which 11 occurred under age 65 years, resulting in PMRs of 1.48 (95% CI, 1.02–2.07) and 1.36 (95% CI, 0.68–2.43), respectively. Finally, for leukaemia (ICD-9, 204–208), there were 61 deaths overall, of which 33 occurred under age 65 years, resulting in PMRs of 1.19 (95% CI, 0.91–1.53) and 1.71 (95% CI, 1.18–2.40), respectively. [The Working Group noted that point estimates for cancers of lymphatic and haematopoietic tissues were somewhat higher in this study than in others in this section; however, it was hard to evaluate the etiological relevance of these findings given the many limitations of event-only analyses.]

2.4 Cancers of the skin, thyroid, and brain

2.4.1 Studies reporting occupational characteristics of firefighters

Studies first described in Section 2.1.1 are described in less detail in the present section.

See Table 2.7.

The Working Group identified 23 occupational and population-based cohort studies that had investigated the relationship between occupational exposure as a firefighter and risk of skin, thyroid, and/or brain cancer (Feuer & Rosenman, 1986; Vena & Fiedler, 1987; Demers et al., 1992a, 1994; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Bates et al., 2001; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014; Glass et al., 2016a, b, 2017, 2019; Petersen et al., 2018b; Kullberg et al., 2018; Bigert et al., 2020; Colbeth et al., 2020a; Pinkerton et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a, b). One of these studies was from Asia, six were from Europe, fifteen were from North America, and five were from Oceania. Four of these studies were excluded because they represented earlier follow-up of included studies (Heyer et al., 1990; Beaumont et al., 1991; Baris et al., 2001) or covered similar data to that in an included study (Demers et al., 1992b).

A cohort study of cancer incidence among 33 416 male professional [career] emergency responders (of whom 29 438, or 88%, were firefighters) in the Republic of Korea provided information on the risk of cancers of the brain and thyroid (Ahn et al., 2012). Emergency responders had been employed between 1980 and 2007, and cancer incidence follow-up took place from 1996 through 2007. With the national male population as the referent, there was no evidence of an increased risk of brain cancer among firefighters, based on only four cases (SIR, 0.53; 95% CI, 0.14–1.36). The SIR for thyroid cancer among firefighters was null (SIR, 1.00; 95% CI, 0.60–1.56; 19 cases).

An incidence and mortality study in a cohort of 3881 male professional [career] firefighters from several departments in Norway provided information on the risk of cutaneous melanoma, non-melanoma skin cancer, brain and other central nervous system cancers, and thyroid cancer (Marjerrison et al., 2022a, b). The cohort included mostly full-time firefighters employed between 1950 and 2019, with past or present employment in positions entailing active firefighting duties. The follow-up period for both cancer incidence and mortality analyses was from 1960 through 2018. For those ever employed as a firefighter, the incidence (SIR,

Table 2.7 Cohort studies reporting occupational characteristics of firefighters and cancers of the skin, thyroid, and brain

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) Republic of Korea Enrolment, 1980–2007/follow-up, 1996–2007 Cohort	33 416 men employed as emergency responders for ≥ 1 mo in 1980–2007 with (29 438) and without (3978) firefighting experience and not deceased in 1995 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Brain and other CNS (ICD-10, C70–C72), incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include rural and municipal firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: no information on personal characteristics or confounders (except the firefighter cohort had a lower BMI and smoked less than the comparison population for the SIR analysis); follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	2	0.74 (0.08–2.66)		
			≥ 10 yr	2	0.42 (0.05–1.51)		
			Total	4	0.53 (0.14–1.36)		
		Brain and other CNS (ICD-10, C70–C72), incidence	SRR:				
			Non-firefighters	0	0 (NR)		
			Ever employed as a firefighter	4	NR		
		Thyroid, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	9	1.21 (0.55–2.29)		
			≥ 10 yr	10	0.86 (0.41–1.59)		
			Total	19	1.00 (0.60–1.56)		
		Thyroid, incidence	SRR:				
			Non-firefighters	1	1		
			Ever employed as a firefighter	19	2.17 (0.29–16.51)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Melanoma, incidence	SIR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions. May include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	47	1.30 (0.95–1.73)		
		Melanoma, incidence	Year of first employment (SIR):				
			Pre-1950	8	1.38 (0.59–2.71)		
			1950–1969	19	1.53 (0.92–2.38)		
			1970 or after	20	1.11 (0.68–1.72)		
		Melanoma, incidence	Time since first employment (SIR):				
			< 20 yr	9	1.33 (0.61–2.53)		
			20–39 yr	21	1.36 (0.84–2.08)		
			≥ 40 yr	17	1.21 (0.70–1.94)		
		Melanoma, incidence	Duration of employment (SIR):				
			< 10 yr	10	1.84 (0.88–3.38)		
			10–19 yr	5	0.85 (0.27–1.98)		
			20–29 yr	13	1.38 (0.73–2.35)		
			≥ 30 yr	19	1.23 (0.74–1.92)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, incidence	SIR:				
			Firefighters	35	0.99 (0.69–1.37)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, incidence	Year of first employment (SIR):				
			Pre-1950	9	0.72 (0.33–1.37)		
			1950–1969	17	1.10 (0.64–1.76)		
			1970 or after	9	1.20 (0.55–2.28)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022a) (cont.)		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, incidence	Time since first employment (SIR):			Age, calendar year	
			< 20 yr	3	2.14 (0.44–6.26)		
			20–39 yr	8	0.97 (0.42–1.96)		
			≥ 40 yr	24	0.93 (0.59–1.38)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, incidence	Duration of employment (SIR):				
			< 10 yr	3	1.02 (0.21–2.98)		
			10–19 yr	5	1.56 (0.51–3.63)		
			20–29 yr	7	0.83 (0.34–1.72)		
			≥ 30 yr	20	0.96 (0.58–1.48)		
Marjerrison et al. (2022b) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Melanoma, mortality	SMR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions. May include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	13	1.55 (0.83–2.65)		
		Melanoma, incidence	Period of follow-up (SIR):				
			1984 or before	5	1.25 (0.40–2.91)		
			1985–1994	11	2.09 (1.04–3.74)		
			1995 or after	31	1.15 (0.78–1.63)		
		Melanoma, mortality	Period of follow-up (SMR):				
			1984 or before	< 5	1.41 (0.17–5.08)		
			1985–1994	< 5	2.83 (0.77–7.25)		
			1995 or after	7	1.26 (0.51–2.60)		
		Melanoma, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	10	1.21 (0.58–2.22)		
			50–69 yr	24	1.42 (0.91–2.12)		
			≥ 70 yr	13	1.18 (0.63–2.01)		
		Melanoma, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–1.94)		
			50–69 yr	10	2.63 (1.26–4.84)		
			≥ 70 yr	< 5	0.99 (0.20–2.88)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, mortality	SMR:			Age, calendar year	
			Firefighters	< 5	0.95 (0.02–5.31)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	0.77 (0.09–2.77)		
			1985–1994	< 5	0.60 (0.12–1.77)		
			1995 or after	30	1.07 (0.73–1.53)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, mortality	Period of follow up (SMR):				
			1984 or before	0	0 (0.00–16.2)		
			1985–1994	0	0 (0.00–18.1)		
			1995 or after	< 5	1.43 (0.04–7.97)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	1.32 (0.16–4.78)		
			50–69 yr	10	1.02 (0.49–1.88)		
			≥ 70 yr	23	0.95 (0.60–1.43)		
		Non-melanoma skin cancer (ICD-10, C44) excluding BCC, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–103)		
			50–69 yr	0	0 (0.00–10.5)		
			≥ 70 yr	< 5	1.36 (0.03–7.58)		
		Brain and other CNS (ICD-10, C70–C72), incidence	SIR:				
			Firefighters	28	1.31 (0.87–1.09)		
		Brain and other CNS (ICD-10, C70–C72), mortality	SMR:				
			Firefighters	14	1.41 (0.77–2.37)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Thyroid, incidence	SIR:			Age, calendar year	
			Firefighters	6	1.45 (0.53–3.15)		
		Thyroid, mortality	SMR:				
			Firefighters	< 5	2.41 (0.29–8.70)		
		Thyroid, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	1.22 (0.03–6.78)		
			1985–1994	0	0 (0.00–5.05)		
			1995 or after	5	1.83 (0.59–4.27)		
		Thyroid, mortality	Period of follow-up (SMR):				
			1984 or before	< 5	4.60 (0.12–25.6)		
			1985–1994	0	0 (0.00–18.32)		
			1995 or after	< 5	2.22 (0.06–12.38)		
		Thyroid, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	0.75 (0.02–4.19)		
			50–69 yr	< 5	2.06 (0.56–5.27)		
			≥ 70 yr	< 5	1.14 (0.03–6.35)		
		Thyroid, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–48.5)		
			50–69 yr	< 5	2.83 (0.07–15.8)		
			≥ 70 yr	< 5	2.4 (0.06–13.4)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bigert et al. (2020) Sweden Enrolment 1960–1990/follow-up, 1961–2009 Cohort	8136 male firefighters identified from national censuses in 1960, 1970, 1980, and 1990 Exposure assessment method: questionnaire; ever employed and categorical duration of employment (years) as firefighter from census surveys	Melanoma, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. May include full-time, part-time, municipal, and rural firefighters. *Strengths*: near complete ascertainment of cancer incidence; long length of follow-up (mean, 28 yr); analyses stratified by calendar period of employment. *Limitations*: no data on job duties, employment type, or potential confounders (aside from age, sex, and calendar year); probable healthy-worker hire bias; potential non-differential misclassification of employment duration.
			Firefighters	69	1.22 (0.95–1.54)		
		Melanoma, incidence	Duration of employment (SIR):				
			1–9 yr	0	0 (0.00–2.30)		
			10–19 yr	17	1.24 (0.72–1.98)		
			20–29 yr	27	1.42 (0.94–2.07)		
			≥ 30 yr	25	1.11 (0.72–1.65)		
			Trend-test *P* value, 0.11				
		Melanoma, incidence	Time period (SIR):				
			1961–1975	5	1.56 (0.51–3.65)		
			1976–1990	14	1.10 (0.60–1.85)		
			1991–2009	50	1.23 (0.91–1.62)		
		Non-melanoma skin cancer, incidence	SIR:				
			Firefighters	101	1.48 (1.20–1.80)		
		Non-melanoma skin cancer, incidence	Duration of employment (SIR):				
			1–9 yr	0	0 (0.00–3.70)		
			10–19 yr	28	1.82 (1.21–2.62)		
			20–29 yr	35	1.56 (1.09–2.17)		
			≥ 30 yr	38	1.28 (0.91–1.76)		
			Trend-test *P* value, < 0.01				
		Non-melanoma skin cancer, incidence	Time period (SIR):				
			1961–1975	2	0.87 (0.11–3.16)		
			1976–1990	15	1.28 (0.71–2.11)		
			1991–2009	84	1.55 (1.23–1.92)		
		Brain and other CNS (ICD-10, C70–C72), incidence	SIR:				
			Firefighters	38	0.89 (0.63–1.23)		
		Brain, incidence (glioma)	SIR:				
			Firefighters	18	0.94 (0.56–1.48)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1958–2012 Cohort	1080 men who worked ≥ 1 yr as a firefighter in Stockholm between 1931 and 1983 Exposure assessment method: ever employed and categorical duration of employment (years) as an urban [municipal] firefighter from annual enrolment records	Melanoma, incidence	Follow-up period (SIR):			Birth year, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence; analyses of duration and era of employment. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year); lack of exposure assessment based on job tasks or fire responses.
			Full: 1958–2012	3	0.30 (0.06–0.88)		
			Former: 1958–1986	1	0.39 (0.01–2.18)		
			Extended: 1987–2012	2	0.27 (0.03–0.97)		
		Non-melanoma skin cancer, incidence	Follow-up period (SIR):				
			Full: 1958–2012	17	0.85 (0.49–1.35)		
			Former: 1958–1986	5	1.49 (0.48–3.48)		
			Extended: 1987–2012	12	0.72 (0.37–1.25)		
		Brain and other nervous system (ICD-7 193), incidence	Follow-up period (SIR):				
			Full: 1958–2012	8	1.16 (0.50–2.28)		
			Former: 1958–1986	6	1.68 (0.62–3.66)		
			Extended: 1987–2012	2	0.60 (0.07–2.15)		
Tornling et al. (1994) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1951–1986 (mortality), 1958–1986 (incidence) Cohort	1116 for mortality/1091 for incidence; male firefighters employed for ≥ 1 yr by the City of Stockholm between 1931 and 1983 identified from annual enrolment records	Brain, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Enhanced exposure assessment (but based on 10% sample of reports) to differentiate exposure based on number of fires fought accounting for job position, station, and year of exposure. Municipal firefighters.
			Firefighters	5	2.79 (0.91–6.51)		
		Brain, incidence	SIR:				
			Firefighters	5	1.37 (0.44–3.20)		
		Brain, mortality	Age (SMR):				
			< 50 yr	0	0 (0–9.88)		
			50–64 yr	2	2.62 (0.32–9.45)		
			≥ 65 yr	3	4.59 (0.95–13.41)		
		Brain, mortality	Duration of employment (SMR):				
			< 20 yr	0	0 (0–8.25)		
			20–30 yr	2	3.04 (0.37–10.97)		
			> 30 yr	3	[4.37 (0.90–12.78)]		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tornling et al. (1994) (cont.)	Exposure assessment method: ever firefighter and duration (years) of firefighting employment from annual enrolment records; number of fires fought ascertained from exposure index developed from fire reports	Brain, mortality	Latency (SMR):			Age, calendar period	*Strengths*: long follow-up period; near complete ascertainment of cancer incidence and mortality; assessed exposure to fire responses for some outcomes. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year); low number of cases.
			< 30 yr	0	0 (0–6.43)		
			30–40 yr	3	5.07 (1.05–14.81)		
			> 40 yr	2	3.20 (0.39–11.15)		
		Brain, mortality	No. of fires (SMR):				
			< 800	0	0 (0–6.11)		
			800–1000	1	2.62 (0.07–14.62)		
			> 1000	4	4.96 (1.35–12.70)		
Petersen et al. (2018a) Denmark Enrolment, 1964–2004/follow-up, 1968–2014 Cohort	9061 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born 2 April 1928 or later, employed before age 60 yr and 31 December 2004, no cancer diagnosis before employment as a firefighter, and a job title/function indicating actual firefighting exposure	Melanoma, incidence	Reference group (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; near-complete ascertainment of cancer incidence; use of three reference groups to evaluate healthy-worker bias; analyses by proxies of exposure including job task. *Limitations*: little information on potential confounders.
			Firefighters vs general population	70	1.24 (0.98–1.57)		
			Firefighters vs sample of employees	70	1.28 (1.01–1.61)		
			Firefighters vs military	70	1.05 (0.83–1.33)		
		Melanoma, incidence	Employment type (SIR):				
			Full-time	40	1.28 (0.94–1.74)		
			Part-time or volunteer	30	1.19 (0.83–1.70)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)	Exposure assessment method: ever employed and categorical duration of employment (years), as well as employment type, job title/function, and work history, ascertained from civil registration, pension, employer personnel, and trade union membership records	Melanoma, incidence	Era of first employment (SIR):			Age, calendar period	
			Pre-1970	25	1.42 (0.96–2.11)		
			1970–1994	32	1.07 (0.76–1.51)		
			1995 or after	13	1.43 (0.83–2.47)		
		Melanoma, incidence	Job function (SIR):				
			Regular	61	1.15 (0.90–1.48)		
			Specialized	9	2.44 (1.27–4.70)		
		Melanoma, incidence	Age at first employment (SIR):				
			< 25 yr	38	1.47 (1.07–2.02)		
			25–34 yr	15	0.77 (0.47–1.28)		
			≥ 35 yr	17	1.52 (0.95–2.45)		
		Melanoma, incidence	Duration of employment (SIR):				
			< 1 yr	13	1.07 (0.62–1.85)		
			≥ 1 yr	57	1.28 (0.99–1.66)		
			≥ 10 yr	43	1.19 (0.88–1.60)		
			≥ 20 yr	24	0.96 (0.64–1.43)		
		Other skin (ICD-10, C44, C46.0), incidence	Reference group (SIR):				
			Firefighters vs general population	318	1.00 (0.90–1.12)		
			Firefighters vs sample of employees	318	1.01 (0.90–1.12)		
			Firefighters vs military	318	0.86 (0.77–0.96)		
		Other skin (ICD-10, C44, C46.0), incidence	Employment type (SIR):				
			Full-time	180	0.96 (0.83–1.11)		
			Part-time or volunteer	138	1.07 (0.90–1.26)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Other skin (ICD-10, C44, C46.0), incidence	Era of first employment (SIR):			Age, calendar period	
			Pre-1970	126	0.97 (0.81–1.15)		
			1970–1994	159	1.04 (0.89–1.21)		
			1995 or after	33	0.98 (0.70–1.38)		
		Other skin (ICD-10, C44, C46.0), incidence	Job function (SIR):				
			Regular	287	0.97 (0.86–1.09)		
			Specialized	31	1.49 (1.04–2.11)		
		Other skin (ICD-10, C44, C46.0), incidence	Age at first employment (SIR):				
			< 25 yr	132	0.89 (0.75–1.05)		
			25–34 yr	117	1.18 (0.98–1.41)		
			≥ 35 yr	69	0.99 (0.78–1.26)		
		Other skin (ICD-10, C44, C46.0), incidence	Duration of employment (SIR):				
			< 1 yr	66	0.82 (0.65–1.05)		
			≥ 1 yr	252	1.06 (0.94–1.20)		
			≥ 10 yr	219	1.09 (0.96–1.25)		
			≥ 20 yr	159	1.08 (0.92–1.26)		
		Brain (ICD-10, C71, C75.1–C75.3, D33.0–D33.2, D43.0–D43.2, D35.2–D35.4, D44.3–D44.5), incidence	Reference group (SIR):				
			Firefighters vs general population	33	0.94 (0.67–1.33)		
			Firefighters vs sample of employees	33	0.87 (0.62–1.23)		
			Firefighters vs military	33	0.90 (0.64–1.26)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Other parts of CNS (ICD-10, C72, D33.3–D33.9, D43.3–D43.9), incidence	Reference group (SIR):			Age, calendar period	
			Firefighters vs general population	12	1.39 (0.79–2.45)		
			Firefighters vs sample of employees	12	1.47 (0.83–2.58)		
			Firefighters vs military	12	1.31 (0.74–2.30)		
		Thyroid, incidence	Reference group (SIR):				
			Firefighters vs general population	6	1.21 (0.54–2.69)		
			Firefighters vs sample of employees	6	1.18 (0.53–2.63)		
			Firefighters vs military,	6	1.05 (0.47–2.35)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Webber et al. (2021) USA 2001–2016 Cohort	10 786 FDNY, 8813 CFHS; FDNY and CFHS cohorts; male firefighters who were active on 11 September 2001; FDNY cohort included men who worked at the WTC site any time between 11 September 2001 and 25 July 2002; CFHS cohort included men who were actively employed on 11 September 2001 and assumed not to be working at the WTC site Exposure assessment method: presence at WTC site from employment records and duty rosters	Melanoma, incidence	Group (SIR, US reference rates):			Age, calendar year, race/ethnicity	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. Qualitative assessment based on presence at the WTC site, exposures complex and probably unique to 9/11 disaster. Municipal firefighters. *Strengths*: ascertainment of cancer incidence; comparison of two firefighter cohorts to evaluate bias. *Limitations*: medical surveillance bias; young age of cohort; relatively short length of follow-up.
			CFHS firefighters	70	1.39 (1.07–1.79)		
			FDNY WTC firefighters	96	1.59 (1.30–1.96)		
		Melanoma, incidence	SIR (2-yr adjustment for potential surveillance bias):				
			FDNY WTC firefighters	NR	1.59 (1.30–1.96)		
		Melanoma, incidence	Group (RR):			Age on 11 September 2001	
			Non-Hispanic White:				
			CFHS firefighters	NR	1		
			FDNY WTC firefighters	NR	1.12 (0.80–1.57)		
		Thyroid, incidence	Group (SIR, US reference rates):			Age, calendar year, race/ethnicity	
			CFHS firefighters	15	1.01 (0.61–1.67)		
			FDNY WTC firefighters	46	2.37 (1.78–3.17)		
		Thyroid, incidence	SIR (2-yr adjustment for potential surveillance bias):				
			FDNY WTC firefighters	46	2.01 (1.47–2.75)		
		Thyroid, incidence	Group (RR):			Age on 11 September 2001, race/ethnicity	
			CFHS firefighters	15	1		
			FDNY WTC firefighters	46	2.53 (1.37–4.70)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Webber et al. (2021) (cont.)		Thyroid, incidence	Group RR (2-yr adjustment for potential surveillance bias):			Age on 11 September 2001, race/ethnicity	
			CFHS firefighters	NR	1		
			FDNY WTC firefighters	NR	2.11 (1.14–3.90)		
Colbeth et al. (2020a) New York, USA 12 September 2001 through 2018 Cohort	14 987 male firefighters and emergency medical service personnel monitored through the Fire Department–WTC Health Program (arrived at the WTC disaster site between the morning of 11 September 2001 and 25 July 2002); reference group included members of the Rochester Epidemiology Project cohort Exposure assessment method: questionnaire; presence at WTC site from employment records and duty rosters	Thyroid, incidence	Group (RR):			Age	*Exposure assessment critique*: Good quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. Five ordinal categories of exposure intensity based on time of arrival at WTC site. Exposures complex and probably unique to 9/11 disaster. Urban [municipal] firefighters. *Strengths*: cohort was defined before exposure; apparently appropriate matching comparison population. *Limitations*: comparison group not from a fire department; misclassification of diagnosis; no information on size or stage of cancer.
			Rochester Epidemiology Project	99	1		
			FDNY WTC firefighters	72	2.3 (1.7–3.2)		
		Thyroid, incidence	Period (RR vs Rochester Epidemiology Project):				
			Early (to 31 December 2009)	NR	1.8 (1.1–3.0)		
			Late (1 January 2010 or later)	NR	2.5 (1.6–3.8)		
		Thyroid, incidence	Symptom type (RR vs Rochester Epidemiology Project):				
			Asymptomatic	53	3.1 (2.1–4.7)		
			Symptomatic	12	0.8 (0.4–1.5)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeig-Owens et al. (2011) New York City, USA Enrolment, 1996/follow-up, 1996–2008 Cohort	9853 male FDNY firefighters employed for ≥ 18 mo, were active firefighters on 1 January 1996, with no prior cancer, and, if alive on 12 September 2001, also had known WTC exposure status Exposure assessment method: questionnaire; WTC-exposed and unexposed firefighters from employment records and questionnaires	Melanoma, incidence	WTC-exposure status (SIR):			Age, race, ethnic origin, calendar year	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. WTC exposure self-reported using three methods. WTC site exposures complex and probably unique to 9/11 disaster. *Strengths*: evaluation of medical surveillance bias. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Non-exposed	15	0.95 (0.57–1.58)		
			Exposed	33	1.54 (1.08–2.18)		
			SIR ratio (exposed vs non-exposed)	NR	1.61 (0.87–2.99)		
		Thyroid, incidence	WTC-exposure status (SIR, 2-yr adjustment for potential surveillance bias):				
			Non-exposed	≤ 5	0.59 (0.15–2.36)		
			Exposed	12	2.17 (1.23–3.82)		
			SIR ratio (exposed vs non-exposed	NR	3.67 (0.82–16.42)		
Pinkerton et al. (2020) San Francisco, Chicago, and Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2016 Cohort	29 992 municipal career firefighters in the CFHS cohort employed by the fire departments of San Francisco, Chicago, or Philadelphia for ≥ 1 day between 1950 and 2009; exposure–response analyses limited to 19 287 male firefighters of known race hired in 1950 or later and employed for ≥ 1 yr	Skin (ICD-10, C43-C44, C46.0, C46.9), mortality	Fire department (SMR):			Gender, race, age, calendar period	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices; adjustment for HWSE. *Limitations*: healthy-worker selection bias in external comparison analyses; little information on potential confounders.
			San Francisco	18	1.21 (0.72–1.92)		
			Chicago	35	1.00 (0.70–1.39)		
			Philadelphia	25	1.02 (0.66–1.51)		
			Overall	78	1.05 (0.83–1.31)		
			Heterogeneity *P* value, 0.79				
		Skin (ICD-10, C43–C44, C46.0, C46.9), mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Fully adjusted RCS	48	0.83 (0.32–2.46)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)	Exposure assessment method: ever employed as a firefighter, and number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Skin (ICD-10, C43–C44, C46.0, C46.9), mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Fully adjusted RCS	39	1.01 (0.52–2.00)		
		Brain and other nervous system (ICD-10, C47, C70–C72), mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	20	1.21 (0.74–1.87)		
			Chicago	37	0.89 (0.63–1.23)		
			Philadelphia	29	1.01 (0.68–1.45)		
			Overall	86	0.99 (0.79–1.23)		
			Heterogeneity *P* value, 0.55				
		Brain and other nervous system (ICD-10, C47, C70–C72), mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Fully adjusted RCS	45	0.46 (0.18–1.38)		
		Brain and other nervous system (ICD-10, C47, C70–C72), mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):				
			Fully adjusted RCS	31	1.07 (0.50–2.38)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) Chicago, San Francisco and Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	29 993 (24 453 for incidence analyses) male and female career firefighters in the CFHS cohort employed for ≥ 1 day in Chicago, San Francisco, or Philadelphia fire departments between 1950 and 2009 Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Melanoma, incidence	SIR:			Gender, race, age, calendar period	*Exposure assessment critique*: Satisfactory quality. Minimum exposure is 1 day of work as a municipal firefighter. *Strengths*: long period of follow-up; ascertained incidence outcomes; included female firefighters. *Limitations*: healthy-worker hire bias in external comparisons; little information on potential confounders.
			All cancers	141	0.87 (0.73–1.03)		
		Melanoma, incidence	Fire department (SIR, all cancers):				
			San Francisco	56	1.89 (1.43–2.46)		
			Chicago	44	0.56 (0.41–0.76)		
			Philadelphia	41	0.75 (0.54–1.02)		
		Brain and other nervous system (ICD-10, C47, C70–C72), incidence	SIR:				
			All cancers	51	1.02 (0.76–1.34)		
			First primary cancer	48	1.06 (0.78–1.41)		
		Brain and other nervous system (ICD-10, C47, C70–C72), incidence	Fire department (SIR, all cancers):				
			San Francisco	17	1.95 (1.14–3.12)		
			Chicago	13	0.53 (0.28–0.91)		
			Philadelphia	21	1.25 (0.77–1.91)		
			Heterogeneity *P* value, 0.007				
		Brain and other nervous system (ICD-10, C47, C70–C72), incidence	Race, men (SIR, all cancers):			Age, calendar period	
			Caucasian [White]	49	1.05 (0.78–1.39)		
			Other	< 5	0.67 (0.08–2.42)		
		Brain and other nervous system (ICD-10, C47, C70–C72), incidence	Age (SIR, all cancers):			Gender, race, age, calendar period	
			17–64 yr	26	1.00 (0.65–1.46)		
			65 to ≥ 85 yr	25	1.04 (0.67–1.54)		
			Heterogeneity *P* value, 1.00				
		Thyroid and other endocrine glands, incidence	SIR:				
			All cancers	28	0.91 (0.60–1.31)		
		Thyroid and other endocrine glands, incidence	Fire department (SIR, all cancers):				
			San Francisco	< 5	0.72 (0.20–1.84)		
			Chicago	15	0.98 (0.55–1.61)		
			Philadelphia	9	0.91 (0.42–1.72)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Thyroid, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	25	0.87 (0.56–1.28)		
		Thyroid, incidence	Fire department (SIR, all cancers):				
			San Francisco	< 5	0.57 (0.12–1.68)		
			Chicago	13	0.90 (0.48–1.55)		
			Philadelphia	9	0.97 (0.44–1.85)		
Demers et al. (1994) Seattle and Tacoma, USA Enrolment, 1944–1979/follow-up, 1974–1989 Cohort	2447 male firefighters employed for ≥ 1 yr between 1944 and 1979, alive as of 1 January 1974 and known to be a resident of one of 13 counties in the catchment area of the tumour registry for ≥ 1 mo; reference group included 1878 local male police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration of employment (years) in direct firefighting positions from employment records	Melanoma, incidence	SIR (local county rates):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Duration (years) involved in direct firefighting (surrogate for fire smoke) was not measured equally in the two study populations. Municipal firefighters. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders.
			Firefighters	9	1.2 (0.6–2.3)		
		Melanoma, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	0	0 (0.0–2.6)		
			10–19 yr	4	2.3 (0.6–5.8)		
			20–29 yr	4	1.1 (0.3–2.7)		
			≥ 30 yr	1	2.4 (0.1–13)		
		Melanoma, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	2	1.3 (0.2–4.4)		
			20–29 yr	2	1.2 (0.1–4.3)		
			≥ 30 yr	5	1.2 (0.4–2.8)		
		Melanoma, incidence	IDR:				
			Local police	6	1		
			Firefighters	9	1.0 (0.4–1.8)		
		Brain, incidence	SIR (local county rates):				
			Firefighters	4	1.1 (0.3–2.9)		
		Brain, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	1	1.6 (0.0–8.8)		
			10–19 yr	0	0 (0.0–4.6)		
			20–29 yr	3	1.6 (0.3–4.6)		
			≥ 30 yr	0	0 (0.0–16)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		Brain, incidence	Years since first employment (SIR, local county rates):			Age, calendar period	
			< 20 yr	0	0 (0.0–7.1)		
			20–29 yr	0	0 (0.0–4.5)		
			≥ 30 yr	4	1.9 (0.5–4.9)		
		Brain, incidence	IDR:				
			Local police	2	1		
			Firefighters	4	1.4 (0.2–11)		
		Thyroid, incidence	SIR (local county rates):				
			Firefighters	1	0.8 (0.2–4.2)		
Demers et al. (1992a) Seattle and Tacoma, Washington; Portland, Oregon, USA Enrolment, 1944–1979/follow-up, 1945–1989 Cohort	4401 male firefighters employed for ≥ 1 yr between 1944 and 1979 in Seattle, Tacoma, or Portland, USA; reference group included 3676 local police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration (years) of exposure to fire combat from employment records	Skin (ICD-9, 172, 173), mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Duration (years) involved in fire combat (surrogate for fire smoke) was not measured equally in the three municipal firefighter populations. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders; ascertained mortality outcomes only.
			Firefighters	6	0.98 (0.36–2.13)		
		Skin (ICD-9, 172, 173), mortality	IDR:				
			Local police	4	1		
			Firefighters	6	1.12 (0.27–4.76)		
		Brain and other nervous system (ICD-9, 191, 192, 237.5–237.7, 239.6–239.7), mortality	SMR:				
			Firefighters	22	2.09 (1.31–3.17)		
		Brain and other nervous system (ICD-9, 191, 192, 237.5–237.7, 239.6–239.7), mortality	IDR:				
			Local police	8	1		
			Firefighters	22	1.88 (0.82–4.31)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1992a) (cont.)		Brain and other nervous system (ICD-9, 191, 192, 237.5–237.7, 239.6–239.7), mortality	Duration of exposed employment (SMR):			Age, calendar period	
			< 10 yr	5	2.57 (0.8–6.0)		
			10–19 yr	8	3.53 (1.5–7.0)		
			20–29 yr	6	1.24 (0.5–2.7)		
			≥ 30 yr	3	2.04 (0.4–5.9)		
		Brain and other nervous system (ICD-9, 191, 192, 237.5–237.7, 239.6–239.7), mortality	Years since first employment (SMR):				
			< 20 yr	6	2.45 (0.9–5.3)		
			20–29 yr	2	0.73 (0.1–2.6)		
			≥ 30 yr	14	2.63 (1.4–4.4)		
		Brain and other nervous system (ICD-9, 191, 192, 237.5–237.7, 239.6–239.7), mortality	Age at risk (SMR):				
			18–39 yr	5	3.75 (1.2–8.7)		
			40–64 yr	11	1.66 (0.8–3.0)		
			≥ 65 yr	6	2.34 (0.9–5.1)		
		Brain and other nervous system (ICD-9, 191, 192), mortality	SMR:				
			Firefighters	18	2.07 (1.23–3.28)		
		Brain and other nervous system (ICD-9, 191, 192), mortality	IDR:				
			Local police	8	1		
			Firefighters	18	1.63 (0.70–3.79)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena & Fiedler (1987) Buffalo, New York, USA 1950–1979 Cohort	1867 White male career firefighters employed by the City of Buffalo for ≥ 5 yr, with ≥ 1 yr as a firefighter Exposure assessment method: ever-employment, timing, and duration of employment from employment records	Brain and other CNS (ICD-8, 191, 192), mortality	Years worked as a firefighter (SMR):			Age, calendar period	*Exposure assessment critique*: Minimal quality. Only assessed ever-employment and duration of employment as a municipal firefighter. *Strengths*: long length of follow-up. *Limitations*: healthy-worker hire bias; little information on potential confounders or exposure to firefighting activities.
			1–9 yr	1	[3.33 (0.2–16.4)]		
			10–19 yr	2	[3.33 (0.6–11.0)]		
			20–29 yr	3	[3.75 (1.0–10.2)]		
			30–39 yr	0	0 (NR)		
			≥ 40 yr	0	0 (NR)		
			Total	6	2.36 (0.86–5.13)		
		Brain and other CNS (ICD-8, 191, 192), mortality	Calendar year of death (SMR):				
			1950–1959	3	[5.0 (1.3–13.6)]		
			1960–1969	0	0 (NR)		
			1970–1979	3	[2.73 (0.7–7.4)]		
		Brain and other CNS (ICD-8, 191, 192), mortality	Year of hire (SMR):				
			Pre-1930	1	[1.54 (0.1–7.6)]		
			1930–1939	0	0 (NR)		
			1940–1949	4	[4.94 (1.6–11.9)]		
			1950 or after	1	[1.61 (0.1–8.0)]		
		Brain and other CNS (ICD-8, 191, 192), mortality	Years of latency (SMR):				
			< 20 yr	3	[4.02 (1.1–11.7)]		
			20–29 yr	3	[4.58 (1.3–13.6)]		
			30–39 yr	0	0 (NR)		
			40–49 yr	0	0 (NR)		
			≥ 50 yr	0	0 (NR)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Feuer & Rosenman (1986) New Jersey, USA 1974–1980 Cohort	263 deceased White male firefighters in the New Jersey Police and Firemen Retirement System (firefighters vested with ≥ 10 yr of service, or firefighters who died while on payroll regardless of employment duration); one reference group included 567 White male police deaths Exposure assessment method: ever employed, and categorical duration of employment (years), as a career firefighter from retirement system records	Skin, mortality	Reference population (PMR):			Age and calendar period	*Exposure assessment critique*: Satisfactory quality. Assessment provides duration of employment categories. May include municipal and rural firefighters. *Strengths*: comparison with other uniformed service occupation. *Limitations*: PMR study design lacks event-free follow-up time; short observation period; little information on potential confounders; small number of cases.
			Firefighters vs US	4	[2.70 (0.86–6.52)]		
			Firefighters vs NJ	4	[1.90 (0.61–4.6)]		
			Firefighters vs White male NJ police	4	[1.35 (0.43–3.26)]		
		Skin, mortality	Duration of employment (PMR):				
			< 20 yr	0	0 (NR)		
			20–25 yr	1	[1.82 (0.09–8.98)]		
			> 25 yr	3	[3.88 (0.99–10.56)]		
		Skin, mortality	Latency (PMR):				
			< 22 yr	1	[1.15 (0.06–5.67)]		
			22–27 yr	1	[1.68 (0.08–8.29)]		
			> 27 yr	2	[3.14 (0.53–10.37)]		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aronson et al. (1994) Toronto, Canada 1950–1989 Cohort	5414 male firefighters employed for ≥ 6 mo at one of six fire departments in Metropolitan Toronto between 1950 and 1989 Exposure assessment method: ever employed and categorical duration of employment (years) as municipal firefighter from employment records	Melanoma, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Likely municipal firefighters. *Strengths*: long period of follow-up, analysis of employment duration. *Limitations*: healthy-worker hire bias; little information on confounders or exposure; ascertained mortality outcomes only.
			Any employment	2	0.73 (0.09–2.63)		
		Melanoma, mortality	Years since first exposure (SMR):				
			< 20 yr	1	0.95 (0.02–5.31)		
			20–29 yr	1	1.30 (0.03–7.24)		
			≥ 30 yr	0	0 (0–3.97)		
		Melanoma, mortality	Years of employment (SMR):				
			< 15 yr	1	1.10 (0.03–6.12)		
			15–29 yr	1	0.90 (0.02–5.02)		
			≥ 30 yr	0	0 (0–5.27)		
		Melanoma, mortality	Age (SMR):				
			< 60 yr	2	0.94 (0.11–3.41)		
			≥ 60 yr	0	0 (0–5.86)		
		Brain and other nervous system (ICD-9, 191, 192), mortality	SMR:				
			Any employment	14	2.01 (1.10–3.37)		
		Brain and other nervous system (ICD-9, 191, 192), mortality	Years since first exposure (SMR):				
			< 20 yr	6	2.83 (1.04–6.16)		
			20–29 yr	2	0.99 (0.12–3.56)		
			≥ 30 yr	6	2.12 (0.78–4.62)		
		Brain and other nervous system (ICD-9, 191, 192), mortality	Years of employment (SMR):				
			< 15 yr	5	2.62 (0.85–6.11)		
			15–29 yr	3	1.06 (0.22–3.10)		
			≥ 30 yr	5	2.29 (0.75–5.35)		
		Brain and other nervous system (ICD-9, 191, 192), mortality	Age (SMR):				
			< 60 yr	10	1.99 (0.95–3.66)		
			≥ 60 yr	4	2.04 (0.56–5.22)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) Edmonton and Calgary, Canada 1927–1987 Cohort	3328; all firefighters employed between 1927 and 1987 by either of the fire departments of Edmonton or Calgary Exposure assessment method: ever employed and categorical duration of employment (years) from employment records exposure index of years of employment weighted by time spent in proximity to fires based on job classification	Brain, mortality	SMR: Any employment	3	1.47 (0.30–4.29)	Age, calendar period	*Exposure assessment critique*: Good quality. Good approach to differentiate exposure between ranks. Municipal firefighters. *Strengths*: long length of follow-up; analyses by duration of employment and exposure index. *Limitations*: little information on potential confounders; ascertained mortality outcomes only; low number of cases for stratified analyses.
Glass et al. (2019) Australia Enrolment, varied by agency/follow-up, 1980–2011 (mortality); 1982–2010 (incidence) Cohort	39 644 female firefighters, both paid [career] (1682) and volunteer (37 962), from nine fire agencies in Australia Exposure assessment method: ever career or volunteer firefighter, ever attended an incident, tertiles of cumulative number of incidents and type of incidents attended from personnel records	Melanoma, incidence	SIR: All volunteer firefighters Volunteers who attended incidents	147 57	1.25 (1.05–1.46) 1.11 (0.84–1.44)	Age, calendar year	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents for volunteer firefighters. Included specific incident types, but early exposure was extrapolated from more recent data. Volunteers mainly rural. *Strengths*: study of female firefighters; includes predominantly rural firefighters; ascertained exposure to number and type of incidents.
		Melanoma, incidence	No. of incidents, all volunteers (RIR) [equivalent to rate ratios]: Zero incidents Tertile 1 Tertile 2 Tertile 3 Trend-test *P* value, 0.53	 61 20 18 17	 1 1.04 (0.63–1.73) 0.82 (0.48–1.38) 0.84 (0.49–1.44)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Melanoma, incidence	No. of fire incidents, all volunteers (RIR):			Age, calendar year	*Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			Zero incidents	66	1		
			Tertile 1	21	1.10 (0.67–1.80)		
			Tertile 2	13	0.68 (0.37–1.23)		
			Tertile 3	16	0.84 (0.48–1.45)		
			Trend-test *P* value, 0.42				
		Melanoma, incidence	No. of structure fire incidents, all volunteers (RIR):				
			Zero incidents	99	1		
			Tertile 1	5	0.53 (0.21–1.30)		
			Tertile 2	7	0.66 (0.31–1.43)		
			Tertile 3	5	0.47 (0.19–1.17)		
			Trend-test *P* value, 0.89				
		Melanoma, incidence	No. of landscape fire incidents, all volunteers (RIR):				
			Zero incidents	71	1		
			Tertile 1	18	1.11 (0.66–1.87)		
			Tertile 2	12	0.67 (0.36–1.23)		
			Tertile 3	15	0.83 (0.48–1.46)		
			Trend-test *P* value, 0.41				
		Melanoma, incidence	No. of vehicle fire incidents, all volunteers (RIR):				
			Zero incidents	97	1		
			Tertile 1	9	1.38 (0.69–2.75)		
			Tertile 2	5	0.72 (0.29–1.76)		
			Tertile 3	5	0.71 (0.29–1.75)		
			Trend-test *P* value, 0.24				

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Brain and other CNS (ICD-10, C70–C72), incidence	SIR:			Age, calendar year	
			All volunteer firefighters	15	1.00 (0.56–1.65)		
			Volunteers who attended incidents	6	0.95 (0.35–2.07)		
		Brain, incidence	SIR:				
			All volunteer firefighters	13	0.92 (0.49–1.57)		
			Volunteers who attended incidents	5	0.84 (0.27–1.97)		
		Thyroid and other endocrine (ICD-10, C73–C75), incidence	SIR:				
			All volunteer firefighters	41	1.00 (0.72–1.36)		
			Volunteers who attended incidents	15	0.81 (0.45–1.33)		
		Thyroid, incidence	SIR:				
			All volunteer firefighters	39	0.97 (0.69–1.33)		
			Volunteers who attended incidents	14	0.77 (0.42–1.29)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) Australia Enrolment, date varied by agency (1998–2000)/follow-up to 30 November 2011 (mortality) and 31 December 2010 (cancer incidence) Cohort	163 094 all male volunteer firefighters from five fire agencies enrolled on or after the date on which the agency's roll was complete and who had ever held an active firefighting role Exposure assessment method: ever volunteer firefighter, categorical volunteer duration (years) and era from service records; ever volunteer firefighter who attended an incident, tertiles of cumulative emergency incidents from contemporary incident data	Melanoma, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents. Included specific incident types, but early exposure was extrapolated from more recent data. Firefighters from rural or peri-urban areas. *Strengths*: includes predominantly rural firefighters; ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			All volunteers	912	1.00 (0.93–1.06)		
			Volunteers who attended incidents	590	0.98 (0.91–1.07)		
		Melanoma, incidence	Era of first service (SIR):				
			Pre-1970	168	0.80 (0.69–0.93)		
			1970–1994	381	1.00 (0.90–1.10)		
			1995 or after	363	1.12 (1.01–1.24)		
		Melanoma, incidence	Duration of service, all volunteers (RIR) [equivalent to rate ratios]:				
			> 3 mo to 10 yr	336	1		
			10–20 yr	194	1.04 (0.87–1.24)		
			≥ 20 yr	370	0.92 (0.78–1.08)		
			Trend-test *P* value, 0.29				
		Melanoma, incidence	Duration of service, volunteers who attended incidents (RIR):				
			> 3 mo to 10 yr	176	1		
			10–20 yr	134	1.12 (0.89–1.41)		
			≥ 20 yr	292	0.95 (0.77–1.16)		
			Trend-test *P* value, 0.52				
		Melanoma, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	558	1		
			Group 1	18	0.71 (0.45–1.14)		
			Group 2	14	1.20 (0.71–2.04)		
		Melanoma, incidence	No. of fire incidents attended by volunteers (RIR):				
			Baseline	559	1		
			Group 1	17	0.67 (0.41–1.08)		
			Group 2	14	1.42 (0.83–2.41)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Melanoma, incidence	No. of structure fire incidents attended by volunteers (RIR):			Age, calendar period	
			Baseline	570	1		
			Group 1	13	0.82 (0.47–1.42)		
			Group 2	7	0.92 (0.44–1.93)		
		Melanoma, incidence	No. of landscape fire incidents attended by volunteers (RIR):				
			Baseline	486	1		
			Group 1	80	0.95 (0.75–1.20)		
			Group 2	24	0.86 (0.57–1.29)		
		Melanoma, incidence	No. of vehicle fire incidents attended by volunteers (RIR):				
			Baseline	558	1		
			Group 1	23	0.85 (0.56–1.30)		
			Group 2	9	0.89 (0.46–1.72)		
		Brain and other CNS (ICD-10, C70–C72), incidence	SIR:				
			All volunteers	116	0.86 (0.71–1.04)		
			Volunteers who attended incidents	81	0.91 (0.73–1.14)		
		Brain and other CNS (ICD-10, C70–C72), incidence	Era of first service (SIR):				
			Pre-1970	25	0.86 (0.56–1.27)		
			1970–1994	34	0.61 (0.42–0.85)		
			1995 or after	57	1.16 (0.88–1.50)		
		Brain, incidence	SIR:				
			All volunteers	114	0.88 (0.73–1.06)		
			Volunteers who attended incidents	80	0.94 (0.74–1.17)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Thyroid and other endocrine (ICD-10, C73–C75), incidence	SIR:			Age, calendar period	
			All volunteers	62	0.81 (0.62–1.04)		
			Volunteers who attended incidents	33	0.65 (0.45–0.92)		
		Thyroid and other endocrine (ICD-10, C73–C75), incidence	Era of first service (SIR):				
			Pre-1970	10	0.85 (0.41–1.57)		
			1970–1994	21	0.64 (0.40–0.98)		
			1995 or after	31	0.98 (0.66–1.39)		
		Thyroid, incidence	SIR:				
			All volunteers	58	0.83 (0.63–1.07)		
			Volunteers who attended incidents	30	0.64 (0.43–0.92)		
Glass et al. (2016a) Australia Enrolment, 1976–2003/follow-up, 1976–2011 (mortality), 1982–2010 (incidence, except two states, 2009) Cohort	30 057 full-time (17 394) or part-time (12 663) paid male firefighters employed at one of eight Australian fire agencies for ≥ 3 mo from start of personnel records (1976–2003, depending on agency)	Melanoma, incidence	Firefighter status (SIR):			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents, including specific incident types. Included specific incident types, but early exposure was extrapolated from more recent data. Municipal firefighters. *Strengths*: internal analysis by exposure to number and type of incidents; ascertained cancer incidence. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Full-time	209	1.45 (1.26–1.66)		
			Part-time	89	1.43 (1.15–1.76)		
			All	298	1.44 (1.28–1.62)		
		Melanoma, incidence	Duration of employment, full-time firefighters (RIR) [equivalent to rate ratios]:				
			> 3 mo to 10 yr	35	1		
			10–20 yr	50	1.26 (0.80–2.00)		
			≥ 20 yr	122	1.11 (0.68–1.81)		
			Trend-test *P* value, 0.79				
		Melanoma, incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	36	1		
			10–20 yr	15	0.88 (0.46–1.69)		
			≥ 20 yr	36	1.64 (0.83–3.23)		
			Trend-test *P* value, 0.18				

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)	Exposure assessment method: employed as a part- or full-time firefighter for ≥ 3 mo, categorical employment duration (years) and era from employment records; tertiles of cumulative emergency incidents and type of incident attended from contemporary incident data	Melanoma, incidence	Duration of employment (RIR):			Age, calendar period	
			> 3 mo to 10 yr	71	1		
			10–20 yr	65	1.14 (0.80–1.64)		
			≥ 20 yr	158	1.23 (0.84–1.80)		
			Trend-test *P* value, 0.29				
		Melanoma, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	26	1		
			Tertile 2	36	1.37 (0.82–2.27)		
			Tertile 3	31	0.82 (0.48–1.40)		
			Trend-test *P* value, 0.40				
		Melanoma, incidence	No. of fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	24	1		
			Tertile 2	36	1.55 (0.92–2.60)		
			Tertile 3	33	0.92 (0.54–1.59)		
			Trend-test *P* value, 0.68				
		Melanoma, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	30	1		
			Tertile 2	29	0.98 (0.59–1.64)		
			Tertile 3	34	0.80 (0.48–1.33)		
			Trend-test *P* value, 0.38				
		Melanoma, incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	24	1		
			Tertile 2	40	1.62 (0.97–2.70)		
			Tertile 3	29	0.86 (0.50–1.50)		
			Trend-test *P* value, 0.50				

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Melanoma, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	26	1		
			Tertile 2	38	1.56 (0.94–2.58)		
			Tertile 3	29	0.81 (0.47–1.39)		
			Trend-test *P* value, 0.39				
		Melanoma, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	35	1.33 (0.93–1.85)		
			10–20 yr	50	1.50 (1.12–1.98)		
			≥ 20 yr	122	1.46 (1.22–1.75)		
		Melanoma, incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	36	1.34 (0.94–1.86)		
			10–20 yr	15	1.01 (0.56–1.66)		
			≥ 20 yr	36	1.78 (1.25–2.46)		
		Melanoma, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	75	1.58 (1.24–1.98)		
			1970–1994	108	1.35 (1.10–1.63)		
			1995 or after	26	1.58 (1.03–2.31)		
		Melanoma, incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	18	2.32 (1.38–3.67)		
			1970–1994	45	1.23 (0.90–1.65)		
			1995 or after	26	1.43 (0.94–2.10)		
		Melanoma, incidence	No. of incidents attended by part-time firefighters (RIR):				
			Tertile 1	9	1		
			Tertile 2	7	0.64 (0.23–1.73)		
			Tertile 3	14	0.90 (0.35–2.26)		
			Trend-test *P* value, 0.89				

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Melanoma, incidence	No. of fire incidents attended by part-time firefighters (RIR):			Age, calendar period	
			Tertile 1	9	1		
			Tertile 2	9	0.80 (0.31–2.03)		
			Tertile 3	12	0.75 (0.29–1.92)		
			Trend-test *P* value, 0.55				
		Melanoma, incidence	No. of structure fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	10	1		
			Tertile 2	7	0.58 (0.22–1.53)		
			Tertile 3	13	0.71 (0.28–1.77)		
			Trend-test *P* value, 0.49				
		Melanoma, incidence	No. of landscape fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	10	1		
			Tertile 2	7	0.58 (0.22–1.53)		
			Tertile 3	13	0.76 (0.31–1.85)		
			Trend-test *P* value, 0.59				
		Melanoma, incidence	No. of vehicle fire incidents attended by part-time firefighters (RIR):				
			Tertile 1	9	1		
			Tertile 2	9	0.93 (0.37–2.34)		
			Tertile 3	12	0.85 (0.34–2.11)		
			Trend-test *P* value, 0.72				
		Brain and other CNS (ICD-10, C70–C72), incidence	Firefighter status (SIR):				
			Full-time	17	0.78 (0.45–1.24)		
			Part-time	13	1.37 (0.73–2.35)		
			All	30	0.96 (0.65–1.37)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Brain and other CNS (ICD-10, C70–C72), incidence	Duration of employment, full-time firefighters (SIR):			Age, calendar period	
			> 3 mo to 10 yr	3	0.71 (0.15–2.08)		
			10–20 yr	4	0.81 (0.22–2.07)		
			≥ 20 yr	10	0.80 (0.38–1.47)		
		Brain and other CNS (ICD-10, C70–C72), incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	4	0.94 (0.26–2.41)		
			10–20 yr	3	1.37 (0.28–4.00)		
			≥ 20 yr	6	2.02 (0.74–4.40)		
		Brain and other CNS (ICD-10, C70–C72), incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	6	0.82 (0.30–1.79)		
			1970–1994	8	0.67 (0.29–1.32)		
			1995 or after	3	1.12 (0.23–3.27)		
		Brain and other CNS (ICD-10, C70–C72), incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	5	4.40 (1.43–10.26)		
			1970–1994	6	1.11 (0.41–2.42)		
			1995 or after	2	0.68 (0.08–2.46)		
		Brain, incidence	Firefighter status (SIR):				
			Full-time	16	0.76 (0.44–1.24)		
			Part-time	12	1.32 (0.68–2.31)		
			All	28	0.93 (0.62–1.35)		
		Brain, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	3	0.75 (0.15–2.19)		
			10–20 yr	4	0.85 (0.23–2.18)		
			≥ 20 yr	9	0.75 (0.34–1.42)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Brain, incidence	Duration of employment, part-time firefighters (SIR):			Age, calendar period	
			> 3 mo to 10 yr	3	0.75 (0.15–2.18)		
			10–20 yr	3	1.43 (0.29–4.18)		
			≥ 20 yr	6	2.09 (0.77–4.55)		
		Brain, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	5	0.71 (0.23–1.65)		
			1970–1994	8	0.70 (0.30–1.39)		
			1995 or after	3	1.18 (0.24–3.44)		
		Brain, incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	5	4.54 (1.47–10.59)		
			1970–1994	6	1.16 (0.43–2.53)		
			1995 or after	1	0.36 (0.01–2.00)		
		Thyroid and other endocrine (ICD-10, C73–C75), incidence	Firefighter status (SIR):				
			Full-time	13	1.08 (0.58–1.85)		
			Part-time	7	1.16 (0.47–2.39)		
			All	20	1.11 (0.68–1.71)		
		Thyroid and other endocrine (ICD-10, C73–C75), incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	3	1.02 (0.21–2.98)		
			10–20 yr	6	1.87 (0.69–4.06)		
			≥ 20 yr	4	0.70 (0.19–1.78)		
		Thyroid and other endocrine (ICD-10, C73–C75), incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	2	0.62 (0.07–2.22)		
			10–20 yr	2	1.44 (0.17–5.20)		
			≥ 20 yr	3	2.24 (0.46–6.54)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Thyroid and other endocrine (ICD-10, C73–C75), incidence	Era of first employment, full-time firefighters (SIR):			Age, calendar period	
			Pre-1970	2	0.78 (0.09–2.83)		
			1970–1994	7	0.96 (0.38–1.97)		
			1995 or after	4	1.85 (0.50–4.72)		
		Thyroid and other endocrine (ICD-10, C73–C75), incidence	Era of first employment, part-time firefighters (SIR):				
			Pre-1970	3	7.02 (1.45–20.51)		
			1970–1994	4	1.24 (0.34–3.18)		
			1995 or after	0	0 (NR)		
		Thyroid, incidence	Firefighter status (SIR):				
			Full-time	13	1.18 (0.63–2.01)		
			Part-time	7	1.26 (0.51–2.59)		
			All	20	1.20 (0.74–1.86)		
		Thyroid, incidence	Duration of employment, full-time firefighters (SIR):				
			> 3 mo to 10 yr	3	1.11 (0.23–3.25)		
			10–20 yr	6	2.03 (0.75–4.43)		
			≥ 20 yr	4	0.76 (0.21–1.94)		
		Thyroid, incidence	Duration of employment, part-time firefighters (SIR):				
			> 3 mo to 10 yr	2	0.67 (0.08–2.41)		
			10–20 yr	2	1.56 (0.19–5.62)		
			≥ 20 yr	3	2.44 (0.50–7.14)		
		Thyroid, incidence	Era of first employment, full-time firefighters (SIR):				
			Pre-1970	2	0.87 (0.11–3.15)		
			1970–1994	7	1.04 (0.42–2.14)		
			1995 or after	4	1.99 (0.54–5.08)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Thyroid, incidence	Era of first employment, part-time firefighters (SIR):			Age, calendar period	
			Pre-1970	3	7.78 (1.60–22.74)		
			1970–1994	4	1.35 (0.37–3.45)		
			1995 or after	0	0 (NR)		
Glass et al. (2016b) Victoria, Australia Enrolment, 1971–1999/follow-up, 1980–2011 (mortality), 1982–2012 (incidence) Cohort	614; all male (611) and female (3) employed and volunteer Country Fire Authority trainers and a group of paid [career] Country Fire Authority firefighters who trained at the Fiskville site from 1971 to 1999; all analyses limited to men as no deaths or cancers were observed among women Exposure assessment method: employed or volunteer firefighter trainers and career firefighters who trained at training facility for any period of time from human resource records, categorized into risk of low, medium, and high chronic exposure to smoke and other agents based on job assignment	Melanoma, incidence	Risk of chronic exposure and firefighter group (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Incorporated categorical level of exposure into assessment for each type of firefighter. Volunteers mainly rural, paid [career] firefighters were municipal. *Strengths*: included firefighter instructors with high potential exposure to smoke and other hazardous agents; assessed exposure based on job assignment. *Limitations*: low number of cases; young age at end of follow-up.
			Low	3	1.43 (0.29–4.18)		
			Medium	5	1.51 (0.49–3.52)		
			– Paid [career]	3	2.45 (0.50–7.15)		
			–Volunteer	2	0.96 (0.12–3.47)		
			–Volunteer with Fiskville start date	2	1.01 (0.12–3.66)		
			–With Fiskville HR start date	5	3.06 (1.00–7.15)		
			High	6	4.59 (1.68–9.99)		
			–With Fiskville HR start date	6	5.25 (1.93–11.4)		
		Brain and other CNS (ICD-10, C70–C72), incidence	Risk of chronic exposure and firefighter group (SIR):				
			Low	0	0 (NR)		
			Medium	4	5.74 (1.56–14.7)		
			–Paid [career]	2	7.59 (0.92–27.4)		
			–Volunteer	2	4.62 (0.56–16.67)		
			–Volunteer with Fiskville start date	0	0 (NR)		
			–With Fiskville HR start date	2	5.76 (0.70–20.8)		
			High	1	3.63 (0.09–20.3)		
			–With Fiskville HR start date	1	4.15 (0.11–23.1)		

Table 2.7 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bates et al. (2001) New Zealand Enrolment, 1977 through June 1995/ follow-up, 1977–1995 (mortality), 1977–1996 (incidence) Cohort	4305; the cohort comprised all male (4221) and female (84) firefighters (paid [career] and volunteer) employed as a career firefighter for ≥ 1 yr and who also worked as a career firefighter for ≥ 1 day between 1977 and 1995; all analyses limited to men due to small numbers of women Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Melanoma, incidence	Follow-up period (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job classification. May include urban [municipal] and rural firefighters. *Strengths*: ascertained both incidence and mortality outcomes. *Limitations*: little information on confounders; significant loss to follow-up; low number of cases in stratified analyses.
			1977–1996	23	1.26 (0.8–1.9)		
			1990–1996	15	1.49 (0.8–2.5)		
		Melanoma, incidence	Duration of paid service (SIR):				
			0–10 yr	7	1.72 (0.7–3.5)		
			11–20 yr	6	1.75 (0.6–3.8)		
			> 20 yr	6	1.67 (0.6–3.6)		
			Trend-test *P* value, 0.97				
		Melanoma, incidence	Duration of paid and volunteer service (SIR):				
			0–10 yr	4	1.58 (0.4–4.0)		
			11–20 yr	6	1.83 (0.7–4.0)		
			> 20 yr	9	1.70 (0.8–3.2)		
			Trend-test *P* value, 0.93				
		Melanoma, incidence	SMR:				
			Firefighters vs male New Zealand population	2	0.65 (0.1–2.4)		
		Brain, incidence	Follow-up period (SIR):				
			1977–1996	5	1.27 (0.4–3.0)		
			1990–1996	3	1.59 (0.3–4.6)		
		Brain, mortality	SMR:				
			Firefighters vs male New Zealand population	2	0.68 (0.1–2.4)		

9/11, World Trade Center disaster, 11 September 2001; BCC, basal cell carcinoma; BMI, body mass index; CFHS, Career Firefighter Health Study; CI, confidence interval; CNS, central nervous system; FDNY, Fire Department of the City of New York; HR, hazard ratio; HWSE, healthy-worker survivor effect; ICD, International Classification of Diseases; IDR, incidence density ratio; JEM, job-exposure matrix; LRT, likelihood ratio test; NJ, New Jersey; NR, not reported; PMR, proportionate mortality ratio; RCS, restricted cubic splines; RIR, relative incidence ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States; vs, versus; WTC, World Trade Center; yr, year.

1.30; 95% CI, 0.95–1.73; 47 cases) and mortality (SMR, 1.55; 95% CI, 0.83–2.65; 13 deaths) of cutaneous melanoma appeared higher than in the general male population of Norway. There was little evidence to suggest that the risk of non-melanoma skin cancer was higher than in the general population, whether based on incidence (SIR, 0.99; 95% CI, 0.69–1.37; 35 cases) or mortality (SMR, 0.95; 95% CI, 0.02–5.31; < 5 deaths). There was some evidence to suggest that the risk of cancer of the thyroid was raised when the general population was the referent, whether based on incidence (SIR, 1.45; 95% CI, 0.53–3.15; 6 cases) or mortality (SMR, 2.41; 95% CI, 0.29–8.70; < 5 deaths). Similarly, there was some evidence to suggest that the risk of brain and other central nervous system cancers was higher than in the general population, whether based on incidence (SIR, 1.31; 95% CI, 0.87–1.90; 28 cases) or mortality (SMR, 1.41; 95% CI, 0.77–2.37; 14 deaths). Separate stratified analyses were also conducted examining calendar period of first employment, duration of employment, time since first employment, period of follow-up, and age at diagnosis, although results for most of these were very imprecise. For melanoma, the SIR was raised for follow-up from 1985 through 1994, the SMR was raised for firefighters aged 50–69 years at diagnosis, and there was some evidence of an increased SIR regardless of year of first employment, years since first employment, and duration of employment. The estimate for non-melanoma skin cancer incidence increased from below unity to 1.20 with more recent year of first employment. There were no other findings of note in the stratified analyses.

A census-based cancer incidence study in a cohort of 8136 male firefighters in Sweden provided information on the risk of melanoma, non-melanoma skin cancer, and brain cancer (Bigert et al., 2020). Employment information was ascertained from national decennial censuses between 1960 and 1990. Cancer incidence data were ascertained from the Swedish Cancer Registry with follow-up from 1961 through 2009. The SIR for ever-employment as a firefighter was raised for non-melanoma skin cancer (SIR, 1.48; 95% CI, 1.20–1.80; 101 cases), with SIRs decreasing with increasing duration of employment ($P < 0.01$) and increasing for cancers diagnosed in more recent calendar periods (no results from test for trend were provided). The SIR for the most recent cancers (diagnosed 1991–2009) was 1.55 (95% CI, 1.23–1.92; 84 cases). The SIR for cutaneous melanoma appeared to be raised (SIR, 1.22; 95% CI, 0.95–1.54; 69 cases), and there was no apparent relation with duration of employment or calendar year of diagnosis. The SIR was not raised for cancer of the brain (SIR, 0.89; 95% CI, 0.63–1.23; 38 cases). Stratified results were not presented for brain cancer.

A cancer incidence study in a cohort of 1080 male firefighters in Stockholm, Sweden provided information on the risk of melanoma, non-melanoma skin cancer, and brain cancer (Kullberg et al., 2018). Firefighters were identified through annual enrolment records from 15 fire stations and had worked for ≥ 1 year between 1931 and 1983. This was an update to a previous study (Tornling et al., 1994) and added 26 years of cancer incidence follow-up from 1958 through 2012 in the Swedish Cancer Registry. The overall SIR for melanoma diagnosed any time during the follow-up period (1958–2012) was below one (SIR, 0.30; 95% CI, 0.06–0.88; 3 cases), and the overall SIR was not raised for non-melanoma skin cancer (SIR, 0.85; 95% CI, 0.49–1.35; 17 cases). The SIR for brain cancer was modestly elevated (SIR, 1.16; 95% CI, 0.50–2.28; 8 cases), although the confidence interval was wide.

The earlier study of the same cohort also investigated both cancer incidence and mortality in a slightly larger population of 1116 male firefighters with mortality follow-up from 1951 through 1986 (Tornling et al., 1994) and provided information on the risk of brain cancer. Exposure to fire events was assessed using reports of fires fought by the Stockholm fire brigade between

1933 and 1983. With male regional mortality rates as the referent, the overall SMR for brain cancer mortality appeared raised (SMR, 2.79; 95% CI, 0.91–6.51; 5 cases). In stratified analyses, the SMRs for brain cancer were statistically imprecise but appeared raised in firefighters aged ≥ 65 years (SMR, 4.59; 95% CI, 0.95–13.41; 3 cases), 30–40 years after first exposure (SMR, 5.07; 95% CI, 1.05–14.81; 3 cases), and in firefighters who had attended more than 1000 fires (SMR, 4.96; 95% CI, 1.35–12.70; 4 cases). SMRs were not raised for different latencies or fewer fires attended, or within other strata of age or years of employment. SMRs appeared to increase with increasing age, years of employment, and number of fires attended. Stratified results for brain cancer incidence outcomes were similar to those for mortality. [The Working Group noted that the exposure assessment method was a strength and that the number of deaths from brain cancer was small.]

A cancer incidence study in a cohort of 9061 male full-time, part-time, and volunteer firefighters provided information on the risk of melanoma, brain cancer, and thyroid cancer (Petersen et al., 2018a). Cohort members had been employed as firefighters at some time between 1964 and 2004, and cancer incidence follow-up was conducted in the Danish Cancer Registry from 1968 through 2014. External comparisons were made with the general male population, a random sample of the employed Danish population, and the Danish military. The SIR for melanoma was raised in firefighters compared with a sample of Danish employees (SIR, 1.28; 95% CI, 1.01–1.61; 70 cases), and with the general population (SIR, 1.24; 95% CI, 0.98–1.57), but not when compared with the military (SIR, 1.05; 95% CI, 0.83–1.33). An excess of melanoma was also observed among those with a "specialized" job function who were presumed to have a heavier exposure to smoke (SIR, 2.44; 95% CI, 1.27–4.70; 9 cases) and in those who were aged < 25 years at first employment (SIR, 1.47; 95% CI, 1.07–2.02; 38 cases) compared with the general population. The SIR was also raised for non-melanoma skin cancer in those with a specialized job function (SIR, 1.49; 95% CI, 1.04–2.11; 31 cases) compared with the general population. Otherwise, there was no apparent relation between employment type, era of first employment, age at first employment, or employment duration and the incidence of melanoma or non-melanoma skin cancer. The SIR estimates for thyroid cancer were modestly raised when using all three comparison populations (SIRs ranged from 1.05 to 1.21) but were imprecise. The overall SIR estimates for brain cancer were below one for all three comparison populations. Stratified analyses were not available for thyroid cancer or brain cancer.

[The investigation of cancer mortality in the same cohort by Petersen et al. (2018b) did not report results for brain or thyroid cancer. Skin cancer outcomes were combined with those for bone cancer in analyses, making these results uninformative for the risk of skin cancer alone.]

A cancer incidence study in a cohort of 10 786 male firefighters from the FDNY exposed to the WTC disaster site and 8813 firefighters in the CFHS, which included firefighters from Philadelphia, Chicago, and San Francisco fire departments, provided information on the risk of melanoma and cancer of the thyroid (Webber et al., 2021). Cancer incidence follow-up was conducted using several state cancer registries selected on the basis of residential history information and began on 11 September 2001 and ended in 2016. With the US male general population as the referent, overall SIRs for melanoma were increased in both the FDNY (SIR, 1.59; 95% CI, 1.30–1.96; 96 cases) and CFHS (SIR, 1.39; 95% CI, 1.07–1.79; 70 cases) cohorts. After adjustment for medical surveillance bias with the addition of a 2-year lag to the diagnosis date of certain cases, the SIR for melanoma for the FDNY cohort was unchanged. Among non-Hispanic White men, the risk of melanoma appeared modestly increased in FDNY firefighters compared with

CFHS firefighters in internal comparisons, but the estimate was relatively imprecise (RR, 1.12; 95% CI, 0.80–1.57). With the US male general population as the referent, SIRs for thyroid cancer were increased for the FDNY cohort (SIR, 2.37; 95% CI, 1.78–3.17; 46 cases) but appeared to be the same for the CFHS cohort (SIR, 1.01; 95% CI, 0.61–1.67; 15 cases). After applying the adjustment for medical surveillance bias, the SIR for thyroid cancer for the FDNY cohort remained high (SIR, 2.01; 95% CI, 1.47–2.75). In internal comparison analyses, the risk of thyroid cancer was increased in FDNY firefighters compared with CFHS firefighters (RR, 2.53; 95% CI, 1.37–4.70). This was also the case after adjustment for surveillance bias (RR, 2.11; 95% CI, 1.14–3.90). [The Working Group noted that this study was limited by a possible incompletely controlled effect of greater medical surveillance bias in FDNY firefighters than in CFHS firefighters or the US general population. This bias may be particularly influential on results for thyroid cancer.]

A study of 14 987 male firefighters employed by FDNY and who had worked on the WTC disaster site between September 2001 and July 2002 provided information on the risk of thyroid cancer (Colbeth et al., 2020a). Age-adjusted relative rates [rate ratios or RRs] were calculated using a reference group that the authors described as "demographically similar" (all male residents of Olmsted County, Minnesota, from 1 January 2000 to 31 December 2018). The age-adjusted RRs were higher among firefighters overall (RR, 2.3; 95% CI, 1.7–3.2; 72 cases) and in subgroups for cancers detected in early (RR for 2001–2009, 1.8; 95% CI, 1.1–3.0) or late (RR for 2010–2018, 2.5; 95% CI, 1.6–3.8) calendar periods, and for cases that were asymptomatic (RR, 3.1; 95% CI, 2.1–4.7; 53 cases). However, the rate did not appear to be raised for symptomatic cancers (RR, 0.8; 95% CI, 0.4–1.5; 12 cases). [The Working Group concurred with the authors' conclusion that the thyroid cancer excess was attributable to asymptomatic cancers and that this was probably because of increased medical surveillance in the firefighter group compared with the reference group.]

An earlier cancer incidence study of an overlapping cohort of 9853 male FDNY firefighters reported risks among WTC-exposed and unexposed firefighters for additional cancer sites, including melanoma and thyroid cancer (Zeig-Owens et al., 2011). Cancer incidence follow-up was conducted in state cancer registries from 1996 through 2008. With the US male general population as the referent, the SIR for melanoma was raised when restricted to exposed person-time in firefighters (SIR, 1.54; 95% CI, 1.08–2.18; 33 cases) but not when restricted to unexposed person-time in firefighters (SIR, 0.95; 95% CI, 0.57–1.58; 15 cases). For thyroid cancer, the SIR (corrected for medical surveillance bias) was raised when restricted to exposed person-time in firefighters (SIR, 2.17; 95% CI, 1.23–3.82; 12 cases) but not when restricted to unexposed person-time in firefighters (SIR, 0.59; 95% CI, 0.15–2.36; ≤ 5 cases). [The Working Group noted that the increased risk of thyroid cancer and melanoma may be influenced by medical surveillance bias in this cohort.]

A mortality study was carried out in a cohort of 29 992 male and female municipal career firefighters in the USA. The CFHS from San Francisco, Chicago, and Philadelphia provided information on the risk of cancers of the prostate, kidney, and urinary bladder (Pinkerton et al., 2020). Mortality follow-up was conducted from 1950 through 2016. With the US general population as the referent, the SMRs among firefighters for melanoma and other skin cancers (SMR, 1.05; 95% CI, 0.83–1.31; 78 cases) and for brain cancer (SMR, 0.99; 95% CI, 0.79–1.23; 86 cases) were not elevated overall. Results stratified by municipal fire department were similar and likewise not elevated. In internal regression analyses, there was also no suggestion of an association between the number of exposed days or fire-runs and either cancer site (fire-hours were not evaluated

because of small numbers). [The Working Group noted that the use of mortality outcomes was a limitation for the assessment of melanoma risk because of potential outcome misclassification.]

An additional study of the CFHS cohort investigated cancer incidence among 29 993 municipal career firefighters and reported external and internal comparison analyses with follow-up to the end of 2009 (Daniels et al., 2014). The methods were similar to those used in the study by Pinkerton et al. (2020). Cancer incidence follow-up was conducted in state cancer registries relevant to each fire department to the end of 2009, with start years varying between 1985 and 1988. Residential history information was used to select state registries for follow-up. With the US general population as the referent, the overall SIR among firefighters for cancers of the brain and other nervous system tissues (including all primary cancers) was not elevated (SIR, 1.02; 95% CI, 0.76–1.34; 51 cases). There was strong evidence of heterogeneity in the results for different fire departments for brain cancer incidence (P = 0.007), with the San Francisco Fire Department subcohort having an elevated rate (SIR, 1.95; 95% CI, 1.14–3.12; 17 cases) and the Chicago Fire Department subcohort having a reduced rate (SIR, 0.53; 95% CI, 0.28–0.91; 13 cases). There was no suggestion of heterogeneity by age (P = 1.0). For thyroid cancer, the overall SIR among firefighters was not elevated (SIR, 0.87; 95% CI, 0.56–1.28; 25 cases). Similar results were seen for the individual fire department subcohorts and for the expanded case definition of "thyroid and other endocrine glands". For melanoma, the overall SIR among firefighters was not elevated (SIR, 0.87; 95% CI, 0.73–1.03; 141 cases). There appeared to be marked heterogeneity between the results for melanoma for different fire departments (no formal test results were available), with the San Francisco Fire Department having an elevated rate (SIR, 1.89; 95% CI, 1.43–2.46; 56 cases) and the Chicago Fire Department having a reduced rate (SIR, 0.56; 95% CI, 0.41–0.76; 44 cases). [The Working Group noted that a strength of this study was that results for melanoma were standardized by race to reduce confounding by skin tone.]

A cancer incidence study in a cohort of 2447 male municipal firefighters from Seattle and Tacoma, USA, provided information on the risk of melanoma, and cancers of the brain and thyroid, in comparison to that in the local male general population and in a cohort of male police officers from Washington state (Demers et al., 1994). Firefighters had been employed for ≥ 1 year between 1944 and 1979, and cancer incidence follow-up was conducted from 1974 through 1989 in the regional SEER cancer registry using residential history information to reduce loss to follow-up. With the local general population as the referent, the overall SIR for melanoma appeared modestly raised (SIR, 1.2; 95% CI, 0.6–2.3; 9 cases), and the SIR for brain cancer was close to unity and imprecise (SIR, 1.1; 95% CI, 0.3–2.9; 4 cases). All four cases of brain cancer occurred in firefighters with ≥ 30 years since first employment, giving a raised, but still imprecise, SIR for this group (SIR, 1.9; 95% CI, 0.5–4.9; 4 cases). Apart from this, duration of employment, time since first employment, and comparisons with police officers as the reference group yielded little evidence of positive associations for melanoma or cancer of the brain. However, analyses were statistically imprecise because of small case numbers. There was only one case of thyroid cancer.

An earlier study of 4401 male municipal firefighters, who included firefighters from Portland (Oregon), Seattle, and Tacoma, reported findings for mortality from cancer of the skin (melanoma and non-melanoma skin cancer combined) and cancer of the brain and nervous system (Demers et al., 1992a). The mortality follow-up period was from 1945 to the end of 1989. Comparison of mortality rates was made with US White males in the general population and with a cohort of local male police officers. With the general

population as the referent, the overall SMR for skin cancer among firefighters was close to one (SMR, 0.98; 95% CI, 0.36–2.13; 6 deaths), and with the police officers as the referent, there was little evidence of an increase in skin cancer mortality (IDR, 1.12; 95% CI, 0.27–4.76). There were too few deaths from skin cancer to allow stratification by age or employment characteristics. Mortality from brain and nervous system cancers (ICD-9, 191 and 192) was higher (SMR, 2.07; 95% CI, 1.23–3.28; 18 deaths) than that in the general population, although the association was attenuated when police officers were used as the reference group (IDR, 1.63; 95% CI, 0.7–3.79). The SMR for brain and nervous system tumours (ICD-9, 191, 192, 237.5–237.7, 239.6–239.7) was raised for 10–19 years of exposed employment (SMR, 3.53; 95% CI, 1.5–7.0; 8 deaths), ≥ 30 years after first employment (SMR, 2.63; 95% CI, 1.4–4.4; 14 deaths), and people aged 18–39 years (SMR, 3.75; 95% CI, 1.2–8.7; 5 deaths), but there was no clear relation with duration of exposed employment, years since first employment, or age. Stratified analyses for brain cancer mortality were limited by the small number of cases.

A mortality study in a cohort of 1867 White male municipal firefighters who worked for the City of Buffalo, USA, provided information on the risk of brain cancer (Vena & Fiedler, 1987). Firefighters had been employed in the occupation for ≥ 1 year between 1950 and 1979 and mortality follow-up was from 1950 through 1979. With the US White male general population as the referent, the overall SMR for brain cancer appeared raised but was imprecise (SMR, 2.36; 95% CI, 0.86–5.13; 6 deaths). In stratified analyses, SMRs were raised for those working as a firefighter for 20–29 years (SMR, 3.75; 95% CI, [1.0–10.2]; 3 deaths), and for latencies of < 20 years (SMR, 4.02; 95% CI, [1.1–11.7]; 3 deaths) and 20–29 years (SMR, 4.58; 95% CI, [1.3–13.6]; 3 deaths). There was no clear positive relation between brain cancer mortality and the categories of duration of employment or other time-related characteristics. [This study was limited by the small number of cases.]

A proportionate mortality study of deceased police and firefighters was conducted in New Jersey, USA (Feuer & Rosenman, 1986). Analyses were based on 263 deaths in White male firefighters that were reported to the state comprehensive retirement system for police and firefighters in 1974–1980. There were four deaths from skin cancer (all types combined) among firefighters. Overall PMR estimates were elevated for skin cancer mortality when using either the general population (national and state) or police officers as the referent, although estimates were imprecise. Analyses stratified by duration of employment and latency were too imprecise to make inferences.

A mortality study in a cohort of 5414 male career firefighters in Toronto, Canada, who had worked for ≥ 6 months between 1950 and 1989 provided information on the risk of melanoma and cancer of the brain and other nervous system tissues (Aronson et al., 1994). Mortality follow-up was conducted in a national mortality database from 1950 through 1989. There were only two deaths from melanoma. With the male general population of Ontario as the referent, the SMR for brain cancer among firefighters was raised overall (SMR, 2.01; 95% CI, 1.10–3.37; 14 deaths) and in those with < 20 years since first exposure (SMR, 2.83; 95% CI, 1.04–6.16; 6 deaths). There was little evidence of a relation between SMR and duration of employment, time since first exposure, or age.

A study of 3328 municipal firefighters in two cohorts from Calgary and Edmonton, Canada, investigated mortality from melanoma and brain cancer (Guidotti, 1993). Firefighters had been employed between 1927 and 1987 and mortality follow-up was conducted in both provincial and national sources from 1927 through 1987. Results showed no deaths from melanoma. With the general population of Alberta as the referent, the SMR for brain cancer appeared to be raised

but was very imprecise (SMR, 1.47; 95% CI, 0.30–4.29; 3 deaths).

A cancer incidence study in an entirely female cohort of 37 962 volunteer firefighters in Australia provided information on the risk of melanoma, cancer of the thyroid, and brain and other central nervous system cancers (Glass et al., 2019). Cancer incidence follow-up was conducted in a national cancer registry from 1982 through 2010. Work history information describing the number and type of incidents attended was ascertained from fire agency personnel records. With the female general population of Australia as the referent, SIRs were above one for melanoma among all volunteer firefighters (SIR, 1.25; 95% CI, 1.05–1.46; 147 cases) and also among those who had attended incidents (SIR, 1.11; 95% CI, 0.84–1.44; 57 cases). External comparison results showed no excess of brain or thyroid cancer incidence among either group of volunteers. In internal regression analyses, there was no association between any tertile of the number of incidents attended and the rate of melanoma relative to firefighters who never attended incidents. Trend tests across tertile categories did not suggest a relation between risk of melanoma and the total number of incidents overall ($P = 0.53$) or all fire incidents ($P = 0.42$), structure fire incidents ($P = 0.89$), landscape fire incidents ($P = 0.41$), or vehicle fire incidents ($P = 0.24$). [The Working Group noted that the volunteer firefighters were more likely to live in rural areas and may have had more sun exposure through outdoor jobs (e.g. farming) than people who live in cities. In Australia, more than 85% of people live in cities and using the general population as the reference group in external comparisons may have introduced positive confounding. Non-melanoma skin cancer results were not available.]

Using the same methods as those in the study of female firefighters, cancer incidence was also investigated in a parallel cohort of 163 094 male volunteer firefighters in Australia (Glass et al., 2017). With the male general population of Australia as the referent, SIRs for all volunteer firefighters were not increased for melanoma (SIR, 1.00; 95% CI, 0.93–1.06; 912 cases), brain cancer (SIR, 0.88; 95% CI, 0.73–1.06; 114 cases) (a similar result was found for brain and other central nervous system cancers), or thyroid cancer (SIR, 0.83; 95% CI, 0.63–1.07; 58 cases). In internal regression analyses, there was little suggestion that risk of melanoma was related to duration of service ($P = 0.29$). All results were similar when analyses were restricted to volunteer firefighters who attended incidents. Analysis by incident type (using tertiles of number of incidents attended) suggested risk of melanoma increased with increasing number of total and fire incidents, but confidence intervals were wide and there was no formal trend test. There was no association suggested with structure fire incidents, landscape fire incidents, or vehicle fire incidents. The SIR for melanoma appeared to increase with more recent calendar time periods and was raised for the most recent time period of 1995 or later (SIR, 1.12; 95% CI, 1.01–1.24; 363 cases). There was little evidence suggesting increased risk of brain and other central nervous system cancers or thyroid cancer in external or internal comparison analyses.

Using methods similar to those in the two studies of volunteer firefighters, a cancer incidence study in a cohort of 30 057 paid full-time and part-time male firefighters in Australia provided information on the risk of melanoma and cancers of the brain and thyroid (Glass et al., 2016a). Included firefighters had worked between 1976 and 2003 and were primarily municipal or semi-metropolitan firefighters. Cancer incidence follow-up was conducted in a national registry to the end of 2010. With the male general population of Australia as the referent, the SIR for melanoma overall was elevated for all firefighters (SIR, 1.44; 95% CI, 1.28–1.62; 298 cases) and was also elevated within each stratum of full-time and part-time firefighters. The SIR for melanoma among full-time firefighters was raised regardless

of duration of employment and year of diagnosis and was elevated in both categories of duration of employment in internal regression analyses. However, internal analyses by number of incidents attended did not indicate a positive monotonic relation between risk of melanoma for all incident types, fire incidents ($P = 0.68$), structure fire incidents ($P = 0.38$), landscape fire incidents ($P = 0.50$), or vehicle fire incidents ($P = 0.39$). The SIR for brain cancer among all firefighters was not raised (SIR, 0.93; 95% CI, 0.62–1.35; 28 cases), although it was raised for thyroid cancer (SIR, 1.20; 95% CI, 0.74–1.86; 20 cases).

A study of cancer incidence was conducted in a cohort of 614 firefighters and trainers who attended a firefighter-training facility in Australia (Glass et al., 2016b). Three female firefighters were excluded from the analysis. Cancer incidence follow-up was conducted from 1982 through 2012. Participants were grouped into risk categories of low, medium, and high chronic exposure (to smoke and other hazardous agents) on the basis of job assignment. With the male general population of Victoria as the referent, a raised SIR for melanoma was observed among firefighters with a high risk of chronic exposure (SIR, 4.59; 95% CI, 1.68–9.99; 6 cases) but not among those with a low (SIR, 1.43; 95% CI, 0.29–4.18; 3 cases) or medium (SIR, 1.51; 95% CI, 0.49–3.52; 5 cases) risk of chronic exposure. A raised SIR for brain and other central nervous system cancers was observed among firefighters with a medium risk of chronic exposure (SIR, 5.74; 95% CI, 1.56–14.7; 4 cases).

A mortality and cancer incidence study in a cohort of 4305 paid [career] and volunteer firefighters in New Zealand provided information on the risk of melanoma and cancer of the brain (Bates et al., 2001). The cohort included 84 female firefighters who were excluded from the analysis. Included firefighters had worked for ≥ 1 year as a career firefighter and were employed for ≥ 1 day between 1977 and 1995. Follow-up for cancer mortality and incidence was conducted in a national data source to the end of 1995 (for mortality) or 1996 (for incidence). With the male general population of New Zealand as the referent, the overall SIR among firefighters appeared slightly raised for melanoma (SIR, 1.26; 95% CI, 0.8–1.9; 23 cases) and for brain cancer incidence (SIR, 1.27; 95% CI, 0.4–3.0; 5 cases), although the estimate for brain cancer was imprecise. Results were similar when restricted to recent calendar years (1990–1996) of diagnosis. There was no evidence of a positive relation between melanoma incidence and either duration of career service ($P = 0.97$) or duration of total (career and volunteer) service ($P = 0.93$). Similar analyses for brain cancer were not reported. Results for melanoma and brain cancer mortality were based on only two cases.

2.4.2 *Studies only reporting having ever worked as a firefighter*

(a) Occupational cohort studies

Studies first described in Section 2.1.2(a) are described in less detail in the present section.

See Table S2.8 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Six studies that assessed cancer among firefighters from five retrospective occupational cohorts were reviewed (Musk et al., 1978; Grimes et al., 1991; Giles et al., 1993; Ma et al., 2005, 2006; Amadeo et al., 2015). A descriptive study of skin cancer incidence and mortality among firefighters in Scotland was not reviewed because it lacked measures of association (Ide, 2014). A cohort study by Deschamps et al. (1995) that followed firefighters in Paris, France, for 14 years and compared mortality with that of the male general population of France was also not reviewed because it did not report tabulated results for skin, thyroid, or brain cancer. However, in the discussion the authors noted that they did not observe any cases of brain cancer in this

cohort. Five of the reviewed studies compared cancer incidence or mortality rates in a firefighter cohort to those in one or more general population reference groups, controlling for age and calendar year; the other study (Grimes et al., 1991) examined proportionate mortality. [A potential limitation for estimating associations for cancers of the skin, thyroid, and brain was that most of the studies lacked information on tumour histology, which may bias findings towards the null for certain tumour types if occupation as a firefighter is causally associated with some, but not all, tumour types. An additional limitation was that none of the studies included information on potential confounding factors specific to these cancer sites including, for cancers of the skin, early-age sunburn and non-firefighting-related sun exposure and, for cancers of the thyroid, body mass index (BMI) or history of ionizing radiation exposure. The studies of thyroid cancer incidence may be susceptible to surveillance bias for firefighters who underwent routine occupational health screening. Many of the estimates for the reviewed cancer sites were based on a small sample size, resulting in imprecise risk estimates that hindered interpretation.]

Amadeo et al. (2015) compared the mortality experience of male career firefighters (n = 10 829) in France to that of the male general population. This cohort followed career firefighters (who were actively employed in 1979) for up to 29 years. No excess skin cancer was observed. The SMR, based on five deaths, was 0.65 (95% CI, 0.21–1.51). [A limitation of this study was that skin cancer was defined as any malignant neoplasm of skin, including melanoma and non-melanoma skin cancers, which may have different etiologies.]

Ma and colleagues followed a cohort of career firefighters in Florida, USA, from 1981 through 1999 and reported incidence (Ma et al., 2006) and mortality (Ma et al., 2005) for cancers of the skin, brain, and thyroid compared with that in the age- and calendar year-standardized general population of Florida. Excess incident non-melanoma skin cancer (ICD-O-3, C44) was observed among both male and female firefighters (Ma et al., 2006), with SIRs of 1.17 (95% CI, 0.95–1.42; 99 cases) and 3.01 (95% CI, 0.97–7.03; 5 cases), respectively. A lower incidence of cancers of the brain (ICD-10, C71) was seen among male firefighters than in the general population (SIR, 0.58; 95% CI, 0.31–0.97; 14 cases). A higher incidence of thyroid cancer (C73) was seen among both male firefighters and female firefighters, although the latter was based on six cases, with SIRs of 1.77 (95% CI, 1.08–2.73) and 3.97 (95% CI, 1.45–8.65), respectively. Ma et al. (2005) observed no excess of skin cancer mortality among male firefighters (SMR, 0.89; 95% CI, 0.52–1.42; 17 deaths). In a sensitivity analysis restricted to the 15 deaths occurring in firefighters certified between 1972 and 1976, the subgroup with the longest estimated occupational exposure had an SMR of 1.21 (95% CI, 0.68–2.00). No excess mortality was observed for cancers of the brain and central nervous system among male firefighters (SMR, 0.66; 95% CI, 0.35–1.13; 13 deaths), with a similar finding among the subset who entered the cohort between 1972 and 1976. A higher rate of mortality from thyroid cancer was seen in the firefighters than in the general population (SMR, 4.82; 95% CI, 1.30–12.3; 4 deaths). None of the 38 deaths among women firefighters was attributed to cancers of the skin, brain, or thyroid. [The Working Group noted that a strength of these two studies was the availability of results for male and female firefighters; however, findings for incident cancers were imprecise because of the relatively young age at end of follow-up of the firefighters. Although 7% of the cohort members were lost to follow-up, this was unlikely to introduce substantial bias unless the loss was strongly influenced by cancer diagnosis, which may be more likely for cancers with poorer prognosis (e.g. glioma).]

Grimes et al. (1991) examined proportionate mortality for 205 deaths among male firefighters with ≥ 1 year of service in the City of Honolulu

fire department, Hawaii, USA (1969–1988). The PMR for deaths from brain and other cancers of the central nervous system was 3.78 (95% CI, 1.22–11.71; [3] deaths) with the state population as the referent, with no indication of effect modification by race (Caucasian [White] versus Pacific Islander). [The Working Group noted the lack of standardization of PMRs by age and calendar year as an important limitation.]

Musk et al. (1978) examined the mortality experience of 5655 male firefighters employed for ≥ 3 years between 1915 and 1975 in Boston, Massachusetts, USA. On the basis of eight cases, mortality from cancers of the brain and central nervous system (ICD-7, 193) was similar to that in both the state and US populations (SMR, 1.03; 95% CI, [0.48–1.95]; and SMR, 1.13; 95% CI, [0.52–2.14]; respectively).

Giles et al. (1993) studied cancer incidence among 2865 male career firefighters from Melbourne, Victoria, Australia, compared with the adult male state population. The rate of mortality from melanoma was similar to that in the general population (SMR, 1.08; 95% CI, 0.35–2.53; 5 deaths). [Strengths of this study were the inclusion of operational firefighter personnel only (who were likely to have responded to fires), and the reporting of melanoma of the skin (ICD-9, 172) rather than all skin cancers. Limitations included the lack of description of linkage methods with the national cancer registry and resulting inability to assess related potential bias because of matching errors.]

(b) Population-based studies

Studies first described in Section 2.1.2(b) are described in less detail in the present section.

See Table S2.8 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

During the period 1990–2021, four studies in population-based cohorts investigated firefighters' risk of cancers of the skin (melanoma and non-melanoma), thyroid, and brain (Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020; Sritharan et al., 2022), and eight case–control studies reported results for cancers of the skin, thyroid, and brain among firefighters in the USA (Sama et al., 1990; Ma et al., 1998; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Muegge et al., 2018; Lee et al., 2020; McClure et al., 2021). One mortality surveillance study evaluated PMRs for skin cancer and for brain and other nervous system cancers among firefighters compared with the national general population in the USA (Burnett et al., 1994).

Three of the cohort studies were based on census data, and compared sex-, age-, and calendar year-adjusted cancer incidence (Pukkala et al., 2014; Harris et al., 2018) or mortality (Zhao et al., 2020) among firefighters to that for reference groups. The fourth study examined a relatively large cohort via linkage of a Canadian occupational injury and disease claim database to person and cancer registries (Sritharan et al., 2022).

Four of the case–control studies were based on incident cancer registry information only, including self-reported job information, and both site-specific cancer cases and controls diagnosed with other cancers were extracted from the same registries (Sama et al., 1990; Bates, 2007; Kang et al., 2008; Tsai et al., 2015). Two overlapping case–control studies were based on record linkage of firefighter employment records with incident cancer registry data (Lee et al., 2020; McClure et al., 2021). The two remaining studies examined records limited to information obtained from death certificates, including cancer diagnosis and job title (Ma et al., 1998; Muegge et al., 2018). [The Working Group noted that the study strengths and limitations pertaining to design that were previously described for cancers of the respiratory system in Section 2.1.2(b) also apply to cancer types in the present section. Also, the limitations associated with cancer survival, surveillance bias, and lack of information on

potential confounders for studies of the same cancers, as described in Section 2.4.2(a), also apply to studies in this section.]

Cancer mortality was examined prospectively (2001–2011) in a census-based cohort of men aged 20–64 years employed in Spain in 2001 (Zhao et al., 2020). Age-standardized MRRs were calculated for firefighters compared with all other occupations. MRRs were 1.07 (95% CI, 0.63–1.81) for brain cancer, 2.34 (95% CI, 0.53–10.29) for thyroid cancer, and 0.63 (95% CI, 0.19–2.10) for melanoma. [The Working Group noted the small number of cases, which made estimates imprecise. A strength was the use of the working population as the referent.]

The large Nordic linkage study (NOCCA), including 16 422 male firefighters and based on linkage of census data (1960–1990) and nationwide cancer registry data (1961–2005), found an overall increased risk of non-melanoma skin cancer (SIR, 1.33; 95% CI, 1.10–1.59) and (similarly) of melanoma (SIR, 1.25; 95% CI, 1.03–1.51) (Pukkala et al., 2014). The SIR for thyroid cancer was 1.28 (95% CI, 0.75–2.05). The overall SIR for brain cancer was 0.86 (95% CI, 0.66–1.10) and was 0.92 (95% CI, 0.64–1.30) in the subgroup of glioma. [The Working Group noted the evaluation of brain cancer subtype and the long follow-up period as strengths. The main limitation was the lack of information on duration and intensity of firefighting.]

Cancer incidence was explored in a cohort of 13 642 firefighters from Ontario, Canada (Sritharan et al., 2022). The study used information from an occupational injury and disease claims database (ODSS) and linked claimants between 1983 and 2019 to a person register and to the Ontario Cancer Registry. Workers were followed from the first claim date to first cancer diagnosis date, emigration out of Ontario, attained age of 85 years, death, or study end in 2020, whichever was earliest. Site-specific cancer risk, comparing cancer incidence in firefighters with that in all other occupations and in police, was assessed using Cox proportional hazards regression, controlling for age at start of follow-up, birth year, and sex. When comparing firefighters with all other workers, the hazard ratio was 2.38 (95% CI, 1.99–2.84) for melanoma, 1.26 (95% CI, 0.91–1.74) for brain cancer, and 1.11 (95% CI, 0.76–1.62) for thyroid cancer. The excesses were greatly attenuated when the police group was used as the referent. [The Working Group noted that the relatively large size, inclusion of women, and access to tumour information were study strengths. Among limitations, exposure information was limited to the job title available at the time of the worker compensation claim, which may introduce bias in either direction.]

CanCHEC, a census and cancer registry-based study from Canada (1991–2010), estimated risks of incident cancers in firefighters (Harris et al., 2018). The census used data collected in 1991 for about 20% of the households in Canada. Firefighter status was assessed on the basis of the longest-held job in the previous year, and the cohort was restricted to men aged 25–74 years at census. Average follow-up time was almost 18 years. Adjusted hazard ratios (for age group, region, and education level) for brain and thyroid cancers were 1.11 (95% CI, 0.61–2.01) and 1.35 (95% CI, 0.61–3.02), respectively. The adjusted hazard ratio for melanoma was elevated (1.67; 95% CI, 1.17–2.37) [The Working Group noted the relatively large population of firefighters and the long follow-up period, and adjustment for educational level as strengths. The main limitation was the lack of information on duration and intensity of firefighting.]

A case–control study reported age- and calendar year-adjusted ORs for various incident primary cancers of male and female firefighters from Florida, USA (Lee et al., 2020). Career firefighter certification records (1972 or after) were linked with state cancer registry data (1981–2014) to identify cases in firefighters. Controls were individuals with all other cancer types, excluding the cancer of interest. ORs for

melanoma of the skin were increased in both female and male firefighters, with estimates of 1.68 (95% CI, 0.97–2.90) and 1.56 (95% CI, 1.39–1.76), respectively. Elevated ORs were also observed for thyroid cancer in male and female firefighters, with estimates of 2.17 (95% CI, 1.78–2.66) and 2.42 (95% CI, 1.56–3.74), respectively. In contrast, brain cancer was elevated only among female firefighters (OR, 2.54; 95% CI, 1.19–5.42). For men, ORs were further stratified by tumour stage. Only the ORs for thyroid cancer differed between early-stage cancer (OR, 1.78; 95% CI, 1.38–2.31) and late-stage cancer (OR, 2.70; 95% CI, 1.94–3.76). Finally, the ORs for men were stratified by age < 50 years and ≥ 50 years at diagnosis. The ORs for both melanoma (1.87; 95% CI, 1.55–2.26) and thyroid cancer (2.55; 95% CI, 1.96–3.31) tended to be higher in the younger firefighters. A study by McClure et al. (2021) evaluated the impact of misclassification of firefighter status within this cohort by comparing two occupation ascertainment methods. The ORs calculated when firefighter status was obtained from the cancer registry were compared with those when the designation of firefighter was obtained from state firefighter certification. ORs for all skin cancers were 1.06 (95% CI, 0.87–1.29) based on 109 cases in firefighters identified from the cancer registry, and 1.54 (95% CI, 1.37–1.73) based on 316 cases in firefighters identified from certification records. [The Working Group noted small numbers for female firefighters and consequently imprecise results in the study by Lee et al. (2020). Further, McClure et al. (2021) found that a high proportion of firefighters was not identified by job title from the cancer registry. Therefore, ascertainment of firefighting exposure classification from cancer registries alone resulted in the potential for exposure misclassification.]

ORs for cancer mortality were examined among firefighters compared with non-firefighters in Indiana, USA, using death certificate records for the period 1985–2013 (Muegge et al., 2018). People aged ≥ 18 years at death, with known race and ethnicity, were identified as either firefighters or non-firefighters (reference group) using job information recorded at the time of death. Each firefighter was matched on attained age, sex, race, ethnicity, and year of death to four randomly selected non-firefighter deaths. An increased OR for cancer of the brain and nervous system (1.98; 95% CI, 1.23–3.12) was observed. [The Working Group noted that the use of death certificates may result in misclassification of both job and cancer diagnosis. Furthermore, this source of information is less accurate for cancers with higher survival rates. Finally, the study did not provide a specific definition of brain cancer, which comprises a diverse group of cancers with different survival rates.]

Cancer risk by race was examined in a registry-based case–control study of 678 132 cases of cancer diagnosed among adult men in California, USA, during the period 1988–2007, and which included 3996 diagnoses of cancer among firefighters (Tsai et al., 2015). This study included only men from the California Cancer Registry for whom information on longest-held job was available. Cases of cancers not thought to be associated with firefighting, i.e. cancers of the pharynx, stomach, liver, and pancreas, were used as controls. Increased ORs were observed for melanoma (OR, 1.75; 95% CI, 1.44–2.13) and brain cancer (OR, 1.54; 95% CI, 1.19–2.00). Rates of these cancers were notably increased in the subgroup of non-White firefighters, although this was based on small numbers (OR for melanoma, 4.51; 95% CI, 1.85–10.97; and OR for brain cancer, 3.58; 95% CI, 1.65–7.74). The OR for thyroid cancer was also elevated (OR, 1.27; 95% CI, 0.88–1.84). Bates (2007) conducted a similar study using the California Cancer Registry, 1988–2003, but these data were also included in the study by Tsai et al. (2015). [The Working Group noted a high proportion of cancer registrants missing occupational information overall

in the registry, which may bias results unpredictably, if missingness is related to occupational or demographic factors.]

An incidence-based cancer registry study in Massachusetts, USA, reported site-specific cancer risks in White male firefighters identified in the state cancer registry (1987–2003) (Kang et al., 2008). Longest-held job, identified from the same registry, was classified as firefighter, police, or other occupations, and the methodology was similar to that in an earlier study (Sama et al., 1990) that considered cancer diagnoses in 1982–1986. Age- and smoking-adjusted SMBORs were calculated for firefighters on the basis of two reference groups: occupations other than firefighters, and police employees. In Kang et al. (2008), the SMBORs for cancer of the brain were increased when using police officers (SMBOR, 1.90; 95% CI, 1.10–3.26) and all other occupations (SMBOR, 1.36; 95% CI, 0.87–2.12) as referents. SMBORs for melanoma and thyroid cancer were not elevated for either reference group. In the earlier study (Sama et al., 1990), the age-adjusted SMBOR for melanoma (18 cases) was elevated when police were used as the referent (SMBOR, 2.92; 95% CI, 1.70–5.03), and to a lesser extent when other employed men were used as the referent (SMBOR, 1.38; 95% CI, 0.60–3.19). The ORs for brain and other nervous system cancers were based on only five cases. [The Working Group noted that the number of cases was small in both studies, and that about the half of the population had no occupational information, which may bias results unpredictably.]

A death certificate-based case–control study in 24 US states (1984–1993) reported MORs for Black and White male firefighters. All non-cancer deaths were used as controls (Ma et al., 1998). The MORs for melanoma, non-melanoma skin cancer, and thyroid cancer for White firefighters were 1.4 (95% CI, 1.0–1.9), 1.0 (95% CI, 0.5–1.9), and 1.3 (95% CI, NR), respectively. The MOR for brain and central nervous system cancer was highly elevated for Black firefighters (MOR, 6.9; 95% CI, 3.0–16.0), but not for White firefighters (MOR, 1.0; 95% CI, 0.8–1.4). [The Working Group noted limited numbers for most cancers, and typically inaccurate occupational information from death certificates, which can bias results to the null. Further, death certificate data is a poor means of identifying non-melanoma skin cancer, which has a low fatality rate.]

Proportionate mortality was investigated in White male US firefighters from 27 states compared with the age-adjusted deceased White male general population, in 1984–1990 (Burnett et al., 1994). Deceased firefighters (n = 5744) were identified by the coded occupation listed on the death certificate. The PMR for melanoma was elevated both overall (PMR, 1.63; 95% CI, 1.15–2.23) and for firefighters aged < 65 years (PMR, 1.67; 95% CI, 1.07–2.48). No increased PMRs were reported for cancers of the brain (PMR, 1.03; 95% CI, 0.73–1.41) and nervous system (PMR, 0.85; 95% CI, 0.52–1.34). [The Working Group noted that PMR analyses might overestimate the cancer risks in firefighters if their overall risk of death were below the risk in the comparison group.]

2.5 Cancers of the colon and rectum, oesophagus, stomach, and other sites

2.5.1 Studies reporting occupational characteristics of firefighters

Studies first described in Section 2.1.1 are described in the present section in less detail.

See Table 2.9.

The Working Group identified 24 occupational and population-based cohort studies that investigated the relation between occupational exposure as a firefighter and risk of cancer of the oral cavity, pharynx, breast, oesophagus, stomach, pancreas, liver, and colon and rectum (Feuer & Rosenman, 1986; Vena & Fiedler, 1987; Demers

Table 2.9 Cohort studies reporting occupational characteristics of firefighters and cancers of the colon and rectum, oesophagus, stomach, and other sites

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn & Jeong (2015) Republic of Korea Enrolment, 1980–2007/follow-up, 1992–2007 Cohort	33 442 men employed as emergency responders for ≥ 1 mo in 1980–2007 with (29 453) and without (3989) firefighting experience and not deceased in 1991 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Stomach, mortality	Duration of firefighting employment, 1-yr lag (SMR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include both municipal and rural firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: no information on personal characteristics or confounders; follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to< 10 yr	11	0.89 (0.44–1.59)		
			10 to < 20 yr	9	0.50 (0.23–0.95)		
			≥ 20 yr	14	0.60 (0.33–1.00)		
			Overall	34	0.63 (0.43–0.88)		
		Stomach, mortality	Duration of firefighting employment, 1-yr lag (RR):				
			< 10 yr (including non-firefighters)	12	1		
			10 to < 20 yr	9	0.63 (0.27–1.50)		
			≥ 20 yr	14	1.03 (0.44–2.44)		
		Colon and rectum, mortality	Duration of firefighting employment, 1-yr lag (SMR):				
			1 mo to < 10 yr	2	0.46 (0.05–1.67)		
			10 to < 20 yr	5	0.81 (0.26–1.90)		
			≥ 20 yr	5	0.63 (0.20–1.48)		
			Overall	12	0.65 (0.34–1.14)		
		Colon and rectum, mortality	Duration of firefighting employment, 1-yr lag (RR):				
			< 10 yr (including non-firefighters)	3	1		
			10 to < 20 yr	5	1.40 (0.33–5.87)		
			≥ 20 yr	5	1.29 (0.27–6.08)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn & Jeong (2015) (cont.)		Liver and bile ducts, mortality	Duration of firefighting employment, 1-yr lag (SMR):			Age, calendar period	
			1 mo to < 10 yr	14	0.69 (0.38–1.16)		
			10 to < 20 yr	13	0.43 (0.23–0.73)		
			≥ 20 yr	23	0.58 (0.37–0.87)		
			Overall	50	0.55 (0.41–0.73)		
		Liver and bile ducts, mortality	Duration of firefighting employment, 1-yr lag (RR):				
			< 10 yr (including non-firefighters)	14	1		
			10 to < 20 yr	13	0.78 (0.37–1.66)		
			≥ 20 yr	23	1.82 (0.85–3.90)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) Republic of Korea Enrolment, 1980–2007/follow-up, 1996–2007 Cohort	33 416 men employed as emergency responders for ≥ 1 mo in 1980–2007 with (29 438) and without (3978) firefighting experience and not deceased in 1995 Exposure assessment method: ever employed and categorical duration of employment (years) as first- or second-line firefighter and non-firefighters from employment records	Oesophagus, incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job title. May include rural and municipal firefighters. *Strengths*: employment duration and internal comparison limits healthy-worker bias; only professional [career] firefighters were included in the cohort. *Limitations*: no information on personal characteristics or confounders (except the firefighter cohort had a lower BMI and smoked less than the comparison population for the SIR analysis); follow-up time was reasonably short; cohort members were fairly young; no direct measure of exposure.
			1 mo to < 10 yr	0	0 (NR)		
			≥ 10 yr	6	0.94 (0.34–2.05)		
			Overall	6	0.75 (0.28–1.64)		
		Oesophagus, incidence	SRR:				
			Non-firefighters	0	0 (NR)		
			Ever employed as a firefighter	6	NR		
		Stomach, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	29	0.98 (0.66–1.41)		
			≥ 10 yr	77	0.92 (0.72–1.14)		
			Overall	106	0.93 (0.76–1.13)		
		Stomach, incidence	SRR:				
			Non-firefighters	8	1		
			Ever employed as a firefighter	106	1.09 (0.53–2.25)		
		Colon and rectum, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	20	1.35 (0.82–2.08)		
			≥ 10 yr	52	1.25 (0.95–1.63)		
			Overall	72	1.27 (1.01–1.59)		
		Colon and rectum, incidence	SRR:				
			Non-firefighters	10	1		
			Ever employed as a firefighter	72	0.55 (0.26–1.19)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) (cont.)		Liver and bile ducts, incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	
			1 mo to < 10 yr	21	0.97 (0.60–1.49)		
			≥ 10 yr	53	0.80 (0.60–1.05)		
			Overall	74	0.84 (0.66–1.06)		
		Liver and bile ducts, incidence	SRR:				
			Non-firefighters	1	1		
			Ever employed as a firefighter	74	5.10 (0.71–36.85)		
		Gallbladder and extrahepatic bile ducts (ICD-10, C23–C24), incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	2	1.04 (0.12–3.74)		
			≥ 10 yr	5	0.76 (0.25–1.78)		
			Overall	7	0.82 (0.33–1.70)		
		Gallbladder and extrahepatic bile ducts (ICD-10, C23–C24), incidence	SRR:				
			Non-firefighters	1	1		
			Ever employed as a firefighter	7	0.48 (0.06–3.94)		
		Pancreas, incidence	Duration of firefighting employment, 1-yr lag (SIR):				
			1 mo to < 10 yr	4	1.80 (0.49–4.62)		
			≥ 10 yr	5	0.93 (0.25–2.37)		
			Overall	9	0.95 (0.44–1.81)		
		Pancreas, incidence	SRR:				
			Non-firefighters	1	1		
			Ever employed as a firefighter	9	0.58 (0.07–4.58)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ahn et al. (2012) (cont.)		Bone and articular cartilage (ICD-10, C40–C41), incidence	Duration of firefighting employment, 1-yr lag (SIR):			Age, calendar period	
			1 mo to < 10 yr	1	1.33 (0.02–7.40)		
			≥ 10 yr	3	2.37 (0.48–6.92)		
			Overall	4	1.98 (0.53–5.07)		
		Bone and articular cartilage (ICD-10, C40–C41), incidence	SRR:				
			Non-firefighters	2	1		
			Ever employed as a firefighter	4	0.24 (0.04–1.37)		
Marjerrison et al. (2022b) Norway Enrolment, 1950–2019/follow-up, 1960–2018 Cohort	3881 male professional [career] firefighters (most were full-time) employed in positions entailing active firefighting at any of 15 fire departments between 1950 and 2019 Exposure assessment method: employment history from personnel records	Oral cavity, incidence	SIR:			Age, calendar year	*Exposure assessment critique*: Satisfactory quality. Included firefighters with current or previous positions entailing active firefighting duties but no assessment of length of time in active firefighting positions. May include municipal and rural firefighters. *Strengths*: long length of follow-up (mean, 28 yr); near complete ascertainment of both cancer incidence and mortality; analyses by duration and timing of employment. *Limitations*: probable healthy-worker effect; no data on potential confounders apart from age, sex, and calendar time.
			Firefighters	< 5	0.73 (0.20–1.86)		
		Oral cavity, mortality	SMR:				
			Firefighters	0	0 (0.00–3.04)		
		Pharynx, incidence	SIR:				
			Firefighters	11	1.61 (0.80–2.88)		
		Pharynx, mortality	SMR:				
			Firefighters	< 5	1.05 (0.29–2.69)		
		Oesophagus, incidence	SIR:				
			Firefighters	13	1.55 (0.83–2.66)		
		Oesophagus, mortality	SMR:				
			Firefighters	13	1.82 (0.97–3.11)		
		Oesophagus, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	2.15 (0.44–6.29)		
			1985–1994	< 5	1.60 (0.19–5.78)		
			1995 or after	8	1.40 (0.60–2.76)		
		Oesophagus, mortality	Period of follow-up (SMR):				
			1984 or before	< 5	2.35 (0.48–6.86)		
			1985–1994	< 5	1.74 (0.21–6.29)		
			1995 or after	8	1.69 (0.73–3.33)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Oesophagus, incidence	Age at diagnosis (SIR):			Age, calendar year	
			≤ 49 yr	0	0 (0.00–6.22)		
			50–69 yr	7	1.54 (0.62–3.17)		
			≥ 70 yr	6	1.80 (0.66–3.91)		
		Oesophagus, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–9.96)		
			50–69 yr	7	1.88 (0.76–3.88)		
			≥ 70 yr	6	1.91 (0.70–4.16)		
		Stomach, incidence	SIR:				
			Firefighters	38	1.35 (0.95–1.85)		
		Stomach, mortality	SMR:				
			Firefighters	28	1.28 (0.85–1.84)		
		Stomach, incidence	Period of follow-up (SIR):				
			1984 or before	15	1.39 (0.78–2.29)		
			1985–1994	10	1.64 (0.79–3.02)		
			1995 or after	13	1.15 (0.61–1.96)		
		Stomach, mortality	Period of follow-up (SMR):				
			1984 or before	12	1.35 (0.70–2.36)		
			1985–1994	9	1.88 (0.86–3.56)		
			1995 or after	7	0.85 (0.34–1.75)		
		Stomach, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	1.34 (0.28–3.91)		
			50–69 yr	21	1.56 (0.97–2.39)		
			≥ 70 yr	14	1.11 (0.61–1.87)		
		Stomach, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	< 5	1.93 (0.40–5.63)		
			50–69 yr	12	1.20 (0.62–2.10)		
			≥ 70 yr	13	1.25 (0.67–2.14)		
		Colon, incidence	SIR:				
			Firefighters	74	1.24 (0.98–1.56)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Colon, mortality	SMR:			Age, calendar year	
			Firefighters	34	1.26 (0.87–1.76)		
		Colon, incidence	Period of follow-up (SIR):				
			1984 or before	16	2.02 (1.15–3.28)		
			1985–1994	14	1.41 (0.77–2.37)		
			1995 or after	44	1.05 (0.77–1.42)		
		Colon, mortality	Period of follow-up (SMR):				
			1984 or before	10	2.33 (1.12–4.29)		
			1985–1994	9	1.79 (0.82–3.39)		
			1995 or after	15	0.85 (0.48–1.40)		
		Colon, incidence	Age at diagnosis (SIR):				
			≤ 49 yr	< 5	0.80 (0.16–2.33)		
			50–69 yr	29	1.16 (0.78–1.67)		
			≥ 70 yr	42	1.36 (0.98–1.84)		
		Colon, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	< 5	0.75 (0.02–4.19)		
			50–69 yr	16	1.63 (0.93–2.65)		
			≥ 70 yr	17	1.07 (0.62–1.72)		
		Rectum, incidence	SIR:				
			Firefighters	37	0.96 (0.68–1.33)		
		Rectum, mortality	SMR:				
			Firefighters	18	1.16 (0.69–1.84)		
		Rectum, incidence	Period of follow-up (SIR):				
			1984 or before	< 5	0.63 (0.17–1.62)		
			1985–1994	6	0.86 (0.31–1.87)		
			1995 or after	27	1.07 (0.71–1.56)		
		Rectum, mortality	Period of follow-up (SMR):				
			1984 or before	< 5	0.89 (0.18–2.60)		
			1985–1994	< 5	0.57 (0.07–2.05)		
			1995 or after	13	1.51 (0.80–2.58)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Rectum, incidence	Age at diagnosis (SIR):			Age, calendar year	
			≤ 49 yr	< 5	1.22 (0.25–3.56)		
			50–69 yr	16	0.83 (0.47–1.35)		
			≥ 70 yr	18	1.07 (0.64–1.70)		
		Rectum, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	0	0 (0.00–3.97)		
			50–69 yr	< 5	0.62 (0.17–1.58)		
			≥ 70 yr	14	1.70 (0.93–2.85)		
		Liver (HCC), incidence	SIR:				
			Firefighters	8	1.43 (0.62–2.81)		
		Liver (HCC), mortality	SMR:				
			Firefighters	7	1.38 (0.56–2.85)		
		Bile duct and gallbladder, incidence	SIR:				
			Firefighters	< 5	1.13 (0.31–2.89)		
		Bile duct and gallbladder, mortality	SMR:				
			Firefighters	< 5	2.01 (0.55–5.15)		
		Liver, gall bladder, biliary ducts, incidence	SIR:				
			Firefighters	12	1.31 (0.68–2.29)		
		Liver, gall bladder, biliary ducts, mortality	SMR:				
			Firefighters	11	1.56 (0.78–2.79)		
		Liver, gall bladder, biliary ducts, incidence	Period of follow-up (SIR):				
			1984 or before	5	3.62 (1.17–8.44)		
			1985–1994	< 5	1.46 (0.18–5.29)		
			1995 or after	5	0.78 (0.25–1.82)		
		Liver, gall bladder, biliary ducts, mortality	Period of follow-up (SMR):				
			1984 or before	< 5	3.03 (0.83–7.75)		
			1985–1994	< 5	1.91 (0.23–6.89)		
			1995 or after	5	1.07 (0.35–2.50)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Marjerrison et al. (2022b) (cont.)		Liver, gall bladder, biliary ducts, incidence	Age at diagnosis (SIR):			Age, calendar year	
			≤ 49 yr	< 5	1.45 (0.04–8.07)		
			50–69 yr	< 5	0.91 (0.25–2.33)		
			≥ 70 yr	7	1.72 (0.69–3.55)		
		Liver, gall bladder, biliary ducts, mortality	Age at diagnosis (SMR):				
			≤ 49 yr	< 5	1.95 (0.05–10.9)		
			50–69 yr	< 5	1.26 (0.34–3.24)		
			≥ 70 yr	6	1.78 (0.65–3.87)		
		Pancreas, incidence	SIR:				
			Firefighters	24	1.22 (0.78–1.81)		
		Pancreas, mortality	SMR:				
			Firefighters	20	1.09 (0.67–1.68)		
Bigert et al. (2020) Sweden Enrolment 1960–1990/follow-up, 1961–2009 Cohort	8136 male firefighters identified from national censuses in 1960, 1970, 1980, and 1990 Exposure assessment method: questionnaire; ever employed and categorical duration of employment (years) as firefighter from census surveys	Pharynx, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. May include full-time, part-time, municipal, and rural firefighters. *Strengths*: near complete ascertainment of cancer incidence; long length of follow-up (mean, 28 yr); analyses stratified by calendar period of employment.
			Firefighters	13	1.04 (0.55–1.78)		
		Oesophagus, incidence	SIR:				
			Firefighters	13	0.71 (0.38–1.21)		
		Stomach, incidence	SIR:				
			Firefighters	60	1.08 (0.83–1.39)		
		Stomach, incidence	Duration of employment (SIR):				
			1–9 yr	4	1.43 (0.39–3.66)		
			10–19 yr	22	1.23 (0.77–1.86)		
			20–29 yr	18	1.00 (0.59–1.57)		
			≥ 30 yr	16	0.97 (0.55–1.58)		
			Trend-test *P* value, 0.75				
		Stomach, incidence	Time period (SIR):				
			1961–1975	16	1.85 (1.06–3.00)		
			1976–1990	22	1.16 (0.73–1.76)		
			1991–2009	22	0.79 (0.49–1.19)		
		Colon, incidence	SIR:				
			Firefighters	101	1.01 (0.82–1.23)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
		Rectum, incidence	SIR:			Age, calendar period	*Limitations*: no data on job duties; employment type, or potential confounders (aside from age, sex, and calendar year); probable healthy-worker hire bias; potential non-differential misclassification of employment duration.
			Firefighters	63	0.89 (0.69–1.14)		
		Liver and bile ducts, incidence	SIR:				
			Firefighters	15	0.89 (0.50–1.47)		
		Pancreas, incidence	SIR:				
			Firefighters	43	1.17 (0.85–1.58)		
		Soft tissue sarcoma, incidence	SIR:				
			Firefighters	15	1.46 (0.82–2.41)		
Kullberg et al. (2018) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1958–2012 Cohort	1080 men who worked ≥ 1 yr as a firefighter in Stockholm between 1931 and 1983 Exposure assessment method: ever employed and categorical duration of employment (years) as an urban [municipal] firefighter from annual enrolment records	Lip, incidence	Follow-up period (SIR):			Birth year, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence; analyses of duration and era of employment. Municipal firefighters. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year); lack of exposure assessment based on job tasks or fire responses.
			Full: 1958–2012	2	1.45 (0.18–5.26)		
			Former: 1958–1986	1	1.42 (0.04–7.91)		
			Extended: 1987–2012	1	1.49 (0.38–8.32)		
		Oesophagus, incidence	Follow-up period (SIR):				
			Full: 1958–2012	5	0.99 (0.32–2.30)		
			Former: 1958–1986	1	0.43 (0.01–2.38)		
			Extended: 1987–2012	4	1.46 (0.40–3.75)		
		Stomach, incidence	Follow-up period (SIR):				
			Full: 1958–2012	27	1.89 (1.25–2.75)		
			Former: 1958–1986	20	2.21 (1.35–3.41)		
			Extended: 1987–2012	7	1.35 (0.54–2.78)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) (cont.)		Stomach, incidence	Age at risk (SIR):			Birth year, calendar period	
			< 50 yr	2	3.18 (0.39–11.49)		
			50–64 yr	8	2.38 (1.03–4.70)		
			≥ 65 yr	17	1.65 (0.96–2.65)		
			Trend-test *P* value, 0.07				
		Stomach, incidence	Duration of employment (SIR):				
			1–9 yr	0	0 (NR)		
			10–19 yr	2	2.02 (0.50–8.06)		
			20–29 yr	7	2.03 (0.97–4.26)		
			≥ 30 yr	18	2.05 (1.29–3.26)		
			Trend-test *P* value, 0.19				
		Stomach, incidence	Period of first employment (SIR):				
			1902–1939	15	1.81 (1.09–3.01)		
			1940–1959	8	1.77 (0.88–3.55)		
			1960–1983	4	2.72 (1.02–7.26)		
			Trend-test *P* value, 0.69				
		Colon, incidence	Follow-up period (SIR):				
			Full: 1958–2012	20	0.86 (0.53–1.34)		
			Former: 1958–1986	8	0.92 (0.40–1.81)		
			Extended: 1987–2012	12	0.83 (0.43–1.46)		
		Rectum, incidence	Follow-up period (SIR):				
			Full: 1958–2012	18	1.25 (0.74–1.98)		
			Former: 1958–1986	10	1.74 (0.83–3.19)		
			Extended: 1987–2012	8	0.93 (0.40–1.82)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kullberg et al. (2018) (cont.)		Liver and bile ducts, incidence	Follow-up period (SIR):			Birth year, calendar period	
			Full: 1958–2012	7	0.79 (0.32–1.63)		
			Former: 1958–1986	4	0.90 (0.25–2.31)		
			Extended: 1987–2012	3	0.68 (0.14–2.00)		
		Pancreas, incidence	Follow-up period (SIR):				
			Full: 1958–2012	10	1.06 (0.51–1.94)		
			Former: 1958–1986	6	1.23 (0.45–2.68)		
			Extended: 1987–2012	4	0.87 (0.24–2.23)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tornling et al. (1994) Stockholm, Sweden Enrolment, 1931–1983/follow-up, 1951–1986 (mortality), 1958–1986 (incidence) Cohort	1116 for mortality/1091 for incidence; male firefighters employed for ≥ 1 yr in the City of Stockholm in 1931–1983, identified from annual enrolment records Exposure assessment method: ever firefighter and duration (years) of firefighting employment from annual enrolment records; number of fires fought ascertained from exposure index developed from fire reports	Stomach, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Enhanced exposure assessment (but based on 10% sample of reports) to differentiate exposure based on number of fires fought accounting for job position, station, and year of exposure. Municipal firefighters. *Strengths*: long follow-up period; near complete ascertainment of cancer incidence and mortality; assessed exposure to fire responses for some outcomes. *Limitations*: no data on potential confounders (aside from age, sex, and calendar year).
			Firefighters	12	1.21 (0.62–2.11)		
		Stomach, mortality	Age (SMR):				
			< 50 yr	1	1.90 (0.05–10.57)		
			50–64 yr	4	1.61 (0.44–4.12)		
			≥ 65 yr	7	1.01 (0.41–2.08)		
		Stomach, mortality	Duration of employment (SMR):				
			< 20 yr	1	1.08 (0.03–6.04)		
			20–30 yr	5	1.05 (0.34–2.45)		
			> 30 yr	6	1.41 (0.52–3.07)		
		Stomach, mortality	Latency (SMR):				
			< 30 yr	2	1.92 (0.23–6.92)		
			30–40 yr	3	1.40 (0.29–4.09)		
			> 40 yr	7	1.04 (0.42–2.13)		
		Stomach, mortality	No. of fires (SMR):				
			< 800	1	0.51 (0.01–2.87)		
			800–1000	2	0.59 (0.07–2.12)		
			> 1000	9	1.96 (0.90–3.72)		
		Stomach, incidence	SIR:				
			Firefighters	18	1.92 (1.14–3.04)		
		Stomach, incidence	Age (SIR):				
			< 50 yr	1	2.04 (0.03–11.35)		
			50–64 yr	6	2.58 (0.94–5.61)		
			≥ 65 yr	11	1.68 (0.84–3.00)		
		Stomach, incidence	Duration of employment (SIR):				
			< 20 yr	1	1.02 (0.01–5.68)		
			20–30 yr	5	1.18 (0.38–2.75)		
			> 30 yr	12	2.89 (1.49–5.05)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tornling et al. (1994) (cont.)		Stomach, incidence	Latency (SIR):			Age, calendar period	
			< 30 yr	5	4.81 (1.55–11.22)		
			30–40 yr	12	6.06 (3.13–10.59)		
			> 40 yr	1	0.16 (0–0.88)		
		Stomach, incidence	No. of fires (SIR):				
			< 800	2	1.04 (0.12–3.76)		
			800–1000	4	1.37 (0.37–3.52)		
			> 1000	14	2.64 (1.36–4.61)		
		Colon, mortality	SMR:				
			Firefighters	6	0.85 (0.31–1.85)		
		Colon, incidence	SIR:				
			Firefighters	8	0.90 (0.39–1.77)		
		Rectum, mortality	SMR:				
			Firefighters	8	2.07 (0.89–4.08)		
		Rectum, incidence	SIR:				
			Firefighters	10	1.70 (0.81–3.12)		
		Liver (HCC), mortality	SMR:				
			Firefighters	4	1.49 (0.41–3.81)		
		Liver (HCC), incidence	SIR:				
			Firefighters	4	0.85 (0.23–2.18)		
		Pancreas, mortality	SMR:				
			Firefighters	5	0.84 (0.27–1.96)		
		Pancreas, incidence	SIR:				
			Firefighters	6	1.19 (0.44–2.60)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) Denmark Enrolment, 1964–2004/follow-up, 1968–2014 Cohort	9061 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born 2 April 1928 or later, employed before age 60 yr and 31 December 2004, no cancer diagnosis before employment as a firefighter, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years), as well as employment type, job title/function, and work history, ascertained from civil registration, pension, employer personnel, and trade union membership records	Lip, incidence	Reference group (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; near-complete ascertainment of cancer incidence; use of three reference groups to evaluate healthy-worker bias; analyses by proxies of exposure including job task. *Limitations*: little information on potential confounders.
			Firefighters vs general population	4	1.04 (0.39–2.78)		
			Firefighters vs sample of employees	4	1.13 (0.42–3.01)		
			Firefighters vs military	4	1.60 (0.60–4.28)		
		Mouth (ICD-10, C03-C06, C46.2), incidence	Reference group (SIR):				
			Firefighters vs general population	7	0.60 (0.28–1.25)		
			Firefighters vs sample of employees	7	0.57 (0.27–1.19)		
			Firefighters vs military	7	0.61 (0.29–1.27)		
		Pharynx, incidence	Reference group (SIR):				
			Firefighters vs general population	20	0.91 (0.59–1.41)		
			Firefighters vs sample of employees	20	0.94 (0.60–1.45)		
			Firefighters vs military	20	0.87 (0.56–1.35)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Oesophagus, incidence	Reference group (SIR):			Age, calendar period	
			Firefighters vs general population	21	0.99 (0.65–1.53)		
			Firefighters vs sample of employees	21	1.05 (0.68–1.61)		
			Firefighters vs military	21	1.18 (0.77–1.81)		
		Stomach, incidence	Reference group (SIR):				
			Firefighters vs general population	27	1.09 (0.75–1.59)		
			Firefighters vs sample of employees	27	1.12 (0.77–1.63)		
			Firefighters vs military	27	1.26 (0.87–1.84)		
		Colon, incidence	Reference group (SIR):				
			Firefighters vs general population	57	0.73 (0.57–0.95)		
			Firefighters vs sample of employees	57	0.77 (0.59–0.99)		
			Firefighters vs military	57	0.70 (0.54–0.90)		
		Colon, incidence	Employment type (SIR):				
			Full-time	39	0.79 (0.58–1.08)		
			Part-time or volunteer	18	0.64 (0.40–1.01)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Colon, incidence	Era of first employment (SIR):			Age, calendar period	
			Pre-1970	31	0.78 (0.55–1.11)		
			1970–1994	24	0.73 (0.49–1.09)		
			1995 or after	2	0.40 (0.10–1.59)		
		Colon, incidence	Job function (SIR):				
			Regular	53	0.73 (0.56–0.96)		
			Specialized	4	0.78 (0.29–2.08)		
		Colon, incidence	Age at first employment (SIR):				
			< 25 yr	33	0.85 (0.60–1.19)		
			25–34 yr	13	0.59 (0.34–1.02)		
			≥ 35 yr	11	0.65 (0.36–1.18)		
		Colon, incidence	Duration of employment (SIR):				
			< 1 yr	16	0.70 (0.43–1.14)		
			≥ 1 yr	41	0.75 (0.55–1.02)		
			≥ 10 yr	39	0.82 (0.60–1.12)		
			≥ 20 yr	31	0.84 (0.59–1.20)		
		Rectum, incidence	Reference group (SIR):				
			Firefighters vs general population	64	1.22 (0.95–1.55)		
			Firefighters vs sample of employees	64	1.24 (0.97–1.58)		
			Firefighters vs military	64	1.20 (0.94–1.53)		
		Rectum, incidence	Employment type (SIR):				
			Full-time	38	1.16 (0.84–1.60)		
			Part-time or volunteer	26	1.31 (0.89–1.92)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Rectum, incidence	Era of first employment (SIR):			Age, calendar period	
			Pre-1970	37	1.47 (1.06–2.02)		
			1970–1994	24	1.01 (0.68–1.51)		
			1995 or after	3	0.80 (0.26–2.49)		
		Rectum, incidence	Job function (SIR):				
			Regular	58	1.18 (0.91–1.53)		
			Specialized	6	1.72 (0.77–3.84)		
		Rectum, incidence	Age at first employment (SIR):				
			< 25 yr	29	1.13 (0.79–1.63)		
			25–34 yr	19	1.25 (0.80–1.96)		
			≥ 35 yr	16	1.36 (0.83–2.22)		
		Rectum, incidence	Duration of employment (SIR):				
			< 1 yr	16	1.08 (0.66–1.77)		
			≥ 1 yr	48	1.27 (0.96–1.68)		
			≥ 10 yr	38	1.16 (0.85–1.60)		
			≥ 20 yr	33	1.32 (0.94–1.85)		
		Liver (HCC), incidence	Reference group (SIR):				
			Firefighters vs general population	14	0.97 (0.58–1.64)		
			Firefighters vs sample of employees	14	0.98 (0.58–1.65)		
			Firefighters vs military	14	1.17 (0.69–1.98)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Bile duct/ gallbladder, incidence	Reference group (SIR):			Age, calendar period	
			Firefighters vs general population	5	0.99 (0.41–2.37)		
			Firefighters vs sample of employees	5	1.04 (0.43–2.50)		
			Firefighters vs military	5	1.02 (0.42–2.44)		
		Pancreas, incidence	Reference group (SIR):				
			Firefighters vs general population	34	1.20 (0.86–1.68)		
			Firefighters vs sample of employees	34	1.27 (0.91–1.78)		
			Firefighters vs military	34	1.28 (0.92–1.80)		
		Pancreas, incidence	Employment type (SIR):				
			Full-time	27	1.54 (1.05–2.25)		
			Part-time or volunteer	7	0.65 (0.31–1.37)		
		Pancreas, incidence	Era of first employment (SIR):				
			Pre-1970	22	1.63 (1.08–2.48)		
			1970–1994	10	0.78 (0.42–1.45)		
			1995 or after	2	1.02 (0.26–4.08)		
		Pancreas, incidence	Job function (SIR):				
			Regular	31	1.17 (0.83–1.67)		
			Specialized	3	1.60 (0.52–4.97)		
		Pancreas, incidence	Age at first employment (SIR):				
			< 25 yr	23	1.68 (1.12–2.53)		
			25–34 yr	3	0.36 (0.12–1.13)		
			≥ 35 yr	8	1.27 (0.63–2.53)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018a) (cont.)		Pancreas, incidence	Duration of employment (SIR):			Age, calendar period	
			< 1 yr	14	1.79 (1.05–3.01)		
			≥ 1 yr	20	0.98 (0.63–1.52)		
			≥ 10 yr	13	0.74 (0.43–1.27)		
			≥ 20 yr	10	0.74 (0.40–1.37)		
Petersen et al. (2018b) Denmark Enrolment, 1964–2014/follow-up, 1970–2014 Cohort	11 775 male firefighters (full-time, part-time, and volunteer) identified from employer, trade union, and Danish Civil Registration System records, born in 1928 or later, employed before age 60 yr and 31 December 2004, and a job title/function indicating actual firefighting exposure Exposure assessment method: ever employed and categorical duration of employment (years) as a firefighter ascertained from civil registration, pension, employer personnel, and trade union membership records	Oral cavity and oesophagus (ICD-10, C00–C15), mortality	Employment type (SMR, military reference group):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Includes part-time and full-time firefighters. Excluded those who did not actually fight fires. May include municipal and rural firefighters. *Strengths*: long period of follow-up; use of military reference group to evaluate healthy-worker bias; analyses by duration of employment. *Limitations*: few data on potential confounders.
			Full-time	24	1.27 (0.85–1.89)		
			Part-time/volunteer	8	0.63 (0.32–1.27)		
		Oral cavity and oesophagus (ICD-10, C00–C15), mortality	Duration of employment (SMR, military reference group):				
			Full-time firefighters:				
			< 1 yr	11	1.39 (0.77–2.51)		
			≥ 1 yr	13	1.18 (0.68–2.03)		
			≥ 10 yr	11	1.13 (0.63–2.05)		
			≥ 20 yr	10	1.21 (0.65–2.25)		
		Stomach, mortality	Employment type (SMR, military reference group):				
			Full-time	17	1.96 (1.22–3.16)		
			Part-time/volunteer	1	0.18 (0.03–1.31)		
		Stomach, mortality	Duration of employment (SMR, military reference group):				
			Full-time firefighters:				
			< 1 yr	8	2.13 (1.07–4.26)		
			≥ 1 yr	9	1.84 (0.95–3.53)		
			≥ 10 yr	8	1.85 (0.93–3.70)		
			≥ 20 yr	7	1.90 (0.91–3.99)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petersen et al. (2018b) (cont.)		Colon, rectosigmoid junction, small intestines, mortality	Employment type (SMR, military reference group):			Age, calendar period	
			Full-time	25	1.11 (0.75–1.64)		
			Part-time/ volunteer	8	0.66 (0.33–1.32)		
		Colon, rectosigmoid junction, small intestines, mortality	Duration of employment, full-time firefighters (SMR, military reference group):				
			< 1 yr	14	1.31 (0.78–2.22)		
			≥ 1 yr	11	0.92 (0.51–1.66)		
			≥ 10 yr	11	1.03 (0.57–1.86)		
			≥ 20 yr	8	0.87 (0.43–1.73)		
		Rectum, mortality	Employment type (SMR, military reference group):				
			Full-time	12	1.04 (0.59–1.83)		
			Part-time/ volunteer	8	1.34 (0.67–2.69)		
		Rectum, mortality	Duration of employment, full-time firefighters (SMR, military reference group):				
			< 1 yr	5	0.91 (0.38–2.18)		
			≥ 1 yr	7	1.16 (0.56–2.44)		
			≥ 10 yr	5	0.93 (0.39–2.23)		
			≥ 20 yr	4	0.86 (0.32–2.29)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Moir et al. (2016) USA Follow-up, 11 September 2001 through 2009 Cohort	11 457 White male WTC-exposed firefighters (and 8220 non-WTC firefighters) who were employed at FDNY on or after 1 January 1996, actively employed for ≥ 1.5 yr before end of follow-up (31 December 2009), whose identifying information was sent to state cancer registries; contributing person-years at risk at ages 30–70 yr from 11 September 2001 to study end; referent group included firefighters from San Francisco, Chicago, and Philadelphia Exposure assessment method: presence at WTC site from employment records and duty rosters	Colon, incidence	Group (RR):			Age	*Exposure assessment critique*: Satisfactory quality. Exposure at WTC captured but did not consider previous firefighter work. Only measure of exposure was being a firefighter at WTC. Exposures complex and probably unique to 9/11 disaster. Urban [municipal] firefighters. *Other comments*: only first primaries were included. *Strengths*: relatively large cohort. *Limitations*: short period of follow-up; aimed to investigate effect of WTC exposure, not to firefighting per se.
			Referent group	21	1		
			WTC-exposed FDNY firefighters	14	0.73 (0.33–1.59)		
		Colon, incidence	Group (RR, early time period (11 September 2001 to 31 December 2004) diagnoses only):				
			Referent group	6	1		
			WTC-exposed FDNY firefighters	6	1.69 (0.42–6.80)		
		Colon, incidence	Group (RR, late time period (1 January 2005 to 31 December 2009, diagnoses only):				
			Referent group	15	1		
			WTC-exposed FDNY firefighters	8	0.49 (0.17–1.30)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeig-Owens et al. (2011) New York City, USA Enrolment, 1996/follow-up, 1996–2008 Cohort	9853 male FDNY firefighters employed for ≥ 18 mo, were active firefighters on 1 January 1996, with no prior cancer, and, if alive on 12 September 2001, also had known WTC-exposure status Exposure assessment method: WTC-exposed and unexposed firefighter from employment records and questionnaires	Oesophagus, incidence	WTC-exposure status (SIR):			Age, race, ethnic origin, calendar year	*Exposure assessment critique*: Satisfactory quality. Intensity of exposure at WTC captured but did not consider previous firefighter work. WTC exposure self-reported using three methods. WTC site exposures complex and probably unique to the 9/11 disaster. *Other comments*: evaluation of medical surveillance bias. *Strengths*: evaluation of medical surveillance bias. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Non-exposed	≤ 5	0.44 (0.06–3.13)		
			Exposed	≤ 5	0.58 (0.15–2.32)		
			SIR ratio (exposed vs non-exposed)	NR	1.32 (0.12–14.53)		
		Stomach, incidence	WTC-exposure status (SIR):				
			Non-exposed	≤ 5	1.23 (0.40–3.83)		
			Exposed	8	2.24 (0.98–5.25)		
			SIR ratio (exposed vs non-exposed)	NR	1.82 (0.44–7.49)		
		Colon, incidence	WTC-exposure status (SIR):				
			Non-exposed	9	1.01 (0.53–1.94)		
			Exposed	21	1.52 (0.99–2.33)		
			SIR ratio (exposed vs non-exposed)	NR	1.50 (0.69–3.27)		
		Pancreas, incidence	WTC-exposure status (SIR):				
			Non-exposed	≤ 5	0.31 (0.04–2.20)		
			Exposed	≤ 5	0.78 (0.29–2.09)		
			SIR ratio (exposed vs non-exposed)	NR	2.52 (0.28–22.59)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) San Francisco, Chicago, Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2016 Cohort	29 992 municipal career firefighters in the CFHS cohort employed by the fire departments of San Francisco, Chicago, or Philadelphia for ≥ 1 day between 1950 and 2009; exposure–response analyses limited to 19 287 male firefighters of known race hired in 1950 or later and employed for ≥ 1 yr Exposure assessment method: ever employed as a firefighter, and number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Oesophagus, mortality	Fire department (SMR):			Gender, race, age, calendar period	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices; adjustment for HWSE. *Limitations*: healthy-worker selection bias in external comparison analyses; little information on potential confounders.
			San Francisco	26	1.31 (0.86–1.92)		
			Chicago	68	1.39 (1.08–1.77)		
			Philadelphia	39	1.18 (0.84–1.62)		
			Overall	133	1.31 (1.10–1.55)		
			Heterogeneity *P* value, 0.71				
		Oesophagus, mortality	Race (SMR):				
			White	> 128	1.38 (1.15–1.64)		
			Non-White	< 5	0.50 (0.14–1.28)		
		Oesophagus, mortality	Age (SMR):				
			< 65 yr	54	1.26 (0.94–1.64)		
			≥ 65 yr	79	1.35 (1.07–1.68)		
			Heterogeneity *P* value, 0.70				
		Oesophagus, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	82	0.63 (0.40–1.00)		
			RCS without HWSE adjustment	82	0.60 (0.36–1.02)		
			Fully adjusted loglinear	82	0.73 (0.40–1.36)		
			Fully adjusted RCS	82	0.65 (0.33–1.36)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Oesophagus, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	72	0.97 (0.68–1.36)		
			RCS without HWSE adjustment	72	1.15 (0.74–1.81)		
			Fully adjusted loglinear	72	1.10 (0.75–1.58)		
			Fully adjusted RCS	72	1.45 (0.88–2.44)		
		Oesophagus, mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag):				
			Loglinear without HWSE adjustment	45	0.91 (0.53–1.51)		
			RCS without HWSE adjustment	45	0.95 (0.50–1.83)		
			Fully adjusted loglinear	45	1.17 (0.65–2.05)		
			Fully adjusted RCS	45	1.31 (0.64–2.75)		
		Oesophagus, mortality	Time since first exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Lag to < 20 yr	NR	1.10 (0.36–3.05)		
			20 to < 30 yr	NR	0.92 (0.37–2.12)		
			≥ 30 yr	NR	1.26 (0.69–2.15)		
			LRT *P* value, 0.84				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Oesophagus, mortality	Age at exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			< 40 yr	NR	1.25 (0.69–2.15)		
			≥ 40 yr	NR	0.96 (0.50–1.76)		
			LRT *P* value, 0.58				
		Oesophagus, mortality	Period of exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):				
			Pre-1970	NR	2.00 (1.01–3.69)		
			1970 or after	NR	0.81 (0.49–1.30)		
			LRT *P* value, 0.04				
		Stomach, mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	27	1.13 (0.75–1.65)		
			Chicago	62	1.15 (0.88–1.48)		
			Philadelphia	35	0.90 (0.62–1.25)		
			Overall	124	1.06 (0.88–1.27)		
			Heterogeneity *P* value, 0.46				
		Stomach, mortality	Race (SMR):			Gender, age, calendar period	
			White	118	1.09 (0.91–1.31)		
			Non-White	6	0.68 (0.25–1.48)		
		Stomach, mortality	Age (SMR):				
			< 65 yr	40	0.74 (0.53–1.01)		
			≥ 65 yr	84	1.34 (1.07–1.65)		
			Heterogeneity *P* value, < 0.01				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Stomach, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	52	1.13 (0.62–2.16)		
			RCS without HWSE adjustment	52	1.00 (0.50–2.19)		
			Fully adjusted loglinear	52	1.75 (0.74–4.53)		
			Fully adjusted RCS	52	1.40 (0.51–4.44)		
		Stomach, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):				
			Loglinear without HWSE adjustment	45	1.07 (0.68–1.62)		
			RCS without HWSE adjustment	45	1.28 (0.73–2.28)		
			Fully adjusted loglinear	45	1.25 (0.76–1.95)		
			Fully adjusted RCS	45	1.67 (0.87–3.31)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Stomach, mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	30	1.34 (0.7–2.45)		
			RCS without HWSE adjustment	30	1.37 (0.62–3.20)		
			Fully adjusted loglinear	30	1.45 (0.71–2.87)		
			Fully adjusted RCS	30	1.54 (0.63–3.94)		
		Stomach, mortality	Time since first exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Attained age, race, birthdate (within 5 yr) and department, employment duration	
			Lag to < 20 yr	NR	1.45 (0.42–4.31)		
			20 to < 30 yr	NR	1.69 (0.55–4.67)		
			≥ 30 yr	NR	0.92 (0.38–1.93)		
			LRT *P* value, 0.61				
		Small intestine, colon (ICD-10, C17–C18), mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	59	0.99 (0.75–1.27)		
			Chicago	189	1.37 (1.19–1.58)		
			Philadelphia	122	1.28 (1.07–1.53)		
			Overall	370	1.27 (1.14–1.40)		
			Heterogeneity *P* value, 0.08				
		Small intestine, colon (ICD-10, C17–C18), mortality	Race (SMR):			Gender, age, calendar period	
			White	359	1.30 (1.17–1.44)		
			Non-White	11	0.67 (0.34–1.21)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Small intestine, colon (ICD-10, C17–C18), mortality	Age (SMR):			Gender, race, age, calendar period	
			< 65 yr	104	1.01 (0.82–1.22)		
			≥ 65 yr	266	1.40 (1.24–1.58)		
			Heterogeneity *P* value, < 0.01				
		Colon, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	145	0.83 (0.58–1.18)		
			RCS without HWSE adjustment	145	0.77 (0.51–1.17)		
			Fully adjusted loglinear	145	0.87 (0.56–1.38)		
			Fully adjusted RCS	145	0.75 (0.45–1.31)		
		Colon, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):				
			Loglinear without adjustment	132	0.83 (0.63–1.08)		
			RCS without HWSE adjustment	132	0.80 (0.58–1.09)		
			Fully adjusted loglinear	132	0.89 (0.66–1.18)		
			Full adjusted RCS	132	0.87 (0.61–1.23)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Colon, mortality	Fire-hours (Chicago only) model (HR at 2300 h vs 600 h, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	100	0.79 (0.54–1.12)		
			RCS without HWSE adjustment	100	0.79 (0.51–1.21)		
			Fully adjusted loglinear	100	0.84 (0.56–1.26)		
			Fully adjusted RCS	100	0.84 (0.52–1.36)		
		Colon, mortality	Time since first exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Lag to < 20 yr	NR	0.64 (0.26–1.48)		
			20 to < 30 yr	NR	0.76 (0.36–1.49)		
			≥ 30 yr	NR	1.13 (0.71–1.73)		
			LRT *P* value, 0.37				
		Rectum, mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	20	1.33 (0.81–2.06)		
			Chicago	52	1.53 (1.14–2.01)		
			Philadelphia	25	1.02 (0.66–1.51)		
			Overall	97	1.32 (1.07–1.16)		
			Heterogeneity *P* value, 0.25				
		Rectum, mortality	Race (SMR):			Gender, age, calendar period	
			White	> 92	1.36 (1.10–1.66)		
			Non-White	< 5	0.72 (0.15–2.11)		
		Rectum, mortality	Age (SMR):			Gender, race, age, calendar period	
			< 65 yr	40	1.21 (0.87–1.65)		
			≥ 65 yr	57	1.41 (1.07–1.83)		
			Heterogeneity *P* value, 0.46				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Rectum, mortality	Exposed-days model (HR at 8700 exposed-days vs 2500 exposed-days, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department	
			Loglinear without HWSE adjustment	42	0.45 (0.24–0.88)		
			RCS without HWSE adjustment	42	0.41 (0.21–0.83)		
			Fully adjusted loglinear	42	0.49 (0.21–1.19)		
			Fully adjusted RCS	42	0.43 (0.17–1.20)		
		Rectum, mortality	Fire-runs (Chicago and Philadelphia only) model (HR at 8800 runs vs 2100 runs, 10-yr lag):				
			Loglinear without HWSE adjustment	34	0.32 (0.16–0.61)		
			RCS without HWSE adjustment	34	0.39 (0.17–0.87)		
			Fully adjusted loglinear	34	0.36 (0.16–0.75)		
			Fully adjusted RCS	34	0.47 (0.18–1.22)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pinkerton et al. (2020) (cont.)		Rectum, mortality	Time since first exposure in fire-runs (Chicago and Philadelphia only) fully adjusted loglinear model (HR for 8800 runs vs 2100 runs, 10-yr lag):			Age, race, birthdate (within 5 yr), fire department, employment duration	
			Lag to < 20 yr	NR	0.18 (0.02–1.51)		
			20 to < 30 yr	NR	0.80 (0.15–3.30)		
			≥ 30 yr	NR	0.24 (0.06–0.80)		
			LRT *P* value, 0.54				
		Breast, mortality	Fire department (SMR):			Gender, race, age, calendar period	
			San Francisco	NR	2.11 (0.58–5.41)		
			Chicago	NR	1.16 (0.38–2.71)		
			Philadelphia	NR	0.53 (0.01–2.94)		
			Overall	10	1.24 (0.59–2.27)		
			Heterogeneity *P* value, 0.37				
Daniels et al. (2015) San Francisco, Chicago, Philadelphia, USA Enrolment, 1950–2009/follow-up, 1950–2009 (mortality), 1985–2009 (incidence) Cohort	19 309; all male career firefighters in the CFHS cohort of known race who were on active duty for ≥ 1 day from 1950 through 2009 in the fire departments of Chicago, Philadelphia, or San Francisco with ≥ 1 yr of employment Exposure assessment method: number of exposed days, fire-runs, fire-hours reconstructed using job-exposure matrix based on job titles and assignments and departmental work history records and historical fire-run and fire-hour data	Oesophagus, incidence	Exposed-days model (HR, linear model, 10-yr lag):			Age, race, fire department, birth cohort	*Exposure assessment critique*: Good quality. Minimal bias in exposure assessment in internal analyses. Municipal firefighters. *Strengths*: long period of follow-up; exposure–response modelling for three metrics of exposure assessed using job-exposure matrices. *Limitations*: little information on potential confounders.
			8700 days vs 2500 days	54	0.66 (0.42–1.18)		
		Oesophagus, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, power model, 10-year lag):			Age, race, fire department, birth cohort	
			8800 runs vs 2100 runs	48	1.22 (0.89–1.88)		
		Oesophagus, incidence	Fire-hours (Chicago only) model (HR, linear model, 10-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	29	0.57 (NR–1.10)		
		Colon and rectum, incidence	Exposed-days model (HR, power model, 10-yr lag):			Age, race, fire department, birth cohort	
			8700 days vs 2500 days	289	0.92 (0.84–1.01)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2015) (cont.)		Colon and rectum, incidence	Fire-runs (Chicago and Philadelphia only) model (HR, loglinear model, 10-year lag):			Age, race, fire department, birth cohort	
			8800 runs vs 2100 runs	240	0.89 (0.72–1.09)		
		Colon and rectum, incidence	Fire-hours (Chicago only) model (HR, linear model, 10-yr lag):			Age, race, birth cohort	
			2300 h vs 600 h	158	0.78 (0.63–1.04)		
Daniels et al. (2014) San Francisco, Chicago, Philadelphia, USA Enrolment, 1950–2009/follow-up 1950–2009 (mortality), 1985–2009 (incidence) Cohort	29 993 (24 453 for incidence analyses); male and female career firefighters in the CFHS cohort employed for ≥ 1 day in Chicago, San Francisco, or Philadelphia fire departments between 1950 and 2009 Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Oral cavity and pharynx combined, incidence	SIR:			Gender, race, age, calendar period	*Exposure assessment critique*: Satisfactory quality. Minimum exposure is 1 day of work as a municipal firefighter. *Strengths*: long period of follow-up; ascertained incidence outcomes; included female firefighters. *Limitations*: healthy-worker hire bias in external comparisons; little information on potential confounders.
			All cancers	174	1.39 (1.19–1.62)		
			First primary cancer	148	1.41 (1.20–1.66)		
		Oesophagus, incidence	SIR:				
			All cancers	90	1.62 (1.31–2.00)		
			First primary cancer	80	1.71 (1.36–2.13)		
		Oesophagus, incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men:				
			Caucasian [White]	87	1.70 (1.36–2.09)		
			Other	< 5	0.73 (0.15–2.15)		
		Stomach, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	93	1.15 (0.93–1.40)		
			First primary cancer	72	1.02 (0.80–1.28)		
		Stomach, incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men:				
			Caucasian [White]	87	1.19 (0.96–1.47)		
			Other	6	0.76 (0.28–1.66)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Daniels et al. (2014) (cont.)		Small intestine, colon (ICD-10, C17–C18), incidence	SIR:			Gender, race, age, calendar period	
			All cancers	398	1.21 (1.09–1.33)		
			First primary cancer	351	1.29 (1.16–1.43)		
		Small intestine, colon (ICD-10, C17–C18), incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men:				
			Caucasian [White]	379	1.23 (1.11–1.36)		
			Other	18	0.90 (0.53–1.42)		
		Colon, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	381	1.21 (1.09–1.34)		
			First primary cancer	335	1.28 (1.15–1.43)		
		Rectum, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	166	1.11 (0.95–1.30)		
			First primary cancer	140	1.09 (0.91–1.28)		
		Rectum, incidence	Race (SIR, all cancers):			Age, calendar period	
			Among men:				
			Caucasian [White]	159	1.16 (0.99–1.36)		
			Other	7	0.62 (0.25–1.28)		
		Breast, incidence	SIR:			Gender, race, age, calendar period	
			All cancers	26	1.26 (0.82–1.85)		
			First primary cancer	24	1.32 (0.84–1.96)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) Seattle and Tacoma, Washington, USA Enrolment, 1944–1979/follow-up, 1974–1989 Cohort	2447 male firefighters employed for ≥ 1 yr between 1944 and 1979, alive as of 1 January 1974 and known to be a resident of one of 13 counties in the catchment area of the tumour registry for ≥ 1 mo; reference group included 1878 local male police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration of employment (years) in direct firefighting positions from employment records	Oral cavity and pharynx, incidence	SIR (local county rates):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Duration (years) involved in direct firefighting (surrogate for fire smoke) was not measured equally in the two study populations. Municipal firefighters. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders; small number of cases for some outcomes.
			Firefighters	11	1.1 (0.6–2.0)		
		Oral cavity and pharynx, incidence	IDR:				
			Local police	8	1		
			Firefighters	11	0.8 (0.3–1.9)		
		Oral cavity and pharynx, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	2	1.4 (0.2–5.1)		
			10–19 yr	4	2.5 (0.7–6.4)		
			20–29 yr	2	0.3 (0.0–1.2)		
			≥ 30 yr	3	3.9 (0.8–11)		
		Oral cavity and pharynx, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	1	1.5 (0.0–8.2)		
			20–29 yr	1	0.5 (0.0–2.7)		
			≥ 30 yr	9	1.3 (0.6–2.4)		
		Oesophagus, incidence	SIR (local county rates):				
			Firefighters	4	1.3 (0.4–3.3)		
		Oesophagus, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	0	0 (0.0–9.3)		
			10–19 yr	2	4.8 (0.6–17.2)		
			20–29	2	1.0 (0.1–36.1)		
			≥ 30 yr	0	0 (0.0–12)		
		Oesophagus, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	0	0 (0.0–36.5)		
			20–29 yr	2	4.3 (0.5–15.4)		
			≥ 30 yr	2	0.8 (0.1–2.8)		
		Stomach, incidence	SIR (local county rates):				
			Firefighters	8	1.4 (0.6–2.7)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		Stomach, incidence	IDR:			Age, calendar period	
			Local police	7	1		
			Firefighters	8	0.4 (0.1–1.2)		
		Stomach, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	2	3 (0.4–11)		
			10–19 yr	1	1.2 (0.0–6.9)		
			20–29 yr	4	1.1 (0.3–2.9)		
			≥ 30 yr	1	1.4 (0.0–8.1)		
		Stomach, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	0	0 (0.0–15.7)		
			20–29 yr	2	2.3 (0.3–8.3)		
			≥ 30 yr	6	1.3 (0.5–2.8)		
		Colon, incidence	SIR (local county rates):				
			Firefighters	23	1.1 (0.7–1.6)		
		Colon, incidence	IDR:				
			Local police	8	1		
			Firefighters	23	1.3 (0.6–3.0)		
		Colon, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	2	0.8 (0.1–2.9)		
			10–19 yr	2	0.7 (0.1–2.6)		
			20–29 yr	15	1.1 (0.6–1.9)		
			≥ 30 yr	4	1.5 (0.4–3.9)		
		Colon, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	0	0 (0.0–5.7)		
			20–29 yr	3	1.2 (0.3–3.5)		
			≥ 30 yr	20	1.1 (0.7–1.7)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		Colon, incidence	Duration of exposed employment (IDR):			Age, calendar period	
			< 10 yr	2	1		
			10–19 yr	2	1.0 (0.1–7.2)		
			20–29 yr	15	1.3 (0.3–5.9)		
			≥ 30 yr	4	1.8 (0.3–11.6)		
		Colon, incidence	Duration of exposed employment (IDR):				
			< 10 yr vs local police	2	1.0 (0.2–4.8)		
			10–19 yr vs local police	2	0.9 (0.2–4.4)		
			20–29 yr vs local police	15	1.4 (0.6–3.2)		
			≥ 30 yr vs local police	4	2.0 (0.5–8.0)		
		Rectum, incidence	SIR (local county rates):				
			Firefighters	12	1.0 (0.5–1.8)		
		Rectum, incidence	IDR:				
			Local police	5	1		
			Firefighters	12	1.3 (0.5–3.9)		
		Rectum, incidence	Duration of exposed employment (SIR, local county rates):				
			< 10 yr	2	1.4 (0.2–4.9)		
			10–19 yr	3	1.9 (0.4–5.4)		
			20–29 yr	5	0.7 (0.2–1.6)		
			≥ 30 yr	2	1.6 (0.2–5.6)		
		Rectum, incidence	Years since first employment (SIR, local county rates):				
			< 20 yr	0	0 (0.0–8.8)		
			20–29 yr	4	2.2 (0.6–5.7)		
			≥ 30 yr	8	0.8 (0.4–1.7)		
		Pancreas, incidence	SIR (local county rates):				
			Firefighters	6	1.1 (0.4–2.3)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1994) (cont.)		Pancreas, incidence	IDR:			Age, calendar period	
			Local police	3	1		
			Firefighters	6	1.1 (0.3–5.5)		
		Breast, incidence	SIR (local county rates):				
			Firefighters	1	2.4 (0.1–13.3)		
Demers et al. (1992a) Seattle and Tacoma, Washington, and Portland, Oregon, USA Enrolment, 1944–1979/follow-up, 1944–1989 Cohort	4401 male firefighters employed for ≥ 1 yr between 1944 and 1979 in Seattle, Tacoma, or Portland, USA; reference group included 3676 local police officers Exposure assessment method: ever employed for ≥ 1 yr, and categorical duration (years) of exposure to fire combat from employment records	Oral cavity and pharynx combined, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory/good quality. Duration (years) involved in fire combat (surrogate for fire smoke) was not measured equally in the three municipal firefighter populations. *Strengths*: use of two comparison groups, including comparison with police officers to limit healthy-worker bias. *Limitations*: little information on potential confounders; ascertained mortality outcomes only.
			Firefighters	7	0.81 (0.33–1.66)		
		Oesophagus, mortality	SMR:				
			Firefighters	6	0.83 (0.30–1.80)		
		Stomach, mortality	SMR:				
			Firefighters	16	1.07 (0.61–1.73)		
		Colon, mortality	SMR:				
			Firefighters	24	0.85 (0.54–1.26)		
		Colon, mortality	IDR:				
			Local police	8	1		
			Firefighters	24	1.58 (0.73–3.43)		
		Colon, mortality	Duration of exposed employment (SMR):				
			< 10 yr	4	1.40 (0.4–3.6)		
			10–19 yr	2	0.54 (0.1–2.0)		
			20–29 yr	9	0.62 (0.3–1.2)		
			≥ 30 yr	9	1.21 (0.6–2.3)		
		Colon, mortality	Years since first employment (SMR):				
			< 20 yr	1	0.51 (0.1–2.9)		
			20–29 yr	3	0.66 (0.1–1.9)		
			≥ 30 yr	20	0.91 (0.6–1.4)		
		Colon, mortality	Age at risk (SMR):				
			18–39 yr	1	1.38 (0.1–8.2)		
			40–64 yr	10	0.78 (0.4–1.4)		
			≥ 65 yr	13	0.86 (0.5–1.5)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (1992a) (cont.)		Rectum, mortality	SMR:			Age, calendar period	
			Firefighters	8	0.95 (0.41–1.87)		
		Rectum, mortality	IDR:				
			Local police	5	1		
			Firefighters	8	0.89 (0.30–2.66)		
		Liver and bile ducts, mortality	SMR:				
			Firefighters	6	1.19 (0.44–2.59)		
		Liver and bile ducts, mortality	IDR:				
			Local police	4	1		
			Firefighters	6	0.71 (0.19–2.71)		
		Pancreas, mortality	SMR:				
			Firefighters	14	0.89 (0.49–1.49)		
Vena & Fiedler (1987) Buffalo, New York, USA 1950–1979 Cohort	1867 White male career firefighters employed by the City of Buffalo for ≥ 5 yr, with ≥ 1 yr as a firefighter Exposure assessment method: ever-employment, timing, and duration of employment from employment records	Oesophagus, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Minimal quality. Only assessed ever-employment and duration of employment as a municipal firefighter. *Strengths*: long length of follow-up. *Limitations*: healthy-worker hire bias; little information on potential confounders or exposure to firefighting activities.
			Firefighters	3	1.34 (0.27–3.91)		
		Stomach, mortality	SMR:				
			Firefighters	7	1.19 (0.48–2.46)		
		Colon, mortality	SMR:				
			Firefighters	16	1.83 (1.05–2.97)		
		Colon, mortality	Years worked as a firefighter (SMR):				
			1–9 yr	0	0 (NR)		
			10–19 yr	1	[1.25 (0.1–6.2)]		
			20–29 yr	2	[0.87 (0.1–2.9)]		
			30–39 yr	5	[1.43 (0.5–3.2)]		
			≥ 40 yr	8	[4.71 (2.2–8.9)]		
		Colon, mortality	Calendar year of death (SMR):				
			1950–1959	3	[1.76 (0.4–4.8)]		
			1960–1969	4	[1.38 (0.4–3.3)]		
			1970–1979	9	[2.20 (1.1–4.0)]		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena & Fiedler (1987) (cont.)		Colon, mortality	Year of hire (SMR):			Age, calendar period	
			Pre-1930	10	[2.27 (1.2–4.1)]		
			1930–1939	4	[2.35 (0.7–5.7)]		
			1940–1949	4	[1.11 (0.2–3.7)]		
			1950 or after	0	0 (NR)		
		Colon, mortality	Years of latency (SMR):				
			< 20 yr	0	0 (NR)		
			20–29 yr	2	[1.30 (0.2–4.4)]		
			30–39 yr	4	[1.51 (0.5–3.6)]		
			40–49 yr	7	[2.65 (1.2–5.3)]		
			≥ 50 yr	3	[2.85 (0.7–7.4)]		
		Rectum, mortality	SMR:				
			Firefighters	7	2.08 (0.83–4.28)		
		Liver and bile ducts, mortality	SMR:				
			Firefighters	2	0.98 (0.11–3.52)		
		Pancreas, mortality	SMR:				
			Firefighters	2	0.38 (0.04–1.36)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Feuer & Rosenman (1986) New Jersey (NJ), USA 1974–1980 Cohort	263 deceased White male firefighters in the New Jersey Police and Firemen Retirement System (firefighters vested with ≥ 10 yr of service, or firefighters who died while on payroll regardless of employment duration); one reference group included 567 White male police deaths Exposure assessment method: ever employed, and categorical duration of employment (years), as a career firefighter from retirement system records	Digestive (ICD-8, 150–159), mortality	Reference population (PMR):			Age, race	*Exposure assessment critique*: Satisfactory quality. Assessment provides duration of employment categories. May include municipal and rural firefighters. *Strengths*: comparison with other uniformed service occupation. *Limitations*: PMR study design lacks event-free follow-up time; short observation period; little information on potential confounders.
			Firefighters vs US White men	20	[1.45 (0.91–2.20)]		
			Firefighters vs NJ White men	20	[1.11 (0.70–1.69)]		
			Firefighters vs White male NJ police	20	[0.91 (0.57–1.38)]		
		Digestive (ICD-8, 150–159), mortality	Duration of employment (PMR):				
			≤ 20 yr	5	[1.24 (0.45–2.75)]		
			20–25 yr	5	[0.96 (0.35–2.13)]		
			> 25 yr	10	[1.15 (0.58–2.05)]		
		Digestive (ICD-8, 150–159), mortality	Latency (PMR):				
			≤ 22 yr	4	[0.92 (0.29–2.22)]		
			22–27 yr	7	[1.28 (0.56–2.53)]		
			> 27 yr	9	[1.10 (0.54–2.02)]		
Aronson et al. (1994) Toronto, Canada 1950–1989 Cohort	5414 male firefighters employed for ≥ 6 mo at one of six fire departments in Metropolitan Toronto any time between 1950 and 1989 Exposure assessment method: ever employed and categorical duration of employment (years) as municipal firefighter from employment records	Pharynx, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Unclear if individuals were active firefighters for whole employment. Probably municipal firefighters. *Strengths*: long period of follow-up; analysis of employment duration. *Limitations*: healthy-worker hire bias; little information on confounders or exposure; ascertained mortality outcomes only.
			Any employment	4	1.39 (0.38–3.57)		
		Pharynx, mortality	Years since first exposure (SMR):				
			< 20 yr	0	0 (0–9.46)		
			20–29 yr	1	1.22 (0.03–6.80)		
			≥ 30 yr	3	1.81 (0.37–5.28)		
		Pharynx, mortality	Years of employment (SMR):				
			< 15 yr	1	2.33 (0.06–12.96)		
			15–29 yr	0	0 (0–3.26)		
			≥ 30 yr	3	2.33 (0.48–6.80)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aronson et al. (1994) (cont.)		Pharynx, mortality	Age (SMR):			Age, calendar period	
			< 60 yr	1	0.62 (0.02–3.44)		
			≥ 60 yr	3	2.40 (0.49–7.01)		
		Oesophagus, mortality	SMR:				
			Any employment	2	0.40 (0.05–1.43)		
		Stomach, mortality	SMR:				
			Any employment	7	0.51 (0.20–1.05)		
		Colon, mortality	SMR:				
			Any employment	11	0.60 (0.30–1.08)		
		Rectum, mortality	SMR:				
			Any employment	13	1.71 (0.91–2.93)		
		Rectum, mortality	Years since first exposure (SMR):				
			< 20 yr	1	1.35 (0.03–7.53)		
			20–29 yr	2	1.46 (0.18–5.27)		
			≥ 30 yr	10	1.82 (0.87–3.36)		
		Rectum, mortality	Years of employment (SMR):				
			< 15 yr	0	0 (0–4.67)		
			15–29 yr	5	2.35 (0.76–5.48)		
			≥ 30 yr	8	1.74 (0.75–3.43)		
		Rectum, mortality	Age (SMR):				
			< 60 yr	4	1.39 (0.38–3.56)		
			≥ 60 yr	9	1.91 (0.87–3.63)		
		Liver and bile ducts, mortality	SMR:				
			Any employment	2	0.84 (0.10–3.05)		
		Pancreas, mortality	SMR:				
			Any employment	14	1.40 (0.77–2.35)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aronson et al. (1994) (cont.)		Pancreas, mortality	Years since first exposure (SMR):			Age, calendar period	
			< 20 yr	1	1.03 (0.03–5.74)		
			20–29 yr	2	0.95 (0.12–3.44)		
			≥ 30 yr	11	1.59 (0.80–2.85)		
		Pancreas, mortality	Years of employment (SMR):				
			< 15 yr	2	1.75 (0.21–6.34)		
			15–29 yr	3	0.96 (0.20–2.79)		
			≥ 30 yr	9	1.61 (0.74–3.05)		
		Pancreas, mortality	Age (SMR):				
			< 60 yr	4	0.97 (0.27–2.49)		
			≥ 60 yr	10	1.70 (0.81–3.13)		
Guidotti (1993) Edmonton and Calgary, province of Alberta, Canada 1927–1987 Cohort	3328; all firefighters employed between 1927 and 1987 by either of the fire departments of Edmonton or Calgary Exposure assessment method: ever employed and categorical duration of employment (years) from employment records; exposure index of years of employment weighted by time spent in proximity to fires based on job classification	Oral cavity and pharynx combined, mortality	SMR:			Age, calendar period	*Exposure assessment critique*: Good quality. Good approach to differentiate exposure between ranks. Municipal firefighters. *Strengths*: long length of follow-up; analyses by duration of employment and exposure index. *Limitations*: little information on potential confounders; ascertained mortality outcomes only; low number of cases for stratified analyses.
			Any employment	2	1.14 (0.14–4.10)		
		Stomach, mortality	SMR:				
			Any employment	6	0.81 (0.30–1.76)		
		Colon and rectum, mortality	SMR:				
			Any employment	14	1.61 (0.88–2.71)		
		Colon and rectum, mortality	Year of cohort entry (SMR):				
			Pre-1920	4	[1.49 (0.47–3.60)]		
			1920–29	0	0 (NR)		
			1930–39	2	[2.65 (0.44–8.76)]		
			1940–49	2	[1.23 (0.21–4.05)]		
			1950–59	3	[1.49 (0.38–4.07)]		
			1960–69	2	[3.40 (0.57–11.2)]		
			1970–79	0	0 (NR)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) (cont.)		Colon and rectum, mortality	Latency (SMR):			Age, calendar period	
			< 20 yr	2	[1.48 (0.25–4.90)]		
			20–29 yr	5	[2.68 (0.98–5.93)]		
			30–39 yr	3	[1.24 (0.32–3.39)]		
			40–49 yr	2	[1.20 (0.20–3.96)]		
			≥ 50 yr	2	[1.46 (0.24–4.82)]		
		Colon and rectum, mortality	Exposure index (SMR):				
			0	0	0 (NR)		
			> 0 to < 1	2	[2.83 (0.47–9.31)]		
			1–9	6	[4.58 (1.86–9.53)]		
			≥ 10	6	[0.90 (0.37–1.88)]		
		Colon and rectum, mortality	Latency, exposure index > 0, < 1 (SMR):				
			< 20 yr	0	0 (NR)		
			20–29 yr	1	[5.48 (0.28–27.4)]		
			30–39 yr	1	[5.95 (0.29–29.0)]		
			40–49 yr	0	0 (NR)		
			≥ 50 yr	0	0 (NR)		
		Colon and rectum, mortality	Latency, exposure index 1–9 (SMR):				
			< 20 yr	1	[2.31 (0.12–11.5)]		
			20–29 yr	3	[11.46 (2.94–31.4)]		
			30–39 yr	1	[3.50 (0.17–17.0)]		
			40–49 yr	0	0 (NR)		
			≥ 50 yr	1	[5.80 (0.29–29.0)]		
		Colon and rectum, mortality	Latency, exposure index ≥ 10 (SMR):				
			< 20 yr	1	[1.59 (0.08–7.83)]		
			20–29 yr	1	[0.70 (0.04–3.47)]		
			30–39 yr	1	[0.51 (0.03–2.52)]		
			40–49 yr	2	[1.36 (0.23–4.50)]		
			≥ 50 yr	1	[0.85 (0.04–4.22)]		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guidotti (1993) (cont.)		Pancreas, mortality	SMR:			Age, calendar period	
			Any employment	5	1.55 (0.50–3.62)		
		Pancreas, mortality	Latency (SMR):				
			< 20 yr	0	0 (NR)		
			20–29 yr	1	[1.13 (0.06–5.54)]		
			30–39 yr	1	[0.97 (0.05–4.79)]		
			40–49 yr	0	0 (NR)		
			≥ 50 yr	3	[7.16 (1.82–19.4)]		
		Pancreas, mortality	Exposure index (SMR):				
			0	0	0 (NR)		
			> 0 to < 1	0	0 (NR)		
			1–9	1	[2.12 (0.11–10.5)]		
			≥ 10	4	[1.65 (0.52–3.97)]		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) Australia Enrolment, varied by agency/follow-up, 1980–2011 (mortality); 1982–2010 (incidence) Cohort	39 644 female firefighters, both paid [career] (1682) and volunteer (37 962), from nine fire agencies in Australia Exposure assessment method: ever career or volunteer firefighter, categorical duration (years) and era of firefighting from service records; ever firefighter who attended an incident, tertiles of cumulative number of incidents from contemporary incident data and type of incidents attended from personnel records	Lip, oral cavity, and pharynx, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents for volunteer firefighters. Included specific incident types, but early exposure was extrapolated from more recent data. Volunteers mainly rural. *Strengths*: study of female firefighters; includes predominantly rural firefighters; ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			Volunteer firefighters	16	0.81 (0.46–1.32)		
			Volunteer firefighters who attended incidents	7	0.87 (0.35–1.79)		
		Colon, incidence	SIR:				
			Volunteer firefighters	81	1.09 (0.87–1.36)		
			Volunteer firefighters who attended incidents	31	1.12 (0.76–1.59)		
		Rectum, incidence	SIR:				
			Volunteer firefighters	38	1.35 (0.95–1.85)		
			Volunteer firefighters who attended incidents	14	1.26 (0.69–2.12)		
		Colon and rectum, incidence	No. of incidents, all volunteers (RIR) [equivalent to rate ratios]:				
			Zero incidents	57	1		
			Tertile 1	11	0.74 (0.39–1.41)		
			Tertile 2	20	1.15 (0.69–1.92)		
			Tertile 3	18	1.34 (0.78–2.29)		
			Trend-test *P* value, 0.11				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Colon and rectum, incidence	No. of fire incidents, all volunteers (RIR):			Age, calendar period	
			Zero incidents	58	1		
			Tertile 1	11	0.81 (0.43–1.55)		
			Tertile 2	19	1.33 (0.79–2.24)		
			Tertile 3	18	1.45 (0.85–2.47)		
			Trend-test *P* value, 0.13				
		Colon and rectum, incidence	No. of structure fire incidents, all volunteers (RIR):				
			Zero incidents	78	1		
			Tertile 1	6	1.20 (0.52–2.76)		
			Tertile 2	10	1.55 (0.80–3.00)		
			Tertile 3	12	2.08 (1.13–3.84)		
			Trend-test *P* value, 0.26				
		Colon and rectum, incidence	No. of landscape fire incidents, all volunteers (RIR):				
			Zero incidents	65	1		
			Tertile 1	7	0.62 (0.28–1.36)		
			Tertile 2	17	1.18 (0.69–2.02)		
			Tertile 3	17	1.31 (0.77–2.24)		
			Trend-test *P* value, 0.11				
		Colon and rectum, incidence	No. of vehicle fire incidents, all volunteers (RIR):				
			Zero incidents	86	1		
			Tertile 1	7	1.98 (0.91–4.33)		
			Tertile 2	6	1.30 (0.57–2.97)		
			Tertile 3	7	1.59 (0.73–3.46)		
			Trend-test *P* value, 0.73				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2019) (cont.)		Breast, incidence	SIR:			Age, calendar period	
			Volunteer firefighters	349	0.96 (0.86–1.06)		
			Volunteer firefighters who attended incidents	142	0.93 (0.78–1.09)		
Glass et al. (2017) Australia Enrolment, date varied by agency (1998–2000)/ follow-up to 30 November 2011 (mortality) and 31 December 2010 (cancer incidence) Cohort	163 094; all male volunteer firefighters from five fire agencies enrolled on or after the date on which the agency's roll was complete and who had ever held an active firefighting role Exposure assessment method: ever volunteer firefighter, categorical volunteer duration (years) and era from service records; ever volunteer firefighter who attended an incident; tertiles of cumulative emergency incidents from contemporary incident data	Lip, oral cavity, and pharynx, incidence	SIR:			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents. Included specific incident types, but early exposure was extrapolated from more recent data. Firefighters from rural or peri-urban areas. *Strengths*: includes predominantly rural firefighters; ascertained exposure to number and type of incidents. *Limitations*: short length of follow-up; young age at end of follow-up; probable healthy-worker bias; little information on confounders.
			All volunteers	245	0.71 (0.63–0.81)		
			Volunteers who attended incidents	159	0.70 (0.60–0.82)		
		Lip, oral cavity, and pharynx, incidence	Duration of service, all volunteers (RIR) [equivalent to rate ratios]:				
			> 3 mo to 10 yr	82	1		
			10–20 yr	48	1.05 (0.73–1.50)		
			≥ 20 yr	111	1.08 (0.79–1.46)		
			Trend-test *P* value, 0.64				
		Lip, oral cavity, and pharynx, incidence	Duration of service, volunteers who attended incidents:				
			< 3 mo to 10 yr	41	1		
			10–20 yr	33	1.18 (0.74–1.87)		
			≥ 20 yr	86	1.15 (0.76–1.72)		
			Trend-test *P* value, 0.54				
		Oesophagus, incidence	SIR:				
			All volunteers	77	0.65 (0.52–0.82)		
			Volunteers who attended incidents	57	0.76 (0.57–0.98)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Stomach, incidence	SIR:			Age, calendar period	
			All volunteers	116	0.69 (0.57–0.83)		
			Volunteers who attended incidents	74	0.69 (0.55–0.87)		
		Colon and rectum, incidence	SIR:				
			All volunteers	897	0.85 (0.80–0.91)		
			Volunteers who attended incidents	553	0.82 (0.76–0.89)		
		Colon and rectum, incidence	Era of first service (SIR):				
			Pre-1970	283	0.87 (0.77–0.97)		
			1970–1994	336	0.83 (0.74–0.92)		
			1995 or after	278	0.86 (0.76–0.97)		
		Colon and rectum, incidence	Duration of service, all volunteers (RIR):				
			> 3 mo to 10 yr	268	1		
			10–20 yr	147	0.87 (0.71–1.07)		
			≥ 20 yr	469	1.01 (0.86–1.18)		
			Trend-test *P* value, 0.80				
		Colon and rectum, incidence	Duration of service, volunteers who attended incidents (RIR):				
			< 3 mo to 10 yr	118	1		
			10–20 yr	91	0.98 (0.75–1.29)		
			≥ 20 yr	354	1.09 (0.87–1.35)		
			Trend-test *P* value, 0.39				
		Colon and rectum, incidence	No. of incidents attended by volunteers (RIR):				
			Baseline	517	1		
			Group 2	32	1.35 (0.94–1.93)		
			Group 3	4	0.35 (0.13–0.94)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Colon and rectum, incidence	No. of fire incidents, attended by volunteers (RIR):			Age, calendar period	
			Baseline	518	1		
			Group 2	33	1.33 (0.94–1.89)		
			Group 3	2	0.20 (0.05–0.80)		
		Colon and rectum, incidence	No. of structure fire incidents, attended by volunteers (RIR):				
			Baseline	530	1		
			Group 2	21	1.43 (0.92–2.21)		
			Group 3	2	0.26 (0.07–1.05)		
		Colon and rectum, incidence	No. of landscape fire incidents, attended by volunteers (RIR):				
			Baseline	429	1		
			Group 2	96	1.25 (1.00–1.56)		
			Group 3	28	0.98 (0.67–1.44)		
		Colon and rectum, incidence	No. of vehicle fire incidents, attended by volunteers (RIR):				
			Baseline	519	1		
			Group 2	31	1.24 (0.87–1.79)		
			Group 3	3	0.31 (0.10–0.98)		
		Colon, incidence	SIR:				
			All volunteers	526	0.87 (0.80–0.95)		
			Volunteers who attended incidents	333	0.87 (0.78–0.97)		
		Rectum, incidence	SIR:				
			All volunteers	301	0.90 (0.80–1.01)		
			Volunteers who attended incidents	181	0.84 (0.72–0.97)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2017) (cont.)		Liver and bile ducts, incidence	SIR:			Age, calendar period	
			All volunteers	39	0.33 (0.23–0.45)		
			Volunteers who attended incidents	18	0.24 (0.14–0.37)		
		Pancreas, incidence	SIR:				
			All volunteers	116	0.74 (0.61–0.89)		
			Volunteers who attended incidents	77	0.77 (0.61–0.97)		
		Breast, incidence	SIR:				
			All volunteers	12	0.83 (0.43–1.45)		
			Volunteers who attended incidents	12	1.29 (0.67–2.26)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) Australia Enrolment, 1976–2003/follow-up, 1976–2011 (mortality), 1982–2010 (incidence, except two states, 2009) Cohort	30 057 full-time (17 394) or part-time (12 663) paid male firefighters employed at one of eight Australian fire agencies for ≥ 3 mo from start of personnel records (1976–2003, depending on agency) Exposure assessment method: employed as a part- or full-time firefighter for ≥ 3 mo, categorical employment duration (years) and era from employment records; tertiles of cumulative emergency incidents and type of incident attended from contemporary incident data	Lip, oral cavity, and pharynx, incidence	Firefighter status (SIR):			Age, calendar period	*Exposure assessment critique*: Good quality. Enhanced exposure assessment to differentiate exposure based on number of incidents, including specific incident types. Included specific incident types, but early exposure was extrapolated from more recent data. Municipal firefighters. *Strengths*: internal analysis by exposure to number and type of incidents; ascertained cancer incidence. *Limitations*: healthy-worker hire bias; short length of follow-up; young age at end of follow-up; little information on potential confounders.
			Full-time	55	0.95 (0.71–1.23)		
			Part-time	21	0.89 (0.55–1.36)		
			All	76	0.93 (0.73–1.16)		
		Lip, oral cavity, and pharynx, incidence	Duration of employment, full-time firefighters (RIR) [equivalent to rate ratios]:				
			> 3 mo to 10 yr	9	1		
			10–20 yr	12	1.37 (0.58–3.29)		
			≥ 20 yr	34	1.42 (0.60–3.38)		
			Trend-test *P* value, 0.46				
		Lip, oral cavity, and pharynx, incidence	Duration of employment, part-time firefighters (RIR):				
			> 3 mo to 10 yr	11	1		
			10–20 yr	6	1.50 (0.52–4.37)		
			≥ 20 yr	4	1.24 (0.35–4.42)		
			Trend-test *P* value, 0.65				
		Lip, oral cavity, and pharynx, incidence	Duration of employment (RIR):				
			> 3 mo to 10 yr	20	1		
			10–20 yr	18	1.23 (0.64–2.36)		
			≥ 20 yr	38	1.11 (0.57–2.16)		
			Trend-test *P* value, 0.78				
		Digestive (ICD-10, C15–C25), incidence	Firefighter status (SIR):				
			Full-time	230	1.00 (0.87–1.14)		
			Part-time	85	0.99 (0.79–1.23)		
			All	315	1.00 (0.89–1.11)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Digestive (ICD-10, C15–C25), incidence	Duration of employment, full-time firefighters (RIR):			Age, calendar period	
			> 3 mo to 10 yr	20	1		
			10–20 yr	27	0.78 (0.43–1.41)		
			≥ 20 yr	183	0.92 (0.56–1.53)		
			Trend-test *P* value, 0.97				
		Digestive (ICD-10, C15–C25), incidence	Duration of employment, part-time firefighters (RIR):				
			< 3 mo to 10 yr	25	1		
			10–20 yr	17	0.93 (0.48–1.80)		
			≥ 20 yr	43	1.12 (0.58–2.13)		
			Trend-test *P* value, 0.70				
		Digestive (ICD-10, C15–C25), incidence	Duration of employment (RIR):				
			< 3 mo to 10 yr	45	1		
			10–20 yr	44	0.75 (0.49–1.15)		
			≥ 20 yr	226	0.88 (0.61–1.26)		
			Trend-test *P* value, 0.73				
		Digestive (ICD-10, C15–C25), incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	20	1		
			Tertile 2	18	0.95 (0.50–1.81)		
			Tertile 3	28	0.87 (0.49–1.55)		
			Trend-test *P* value, 0.63				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Digestive (ICD-10, C15–C25), incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	15	1		
			Tertile 2	18	1.44 (0.72–2.87)		
			Tertile 3	33	1.28 (0.69–2.38)		
			Trend-test *P* value, 0.50				
		Digestive (ICD-10, C15–C25), incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	17	1		
			Tertile 2	18	1.23 (0.63–2.40)		
			Tertile 3	31	1.07 (0.59–1.95)		
			Trend-test *P* value, 0.88				
		Digestive (ICD-10, C15–C25), incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	14	1		
			Tertile 2	24	1.87 (0.96–3.62)		
			Tertile 3	28	1.32 (0.69–2.52)		
			Trend-test *P* value, 0.55				
		Digestive (ICD-10, C15–C25), incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	15	1		
			Tertile 2	18	1.54 (0.77–3.09)		
			Tertile 3	33	1.48 (0.80–2.73)		
			Trend-test *P* value, 0.25				
		Oesophagus, incidence	Firefighter status (SIR):				
			Full-time	12	0.76 (0.39–1.33)		
			Part-time	5	0.85 (0.28–1.98)		
			All	17	0.78 (0.46–1.26)		
		Stomach, incidence	Firefighter status (SIR):				
			Full-time	24	0.98 (0.63–1.46)		
			Part-time	9	1.03 (0.47–1.96)		
			All	33	0.99 (0.68–1.39)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Colon and rectum, incidence	Firefighter status (SIR):			Age, calendar period	
			Full-time	157	1.09 (0.92–1.27)		
			Part-time	57	1.06 (0.80–1.37)		
			All	214	1.08 (0.94–1.23)		
		Colon and rectum, incidence	Duration of employment, full-time firefighters (RIR):				
			> 3 mo to 10 yr	14	1		
			10–20 yr	20	0.79 (0.39–1.57)		
			≥ 20 yr	123	0.91 (0.50–1.66)		
		Colon and rectum, incidence	Duration of employment, part-time firefighters (RIR):				
			< 3 mo to 10 yr	16	1		
			10–20 yr	11	0.96 (0.42–2.19)		
			≥ 20 yr	30	1.32 (0.59–2.92)		
			Trend-test *P* value, 0.45				
		Colon and rectum, incidence	Duration of employment (RIR):				
			< 3 mo to 10 yr	30	1		
			10–20 yr	31	0.80 (0.48–1.34)		
			≥ 20 yr	153	0.97 (0.62–1.51)		
			Trend-test *P* value, 0.89				
		Colon and rectum, incidence	No. of incidents attended by full-time firefighters (RIR):				
			Tertile 1	16	1		
			Tertile 2	15	0.98 (0.48–1.99)		
			Tertile 3	23	0.84 (0.44–1.59)		
			Trend-test *P* value, 0.56				

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Colon and rectum, incidence	No. of fire incidents attended by full-time firefighters (RIR):			Age, calendar period	
			Tertile 1	12	1		
			Tertile 2	13	1.28 (0.58–2.83)		
			Tertile 3	29	1.30 (0.66–2.56)		
			Trend-test *P* value, 0.47				
		Colon and rectum, incidence	No. of structure fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	15	1		
			Tertile 2	13	0.97 (0.46–2.05)		
			Tertile 3	26	0.95 (0.50–1.80)		
			Trend-test *P* value, 0.88				
		Colon and rectum, incidence	No. of landscape fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	10	1		
			Tertile 2	21	2.26 (1.06–4.82)		
			Tertile 3	23	1.42 (0.67–2.99)		
			Trend-test *P* value, 0.56				
		Colon and rectum, incidence	No. of vehicle fire incidents attended by full-time firefighters (RIR):				
			Tertile 1	13	1		
			Tertile 2	13	1.28 (0.59–2.77)		
			Tertile 3	28	1.34 (0.69–2.60)		
			Trend-test *P* value, 0.40				
		Liver and bile ducts, incidence	Firefighter status (SIR):				
			Full-time	8	0.52 (0.23–1.03)		
			Part-time	4	0.64 (0.17–1.64)		
			All	12	0.56 (0.29–0.97)		
		Pancreas, incidence	Firefighter status (SIR):				
			Full-time	22	1.07 (0.67–1.62)		
			Part-time	7	0.93 (0.37–1.91)		
			All	29	1.03 (0.69–1.48)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Glass et al. (2016a) (cont.)		Breast, incidence	Firefighter status (SIR):			Age, calendar period	
			Full-time	5	2.49 (0.81–5.82)		
			Part-time	1	1.31 (0.03–7.32)		
			All	6	2.17 (0.80–4.72)		
Glass et al. (2016b) Victoria, Australia Enrolment, 1971–1999/follow-up, 1980–2011 (mortality), 1982–2012 (incidence) Cohort	614; all male (611) and female (3) employed and volunteer Country Fire Authority trainers and a group of paid [career] Country Fire Authority firefighters who trained at the Fiskville site from 1971 to 1999; all analyses limited to men as no deaths or cancers were observed among women Exposure assessment method: employed or volunteer firefighter trainers and career firefighters who trained at training facility for any period of time from human resource records, categorized into risk of low, medium, and high chronic exposure to smoke and other agents based on job assignment	Digestive (ICD-10, C15–C25), incidence	Risk of chronic exposure (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Incorporated categorical level of exposure into assessment for each type of firefighter. Volunteers mainly rural, paid [career] firefighters were municipal. *Strengths*: included firefighter instructors with high potential exposure to smoke and other hazardous agents; assessed exposure based on job assignment. *Limitations*: low number of cases; young age at end of follow-up.
			Low	0	0 (NR):		
			Medium	9	1.25 (0.57–2.38)		
			High	3	1.02 (0.21–2.99)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bates et al. (2001) New Zealand Enrolment, 1977 through June 1995/ follow-up, 1977–1995 (mortality), 1977–1996 (incidence) Cohort	4305, comprising all male (4221) and female (84) firefighters (paid [career] and volunteer) employed as a career firefighter for ≥ 1 yr and who also worked as a career firefighter for ≥ 1 day between 1977 and 1995; all analyses limited to men due to small numbers of women Exposure assessment method: ever employed and categorical duration of employment (years) from employment records	Oesophagus, incidence	Follow-up period (SIR):			Age, calendar period	*Exposure assessment critique*: Satisfactory quality. Heterogeneity of direct firefighter exposure within job classification. May include urban [municipal] and rural firefighters. *Strengths*: ascertained both incidence and mortality outcomes *Limitations*: little information on confounders; significant loss to follow-up; low number of cases in stratified analyses.
			1977–1996	3	1.67 (0.3–4.9)		
			1990–1996	2	1.80 (0.2–6.5)		
		Stomach, incidence	Follow-up period (SIR):				
			1977–1996	3	0.76 (0.2–2.2)		
			1990–1996	2	0.89 (0.1–3.2)		
		Stomach, mortality	SMR:				
			Firefighters vs male New Zealand population	3	1.16 (0.2–3.4)		
		Colon, incidence	Follow-up period (SIR):				
			1977–1996	7	0.60 (0.2–1.2)		
			1990–1996	4	0.58 (0.2–1.5)		
		Colon, incidence	Duration of paid service (SIR):				
			0–10 yr	1	0.41 (0.0–2.3)		
			11–20 yr	1	0.46 (0.0–2.6)		
			> 20 yr	5	1.37 (0.4–3.2)		
			Trend-test *P* value, 0.18				
		Colon, incidence	Duration of paid and volunteer service (SIR):				
			0–10 yr	1	0.82 (0.0–4.6)		
			11–20 yr	1	0.58 (0.0–3.3)		
			> 20 yr	5	0.92 (0.3–2.1)		
			Trend-test *P* value, 0.81				
		Colon, mortality	SMR:				
			Firefighters vs male New Zealand population	6	1.19 (0.4–2.6)		

Table 2.9 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bates et al. (2001) (cont.)		Rectum, incidence	Follow-up period (SIR):			Age, calendar period	
			1977–1996	9	1.15 (0.5–2.2)		
			1990–1996	5	1.08 (0.3–2.5)		
		Rectum, incidence	Duration of paid service (SIR):				
			0–10 yr	2	1.22 (0.1–4.4)		
			11–20 yr	2	1.38 (0.2–5.0)		
			> 20 yr	4	1.61 (0.4–4.1)		
			Trend-test *P* value, 0.74				
		Rectum, incidence	Duration of paid and volunteer service (SIR):				
			0–10 yr	1	1.23 (0.0–6.8)		
			11–20 yr	2	1.75 (0.2–6.3)		
			> 20 yr	5	1.35 (0.4–3.1)		
			Trend-test *P* value, 0.97				
		Rectum, mortality	SMR:				
			Firefighters vs male New Zealand population	4	1.21 (0.3–3.1)		
		Pancreas, incidence	Follow-up period (SIR):				
			1977–1996	3	1.28 (0.3–3.7)		
			1990–1996	3	2.17 (0.4–6.4)		

9/11, World Trade Center disaster, 11 September 2001; CI, confidence interval; FDNY, Fire Department of the City of New York; HCC, hepatocellular carcinoma; HR, hazard ratio; HWSE, healthy-worker survivor effect; ICD, International Classification of Diseases; IDR, incidence density ratio; LRT, likelihood ratio test; mo, month; NJ, New Jersey; NR, not reported; PMR, proportionate mortality ratio; RCS, restricted cubic splines; RIR, relative incidence ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States; vs, versus; WTC, World Trade Center; yr, year.

et al., 1992a, 1994; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Bates et al., 2001; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014, 2015; Ahn & Jeong, 2015; Glass et al., 2016a, b, 2017, 2019; Moir et al., 2016; Petersen et al., 2018a, b; Kullberg et al., 2018; Bigert et al., 2020; Pinkerton et al., 2020; Marjerrison et al., 2022b). Two of these studies were from Asia, six from Europe, eleven from North America, and five from Oceania. Results for other cancer sites not described here or elsewhere in Section 2 were considered uninformative to the evaluation (e.g. cancer of the bone, eye).

(a) Cancers of the digestive tract

Ahn & Jeong (2015) conducted a cohort mortality study among 33 442 professional [career] emergency responders in the Republic of Korea. Emergency responders had been employed between 1980 and 2007, and mortality follow-up took place from 1992 through 2007. Below, cancer mortality results among the subcohort of firefighters (n = 29 453, 88% of total cohort) are reported. With the male population of the Republic of Korea as the referent, the overall SMRs were 0.63 (95% CI, 0.43–0.88) for stomach cancer, 0.65 (95% CI, 0.34–1.14) for colorectal cancer, and 0.55 (95% CI, 0.41–0.73) for cancer of the liver and intrahepatic bile duct. The external comparisons showed no associations with longer duration of employment for any of these sites. In internal analyses of employment duration, for which firefighters employed for < 10 years and other emergency responders served as reference groups, age- and calendar year-adjusted estimates above unity for longer employment durations were seen for colorectal cancer (ARR [adjusted rate ratio] for ≥ 10 years to < 20 years, 1.40; 95% CI, 0.33–5.87; and ARR for ≥ 20 years, 1.29; 95% CI, 0.27–6.08) and for cancer of the liver and intrahepatic bile ducts (ARR for ≥ 20 years, 1.82; 95% CI, 0.85–3.90).

In the same cohort as described above, Ahn et al. (2012) conducted a cancer incidence study among professional [career] emergency responders in the Republic of Korea with cancer incidence follow-up from 1996 through 2007. National male cancer incidence rates served as the referent, and analyses were conducted overall and by duration of employment (< 10 versus ≥ 10 years). SIRs below unity were seen for cancers of the oesophagus, stomach, liver and intrahepatic bile ducts, and pancreas, but estimates were imprecise. In internal comparisons with non-firefighter emergency responders as the referent, SRRs were elevated but imprecise for cancers of the stomach and liver and intrahepatic bile ducts (SRR, 1.09; 95% CI, 0.53–2.25; and SRR, 5.10; 95% CI, 0.71–36.85; respectively). The overall SIR for colorectal cancer was elevated (SIR, 1.27; 95% CI, 1.01–1.59) but did not increase with longer duration of employment.

Marjerrison et al. (2022b) compared cancer incidence and mortality in a cohort of 3881 male professional [career] firefighters with cancer rates in the general population in Norway. The cohort included mostly full-time firefighters employed between 1950 and 2019, with past or present employment in positions entailing active firefighting duties. The follow-up period for both cancer incidence and mortality analyses was from 1960 through 2018. For oesophageal cancer among those ever employed as a firefighter, both incidence and mortality rates were greater than expected (SIR, 1.55; 95% CI, 0.83–2.66; and SMR, 1.82; 95% CI, 0.97–3.11). The highest risks were seen in the earliest follow-up period (up to and including 1984) and oldest age at diagnosis (≥ 70 years), but estimates were imprecise. Stomach cancer risk was moderately elevated, with an imprecise risk estimate (SIR, 1.35; 95% CI, 0.95–1.85). Risk of colon cancer was elevated, with an SIR of 1.24 (95% CI, 0.98–1.56); the SMR of 1.26 (95% CI, 0.87–1.76) was of similar magnitude, but less precise. Incidence and mortality of colon cancer was elevated in the earliest follow-up period: SIR, 2.02 (95% CI, 1.15–3.28); and SMR, 2.33 (95% CI, 1.12–4.29). Smaller and less precise

excess risks were seen for follow-up in 1985–1994. Overall risk of rectal cancer was at the expected level (SIR, 0.96; 95% 0.68–1.33). SIR for overall risk of cancer of the liver, gallbladder, and biliary ducts was 1.31 (95% CI, 0.68–2.29), and SMR was 1.56 (95% CI, 0.78–2.79). For analyses by calendar period of follow-up, risk was elevated in the earliest period (SIR, 3.62; 95% CI, 1.17–8.44), based on five cases only. Pancreatic cancer incidence and mortality were slightly above unity, but estimates were imprecise (SIR, 1.22; 95% CI, 0.78–1.81; and SMR, 1.09; 95% CI, 0.67–1.68).

Bigert et al. (2020) investigated cancer incidence in a cohort of 8136 male firefighters in Sweden. Employment information was ascertained from national decennial censuses between 1960 and 1990. Cancer incidence data were ascertained from the Swedish Cancer Registry with follow-up from 1961 through 2009. With the national male general population as the referent, the overall SIR for stomach cancer was 1.08 (95% CI, 0.83–1.39). Analysis of duration of employment was performed for stomach cancer, but no increasing risk with longer employment duration was seen (*P* for trend, 0.75). The SIR for stomach cancer was highest in the earliest calendar follow-up period from 1961 through 1975 (SIR, 1.85; 95% CI, 1.06–3.00). The overall SIR for pancreatic cancer was 1.17 (95% CI, 0.85–1.58). No excess risk of cancers of the oesophagus (SIR, 0.71; 95% CI, 0.38–1.21), colon (SIR, 1.01; 95% CI, 0.82–1.23), rectum (SIR, 0.89; 95% CI, 0.69–1.14), or liver and bile ducts (SIR, 0.89; 95% CI, 0.50–1.47) was observed.

A cancer incidence study in a cohort of 1080 male firefighters in Stockholm, Sweden, provided information on the risk of cancers of the digestive system (Kullberg et al., 2018). Firefighters were identified through annual enrolment records from 15 fire stations and had worked for ≥ 1 year between 1931 and 1983. As an update to a previous study (Tornling et al., 1994), this study added 26 years of cancer incidence follow-up from 1958 through 2012 in the Swedish Cancer Registry. With the male general population of Stockholm County as the referent, the overall SIR for stomach cancer for the full follow-up period (1958–2012) was 1.89 (95% CI, 1.25–2.75), with the extended follow-up period (1987–2012) contributing 7 of the 27 total cases, yielding an SIR of 1.35 (95% CI, 0.54–2.78). Stomach cancer risk decreased with increasing age (*P* for trend, 0.07) but did not vary with duration of employment (*P* for trend, 0.19) or period of first employment (*P* for trend, 0.69). The overall SIR for rectum cancer was 1.25 (95% CI, 0.74–1.98), but was somewhat higher for the follow-up period 1958–1986 (SIR, 1.74; 95% CI, 0.83–3.19). Rates for cancers of the oesophagus (SIR, 0.99; 95% CI, 0.32–2.30), pancreas (SIR, 1.06; 95% CI, 0.51–1.94), liver and bile ducts (SIR, 0.79; 95% CI, 0.32–1.63), and colon (SIR, 0.86; 95% CI, 0.53–1.34) did not deviate from expected values.

In the original analysis of this cohort, Tornling et al. (1994) investigated both cancer mortality and incidence in a slightly larger population ($n = 1116$). Follow-up was from 1951 through 1986 for mortality and from 1958 through 1986 for cancer incidence. Comparisons were made with the regional male general population. For each firefighter, exposure to fire events was assessed using reports of fires fought by the Stockholm fire brigade between 1933 and 1983. Overall, the risk of stomach cancer mortality was only slightly increased, and the estimate was imprecise (SMR, 1.21; 95% CI, 0.62–2.11). Both stomach cancer mortality and incidence increased with greater number of fire responses (SMR, 1.96; 95% CI, 0.90–3.72; and SIR, 2.64; 95% CI, 1.36–4.61, respectively, for > 1000 fires). The numbers of colon cancer deaths and cases were essentially as expected, whereas rectum cancer mortality was elevated (SMR, 2.07; 95% CI, 0.89–4.08). For liver cancer, an elevated mortality rate was observed, although the estimate was imprecise (SMR, 1.49; 95% CI, 0.41–3.81). Imprecise estimates for pancreatic cancer mortality were seen (SMR, 0.84; 95% CI, 0.27–1.96) based on five deaths.

[The Working Group noted that the exposure assessment method was a strength.]

Petersen et al. (2018a) studied cancer incidence in a cohort of 9061 male full-time, part-time, and volunteer firefighters employed between 1964 and 2004 in Denmark. Follow-up was from 1968 through 2014, and three alternative comparison groups were used in the overall analyses: the general Danish population; a sample of the working population; and a cohort of military employees. For cancers of the colon, rectum, and pancreas, additional analyses by employment type (e.g. full-time, other), era of first employment, job function (e.g. regular, specialized), age at first employment, and duration of employment were performed with the general population as referent. For cancers of the oesophagus and the stomach, comparisons with the cohort of military employees showed the most elevated rates among firefighters, with SIRs of 1.18 (95% CI, 0.77–1.81) and 1.26 (95% CI, 0.87–1.84), respectively. Risk of cancer of the colon, rectum, and pancreas did not vary with choice of reference group. The overall risk of colon cancer was consistently below the expected value in all comparisons (SIR, 0.73; 95% CI, 0.57–0.95; relative to the general population), and in all strata of age at first employment and duration of employment. The overall risks of cancers of the rectum and pancreas were above the expected values, with SIRs of 1.22 (95% CI, 0.95–1.55) and 1.20 (95% CI, 0.86–1.68), respectively, with the general population as the referent. Rectal cancer risk was elevated among those first employed before 1970 (SIR, 1.47; 95% CI, 1.06–2.02), and numbers were higher than expected for the group of specialized firefighters (SIR, 1.72; 95% CI, 0.77–3.84) and for those employed for ≥ 20 years (SIR, 1.32; 95% CI, 0.94–1.85). For pancreatic cancer, elevated risk was seen for full-time employees (SIR, 1.54; 95% CI, 1.05–2.25), for first employment at < 25 years (SIR, 1.68; 95% CI, 1.12–2.53), and for an employment duration of < 1 year (SIR, 1.79; 95% CI, 1.05–3.01). The SIR for liver cancer was elevated in firefighters compared with military personnel (SIR, 1.17; 95% CI, 0.69–1.98), but was at unity compared with other reference populations.

Cancer mortality was investigated in the same cohort of Danish firefighters described above (Petersen et al., 2018b). An expanded study population of 11 775 male firefighters were followed for mortality in the Danish national death registry from 1970 through 2014. With the military as the referent, the stomach cancer mortality rate was elevated among full-time firefighters (SMR, 1.96; 95% CI, 1.22–3.16) and in all strata of employment duration, specifically for < 1 year of employment (SMR, 2.13; 95% CI, 1.07–4.26). Mortality from rectal cancer and "other intestinal cancers" (colon, rectosigmoid, and small intestine) was not different from unity. There was also no evidence of a trend between employment duration and mortality from "other intestinal cancer" or cancer of the rectum.

Moir et al. (2016) and Zeig-Owens et al. (2011) reported results on the incidence of specific cancers of the digestive tract among a cohort of firefighters employed at the FDNY who were present at the WTC disaster site. The studies used different criteria for inclusion and exclusion, and cohorts comprised 11 457 (Moir et al., 2016) and 9853 (Zeig-Owens et al., 2011) FDNY firefighters, respectively. Moir et al. (2016) compared cancer incidence among WTC-exposed firefighters with that in 8220 non-WTC exposed firefighters employed at the same time in cohorts from San Francisco, Chicago, and Philadelphia (combined into the CFHS, and described in Pinkerton et al., 2020). Cancer incidence follow-up was conducted in state registries from 11 September 2001 through 2009. The RR for colon cancer among the WTC-exposed firefighters when considering the whole follow-up period was 0.73 (95% CI, 0.33–1.59). In their first follow-up of this cohort, Zeig-Owens et al. (2011) compared cancer incidence for WTC-exposed and unexposed person-years in the FDNY cohort with that in the US male general population from 1996 through 2008. The

ratios of SIRs for exposure versus non-exposure were elevated for cancers of the oesophagus (SIR ratio, 1.32; 95% CI, 0.12–14.53), stomach (SIR ratio, 1.82; 95% CI, 0.44–7.49), colon (SIR ratio, 1.50; 95% CI, 0.69–3.27), and pancreas (SIR ratio, 2.52; 95% CI, 0.28–22.59), but estimates were imprecise with wide confidence intervals. [The Working Group noted that the SIR ratio is not a standard epidemiological effect measure.]

Three studies of both cancer mortality and incidence have been conducted among municipal career firefighters in the CFHS employed at fire departments in San Francisco, Chicago, and Philadelphia, USA. Most recently, Pinkerton et al. (2020) updated previous analyses by Daniels et al. (2014) with cancer mortality follow-up from 1950 extended through 2016. Compared with that in the US general population, risk of oesophageal cancer was elevated in all municipal fire departments, with an overall SMR of 1.31 (95% CI, 1.10–1.55), but no consistent associations with fire-response exposure metrics in internal regression analyses were observed. For stomach cancer, SMRs above unity were seen in the San Francisco and Chicago subcohorts (SMR for San Francisco subcohort, 1.13; 95% CI, 0.75–1.65; and SMR for Chicago subcohort, 1.15; 95% CI, 0.88–1.48), but estimates were somewhat imprecise. In the fully adjusted regression models, the HRs for stomach cancer according to the number of exposed days (8700 versus 2500 exposed-days), fire-runs (8800 versus 2100 runs), and fire-hours (2300 versus 600 hours), all incorporating a 10-year lag period, were 1.75 (95% CI, 0.74–4.53), 1.25 (95% CI, 0.76–1.95), and 1.45 (95% CI, 0.71–2.87), respectively. Risk of cancer of the small intestine and colon combined was elevated overall (SMR, 1.27; 95% CI, 1.14–1.40) in external comparisons, driven by elevated risks in the Chicago and Philadelphia subcohorts, but the exposure–response analyses for colon cancer (separately) showed lower HRs with higher exposure. SMRs for cancer of the small intestine and colon were specifically elevated among firefighters of White race and age ≥ 65 years. Mortality from cancer of the rectum was elevated in the San Francisco and Chicago subcohorts, with an overall SMR of 1.32 (95% CI, 1.07–1.61), and among White firefighters only, but differences were not observed between those aged < 65 years or > 65 years. In internal regression analyses, a higher number of exposed days and fire-runs was associated with a lower risk of rectal cancer (HR for exposed days, 0.49; 95% CI, 0.21–1.19; and HR for fire-runs, 0.36; 95% CI, 0.16–0.75), in the fully adjusted model).

An earlier study of a subset of 19 309 firefighters from the same CFHS cohort examined internal exposure–response associations with both cancer mortality and incidence with follow-up to the end of 2009 (Daniels et al., 2015). Methods were similar to those used in Pinkerton et al. (2020); however, results in the present study were not adjusted for employment duration. No consistent pattern of risk associated with higher exposure was observed for cancer of the oesophagus. For cancers of the colon and rectum combined, HRs associated with cancer incidence were below unity for all exposure metrics: the HRs were 0.92 (95% CI, 0.84–1.01), 0.89 (95% CI, 0.72–1.09) and 0.78 (95% CI, 0.63–1.04) for exposed-days, fire-hours, and fire-runs, respectively.

An additional study in the CFHS cohort investigated cancer incidence among 29 993 municipal career firefighters and reported external and internal comparison analyses with follow-up to the end of 2009 (Daniels et al., 2014). The methods were similar to those used in the study by Pinkerton et al. (2020). Cancer incidence follow-up was conducted in state cancer registries relevant to each fire department to the end of 2009, with start years varying between 1985 and 1988. With the US general population as the referent, excess risks were observed overall for cancers of the oesophagus (1.62; 95% CI, 1.31–2.00), stomach (SIR, 1.15; 95% CI, 0.93–1.40), colon (SIR, 1.21; 95% CI, 1.09–1.34), and rectum (SIR, 1.11; 95% CI, 0.95–1.30).

Demers et al. (1994) studied cancer incidence in a cohort of 2447 male municipal firefighters who had been employed for ≥ 1 year between 1944 and 1979 in Seattle and Tacoma, Washington, USA. Firefighters were followed for cancer from 1974 through 1989 in the regional SEER cancer registry, using residential history information to reduce loss to follow-up. Duration of active-duty employment in direct firefighting positions was ascertained from employment records in the Seattle subcohort. With the local general male population as the referent, there was no evidence of an overall excess of cancers of the oesophagus, stomach, colon, rectum, or pancreas among firefighters. For colon cancer, risk increased monotonically with longer duration of exposed employment, with an IDR for firefighters with ≥ 30 years of employment of 1.8 (95% CI, 0.3–11.6) compared with firefighters employed < 10 years. Also, compared with incidence rates among police officers, colon cancer risk in the group of firefighters with the longest duration of employment (≥ 30 years) was elevated but imprecise (RR, 2.0; 95% CI, 0.5–8.0). [The Working Group noted that trend tests were not conducted, and that for many analyses the number of cancer cases was small.]

In a cohort study of cancer mortality, Demers et al. (1992a) included firefighters employed in Portland, Oregon, in addition to the Seattle and Tacoma cohorts mentioned above. The mortality follow-up period was from 1945 through 1989. Mortality rates for the US general population and for police officers from the same cities served as referents. Mortality was examined overall and in stratified analyses by years of fire combat exposure (in Seattle and Portland firefighters only), years since first employment as a firefighter, and age at risk. For colon cancer, the overall SMR was 0.85 (95% CI, 0.54–1.26) for firefighters compared with US men, but above unity when comparing with local police (IDR, 1.58; 95% CI, 0.73–3.43), although this estimate was imprecise. No association with duration of exposed employment, time since first employment, or age at risk was observed. [Trend tests were not reported.] SMRs for rectal, oesophageal, and pancreatic cancers were below unity, but estimates were imprecise with wide confidence intervals.

Vena & Fiedler (1987) investigated cancer mortality in a cohort of 1867 White male municipal firefighters who had been employed between 1950 and 1979 in Buffalo, USA. Mortality follow-up was from 1950 through 1979, and comparisons were made with mortality rates among US White men in the general population. Overall, more deaths than expected were seen among firefighters for cancers of the oesophagus (SMR, 1.34; 95% CI, 0.27–3.91; 3 deaths), stomach (SMR, 1.19; 95% CI, 0.48–2.46; 7 deaths), and rectum (SMR, 2.08; 95% CI, 0.83–4.28; 7 deaths). For colon cancer, the SMR was elevated overall (1.83; 95% CI, 1.05–2.97) and in the categories with the longest duration of employment (SMR for employment ≥ 40 years, 4.71; 95% CI, [2.2–8.9]), longest latency (SMR for ≥ 50 years since first employment, 2.85; 95% CI, [0.7–7.4]), and most recent period of death (SMR for death during 1970–1979, 2.20; 95% CI, [1.1–4.0]). For pancreatic cancer, mortality was close to unity (SMR, 0.89; 95% CI, 0.49–1.49). [This study was limited by the small numbers of cases.]

Feuer & Rosenman (1986) conducted a PMR study that included 263 deceased firefighters from New Jersey, USA, who died in 1974–1980. Comparisons were made with the White male general populations of the USA and of New Jersey, as well as New Jersey White police officers. Mortality from digestive tract cancers (ICD-8, 150–159, i.e. cancers of the oesophagus, stomach, small intestine, large intestine, rectum and rectosigmoid junction, liver and intrahepatic bile ducts, gallbladder and bile ducts, pancreas, peritoneum and retroperitoneal tissue, and unspecified digestive organs) was higher than expected (PMR, 1.45; 95% CI, [0.91–2.20]) compared with that in US White men, although the estimate was attenuated when compared with New Jersey

men, and below unity with New Jersey police officers as the referent. Analyses by duration of employment or time since first employment did not indicate any mortality trends.

Aronson et al. (1994) investigated cancer mortality in a cohort of 5414 male career firefighters employed for ≥ 6 months in Toronto, Canada ($n = 5414$). Firefighters had been employed between 1950 and 1989, and mortality follow-up was conducted in a national mortality database from 1950 through 1989. With the male general population of Ontario as the referent, there was no evidence of an increased risk of cancers of the oesophagus, stomach, or colon. The overall SMR for rectal cancer mortality was 1.71 (95% CI, 0.91–2.93), and risk increased with time since first employment. The overall SMR for cancer of the pancreas was 1.40 (95% CI, 0.77–2.35), but no consistent pattern was seen with time since first employment or duration of employment.

Guidotti (1993) examined cancer mortality in a cohort of 3328 firefighters who had been employed between 1927 and 1987 in Edmonton and Calgary, Canada. Mortality follow-up was conducted in both provincial and national sources from 1927 through 1987. External comparisons were made with the male general population of Alberta. SMRs were stratified according to employment characteristics, and an exposure index (with values of 0, > 0 to < 1, 1–9, and ≥ 10) was created on the basis of years of firefighter service weighted by an estimate of the relative time spent in proximity to fires according to job classification. With the general population as the referent, mortality was not elevated overall for stomach cancer (SMR, 0.81; 95% CI, 0.30–1.76). For cancer of the colon and rectum combined, the overall SMR was 1.61 (95% CI, 0.88–2.71) based on 14 deaths. Analyses stratified by year of cohort entry (first employment), latency, the exposure index value, and latency by exposure index generally yielded unstable estimates with wide confidence intervals. Colorectal cancer mortality was highest in the latency period 20–29 years after first employment, with an SMR of 2.68 (95% CI, [0.98–5.93]); 5 deaths), and in the exposure index group "1–9" (SMR, 4.58; 95% CI, [1.86–9.53]; 6 deaths). The SMR for pancreatic cancer was elevated at 1.55 (95% CI, 0.50–3.62), although the estimate was based on only five deaths. Three deaths from pancreatic cancer occurred ≥ 50 years after first employment (SMR, 7.16; 95% CI, [1.82–19.4]). [The Working Group noted that the number of cases was low for many of the comparisons, and estimates were imprecise.]

Glass et al. (2019) investigated cancer incidence in a cohort of female volunteer firefighters (n = 37 962). Cancer incidence follow-up was conducted in a national cancer registry from 1982 through 2010. Work history information describing the number and type of incidents attended was ascertained from fire agency personnel records. The female general population of Australia served as the referent in external comparison analyses. For all volunteers, the overall SIRs for cancers of the colon and rectum were 1.09 (95% CI, 0.87–1.36) and 1.35 (95% CI, 0.95–1.85), respectively. Results were similar in separate analyses restricted to volunteers who had attended incidents. In internal regression analyses, the RIR [equivalent to rate ratio] for colorectal cancer in the highest tertile of total number of incidents attended was 1.34 (95% CI, 0.78–2.29). For structure fire incidents specifically, the corresponding RIR was 2.08 (95% CI, 1.13–3.84).

Using the same methods as in the study of female firefighters, cancer incidence was also investigated in a parallel cohort of 163 094 male volunteer firefighters in Australia (Glass et al., 2017). With the male general population of Australia as the referent, the overall SIRs among firefighters who had attended incidents were lower than expected for cancers of the oesophagus, stomach, pancreas, and liver. SIRs for cancers of the colon and rectum overall and by period of first employment were below unity,

and no trends were seen with period of employment or duration of service. Internal regression analyses by number and type of incident attended generally showed the highest estimates among firefighters in the intermediate tertile of exposure group, whereas risk estimates were below those of the referent in the highest tertile group. For all fire incidents, the RIR [equivalent to rate ratio] was 1.33 (95% CI, 0.94–1.89) in the intermediate group and 0.20 (95% CI, 0.05–0.80) in the highest group. In the analysis of vehicle fire incidents, the highest RIR was found in the intermediate group (RIR, 1.24; 95% CI, 0.87–1.79). Estimates in the highest tertile of exposure were imprecise because of small numbers of cases in that group.

Using similar methods as in the two studies of volunteer firefighters, mortality and cancer incidence were studied in a cohort of 30 057 paid full-time and part-time firefighters in Australia (Glass et al., 2016a). Included firefighters had worked between 1976 and 2003 and were primarily municipal or semi-metropolitan firefighters. Cancer incidence follow-up was conducted in a national registry to the end of 2010. With the male general population of Australia as the referent, SIRs among all firefighters were at unity or below for cancers of the oesophagus, stomach, and pancreas. Overall, risk of cancers of the digestive tract combined (ICD-10, C15–C25, i.e. cancers of the oesophagus, stomach, small intestine, colon, rectum and rectosigmoid junction, anus and anal canal, liver and intrahepatic bile ducts, gallbladder, biliary tract, and pancreas) was at the expected level, and estimates were similar among full-time and part-time firefighters. In internal regression analyses, risk of cancers of the digestive tract did not increase by duration of employment, and no positive trends were seen with increasing number or type of incident attended. Risk of colorectal cancer was similar among full-time and part-time firefighters (overall SIR, 1.08; 95% CI, 0.94–1.23). No association with duration of employment was seen for either group in internal analyses. Among full-time firefighters, attendance at landscape fires was positively associated with elevated risk in the second tertile of the exposure distribution compared with the lowest tertile (RIR [equivalent to rate ratio], 2.26; 95% CI, 1.06–4.82).

Glass et al. (2016b) studied cancer incidence in a small cohort of 614 firefighter trainers and firefighters who attended a firefighter-training facility in Australia. Cancer incidence follow-up was conducted from 1982 through 2012. Participants were grouped into risk categories of low, medium, and high for chronic exposure (to smoke and other hazardous agents) on the basis of job assignment. With the male general population of Victoria as the referent, the SIR for digestive tract cancers combined was highest in the group with medium risk of chronic exposure (SIR, 1.25; 95% CI, 0.57–2.38).

Bates et al. (2001) investigated cancer incidence and mortality in a cohort of 4305 paid [career] and volunteer New Zealand firefighters who had been employed as a career firefighter for ≥ 1 year and worked between 1977 and 1995. The cohort included 84 female firefighters who were excluded from the analysis. External comparisons were made with the male general population of New Zealand. Follow-up for cancer mortality and incidence was conducted in a national data source to the end of 1995 (for mortality) or 1996 (for incidence). For cancer of the oesophagus, a modestly elevated SIR was observed (SIR, 1.67; 95% CI, 0.3–4.9), although the estimate was imprecise and based on only three cases. Limiting the follow-up period to 1990–1996 gave an SIR of 1.80 (95% CI, 0.2–6.5). For stomach cancer, mortality was slightly higher and incidence slightly lower than unity, but estimates were imprecise (SMR, 1.16; 95% CI, 0.2–3.4; and SIR, 0.76; 95% CI, 0.2–2.2). A modestly elevated, but imprecise, incidence rate of pancreatic cancer was seen (SIR, 1.28; 95% CI, 0.3–3.7). Overall mortality from colon cancer was modestly elevated (SMR, 1.19; 95% CI, 0.4–2.6), whereas incidence was reduced (SIR, 0.60; 95% CI,

0.2–1.2), but both estimates were imprecise. The SIR for colon cancer was 1.37 (95% CI, 0.4–3.2) for firefighters with > 20 years of career service, with a *P* for trend of 0.18. When volunteer service was included, the SIR for > 20 years of paid and volunteer service was 0.92 (95% CI, 0.3–2.1; *P* for trend, 0.81). Mortality and incidence of rectal cancer was modestly increased, although the estimates were imprecise (SMR, 1.21; 95% CI, 0.3–3.1; and SIR, 1.15; 95% CI, 0.5–2.2). Analysis by duration of exposure in career service showed monotonically increasing estimates above unity, but *P* for trend was 0.74. [The Working Group noted that, for rectal cancer, all of the SIRs stratified by duration of employment were greater than the overall SIR.]

(b) Cancers of other sites

In the studies included in the present section, results for other cancer sites not reviewed elsewhere in Section 2 were reported sporadically. [The Working Group noted that most analyses for these other cancer sites were based on small numbers because of the rarity of the cancer types or because the cancers were sex-specific and that estimates generally were statistically imprecise.]

Marjerrison et al. (2022b) reported an SIR for cancer of the pharynx of 1.61 (95% CI, 0.80–2.88), based on 11 cases. In the study by Bigert et al. (2020), the SIR for pharyngeal cancer was 1.04 (95% CI, 0.55–1.78), based on 13 cases. Petersen et al. (2018b) combined oral and oesophageal cancer in their analysis and observed a moderately elevated SMR among full-time employed firefighters (SMR, 1.27; 95% CI, 0.85–1.89), whereas the SMR was below unity for part-time firefighters or volunteers. The highest elevation of risk was seen among firefighters with < 1 year of employment (SMR, 1.39; 95% CI, 0.77–2.51). For oral and pharyngeal cancer, Demers et al. (1994) reported an SIR of 1.1 (95% CI, 0.6–2.0) when using local general population reference rates, but risk was below unity when using local police officers as the reference group (IDR, 0.8; 95% CI, 0.3–1.9). No consistent trends were seen with duration of employment or time since first employment. Altogether, seven deaths from oral or pharyngeal cancer were observed by Demers et al. (1992a), giving an SMR of 0.81 (95% CI, 0.33–1.66). In Aronson et al. (1994), four deaths by pharyngeal cancer were reported, resulting in an SMR of 1.39 (95% CI, 0.38–3.57). Three of the deaths occurred ≥ 30 years since first employment (SMR, 1.81; 95% CI, 0.37–5.28). Guidotti (1993) reported an SMR for oral and pharyngeal cancer of 1.14 (95% CI, 0.14–4.10). The SIR for cancers of the lip, oral cavity, and pharynx was below unity for female volunteer firefighters in Glass et al. (2019). Among all male volunteer firefighters, the SIR for cancers of the lip, oral cavity and pharynx was 0.71 (95% CI, 0.63–0.81) and was similar in the subgroup who had attended incidents Glass et al. (2017). Among male paid firefighters, SIRs for cancers of the lip, oral cavity, and pharynx were at or below the expected values among full-time and part-time firefighters in Glass et al. (2016a). For full-time firefighters, risk was elevated with longer duration of employment (*P* = 0.46).

Overall SIRs for cancer of the gall bladder ranged from 0.99 to 1.04 in Petersen et al. (2018a) in firefighters compared with the three reference populations analysed, based on five observed cases. Ahn et al. (2012) found a slightly reduced SIR for cancer of the gall bladder and extrahepatic bile ducts (SIR, 0.82; 95% CI, 0.33–1.70), based on seven cases.

Risk of soft tissue cancer was moderately elevated in Bigert et al. (2020) (SIR, 1.46; 95% CI, 0.82–2.41, 15 cases). In Ahn et al. (2012), the SIR for cancers of bone and articular cartilage was elevated but imprecise (SIR, 1.98; 95% CI, 0.53–5.07; 4 cases).

2.5.2 Studies only reporting having ever worked as a firefighter

(a) Occupational cohort studies

Studies first described in Section 2.1.2(a) are described in less detail in the present section.

See Table S2.10 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Altogether, eight occupational cohort studies reporting on the risk of cancers of the colon and rectum, oesophagus, stomach, pancreas, and other sites among firefighters were available (Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Giles et al., 1993; Deschamps et al., 1995; Ma et al., 2005, 2006; Amadeo et al., 2015). Incidence of cancer was studied in Ma et al. (2006) and Giles et al. (1993), whereas the remaining studies provided estimates for mortality as SMRs (Musk et al., 1978; Deschamps et al., 1995; Ma et al., 2005; Amadeo et al., 2015) or PMRs (Eliopulos et al., 1984; Grimes et al., 1991).

(i) Cancers of the digestive tract

Cancer mortality was investigated in a cohort comprising 10 829 firefighters employed in 1979 and covering 93% of the population of France (Amadeo et al., 2015). Follow-up was to the end of 2008, and comparisons were made with the male general population of France. For cancers of the oesophagus, stomach, and liver, mortality was close to the expected values, with SMRs of 0.93 (95% CI, 0.67–1.27; 40 deaths), 1.15 (95% CI, 0.77–1.65; 29 deaths), and 1.10 (95% CI, 0.80–1.46; 46 deaths), respectively. Colon cancer mortality was lower than expected (SMR, 0.73; 95% CI, 0.44–1.04). Moderately elevated mortality ratios were seen for cancers of the rectum (SMR, 1.36; 95% CI, 0.86–2.04; 23 deaths) and pancreas (SMR, 1.27; 95% CI, 0.92–1.72; 42 deaths), but precision was low.

Deschamps et al. (1995) reported on mortality in a cohort comprising 830 male firefighters in Paris, France. Firefighters had a minimum of 5 years of service on 1 January 1977, and follow-up was until 1 January 1991 (14 years). With the male general population of France as the referent, mortality from digestive tract cancers (i.e. ICD-9, 150–159; including oesophagus, stomach, small intestine including duodenum, colon, rectum, rectosigmoid junction and anus, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, pancreas, retroperitoneum and peritoneum, and other and ill-defined sites within the digestive organs and peritoneum) was modestly elevated, but the estimate was imprecise (SMR, 1.14; 95% CI, 0.37–2.66; 5 deaths).

Ma et al. (2006) examined cancer incidence in a cohort of 34 796 male and 2017 female career firefighters certified since 1972 in Florida, USA, with follow-up from 1981 through 1999. Comparisons were made with cancer rates in Florida. Among men, the SIR for colon cancer was 1.16 (95% CI, 0.92–1.45; 78 cases). For cancers of the oesophagus, stomach, rectum, and pancreas, risk estimates were below unity, but with wide confidence intervals. Among women, no cases of cancer of the oesophagus, stomach, or pancreas occurred. In a mortality study in the same cohorts as described above (Ma et al., 2005), follow-up was from 1972 through 1999. In male firefighters, stratified analyses were also made for those certified between 1972 and 1976, among whom the most cases occurred. For cancers of the oesophagus, stomach, and pancreas, SMRs among men were below unity and did not differ essentially between the full cohort and the cohort restricted to firefighters certified in 1972–1976, whereas no cases occurred among the female firefighters. Mortality rates for colon cancer were modestly increased among male firefighters compared with the general population, but the precision was low (SMR, 1.14; 95% CI, 0.81–1.56; 38 deaths). Among women, only one death from

colon cancer was observed (SMR, 2.27; 95% CI, 0.03–12.7).

Grimes et al. (1991) conducted a proportionate mortality analysis of causes of death in 1969–1988 among 205 deceased male firefighters employed by the City and County of Honolulu, Hawaii. The firefighters had been employed for ≥ 1 year and comparison was made with male mortality rates for the general population of Hawaii. Stratified analyses were also made for Caucasian [White] and Hawaiian firefighters. The PMR for cancer of the stomach was 0.79 (95% CI, 0.30–2.09; [4] deaths) overall. Colon cancer deaths were fewer among firefighters than in the general population, with none occurring among the Hawaiian firefighters.

Musk et al. (1978) conducted a cohort mortality study among 5655 firefighters with ≥ 3 years of service between 1915 and 1975 in Boston, USA. Firefighters were identified from employment records. Information on cause of death came from death certificates, which were lacking for 194 confirmed deaths (7.9%). Mortality for cancers of the digestive tract (i.e. oesophagus, stomach, small intestine including duodenum, colon, rectum, liver, and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, pancreas, peritoneum, and unspecified sites within digestive organs) was below unity when compared with that for Massachusetts men, but at unity when compared with that for US White men.

Giles et al. (1993) conducted a cancer incidence study of 2865 male operational firefighters employed between 1917 and 1989 by the fire brigade in Melbourne, Australia. Follow-up was from 1980 through 1989, and comparisons were made with the State of Victoria as the reference group. For colorectal cancer overall, the SIR was elevated but imprecise (SIR, 1.36; 95% CI, 0.62–2.59; 9 cases), driven by the risk in the age group ≥ 65 years (SIR, 3.65; 95% CI, 1.13–7.94; 6 cases). Risk of pancreatic cancer was at the expected level.

Eliopulos et al. (1984) conducted a PMR study among 990 firefighters employed between 1939 and 1978 in Western Australia. For stomach cancer and intestinal cancer, mortality ratios were elevated but imprecise (PMR, 2.02; 95% CI, 0.65–4.70; 5 deaths; and PMR, 1.59; 95% CI, 0.43–4.07; 4 deaths, respectively). [The Working Group noted that cancer codes were not stated, but as the ICD-8 classification system was used, the group "intestinal cancer" was presumed to comprise the small intestines (including duodenum), large intestine, and rectum.]

(ii) Cancers of other sites

In the studies included in the present section, results for cancer sites not included elsewhere were reported sporadically. Results on these sites are presented below. [The Working Group noted that most analyses in this group were based on small numbers because of the rarity of the cancer sites and that therefore estimates generally were imprecise.]

In Deschamps et al. (1995), the SMR for pharyngeal cancer was 0.81 (95% CI, 0.10–2.93), based on two deaths. For lip, oral cavity, and pharynx cancers, Ma et al. (2006) found a lower incidence rate among male firefighters than in the general population (SIR, 0.67; 95% CI, 0.47–0.91; 39 cases), whereas no cases occurred among women. Mortality from buccal/pharyngeal cancer was lower among male firefighters in Ma et al. (2005) (SMR, 0.42; 95% CI, 0.17–0.87; 7 deaths). For cancer of the upper aerodigestive tract (i.e. lip, tongue, oral cavity, pharynx, oesophagus, nose and sinuses, and larynx), Giles et al. (1993) reported an SIR of 1.46 (95% CI, 0.53–3.18; 6 cases).

The incidence rate of breast cancer among men was lower than expected in Ma et al. (2006) (SIR, 0.51; 95% CI, 0.06–1.84; 2 cases), whereas in Ma et al. (2005), the mortality rate for male breast cancer was substantially elevated (SMR, 7.41; 95% CI, 1.99–19.0; 4 deaths). Among women (Ma et al., 2006), breast cancer risk was as expected

(SIR, 0.96; 95% CI, 0.46–1.76; 10 cases). Amadeo et al. (2015) identified one death from breast cancer in men (SMR, 0.76; 95% CI, 0.02–4.23).

Ma et al. (2006) found risk of bone and soft tissue sarcoma to be as expected among men. Based on one case among women, the SIR for soft tissue sarcoma was 5.56 (95% CI, 0.07–30.91). Mortality from bone cancer among male firefighters in Ma et al. (2005) did not differ from that expected, based on one death; and no deaths from bone cancer occurred among female firefighters.

(b) Population-based studies

Studies first described in Section 2.1.2(b) are described in less detail in the present section.

See Table S2.10 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Three cohort studies (two in Europe and one in Canada) examined the risk of cancers of the digestive tract and other cancers among firefighters by linking national census records to national tumour registry or death records (Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020). An additional cohort study in Canada examined the risk of cancer among firefighters who were former claimants of workers compensation linked to cancer registry records (Sritharan et al., 2022). Case–control (and similar) studies included seven "event-only" studies conducted in the USA that used cancer registry records to identify cancer cases (Sama et al., 1990; Bates, 2007; Kang et al., 2008; Tsai et al., 2015; Langevin et al., 2020; Lee et al., 2020; McClure et al., 2021) and three other US studies that relied solely on death certificates as the source of both occupation and underlying cause of death (Ma et al., 1998; Muegge et al., 2018).

(i) Cancers of the digestive tract

The most recent European study was by Zhao et al. (2020), who linked Spanish census data to a national mortality registry. The study population consisted of 9.5 million employed men, aged 20–64 years in 2001, who were followed for 10 years. Among 27 365 firefighters, excesses of cancers of the stomach (MRR, 1.32; 95% CI, 0.88–1.98) and oesophagus (MRR, 1.11; 95% CI, 0.64–1.92) were observed, although all estimates were imprecise. Mortality for rectal cancer was close to that expected (MRR, 1.08; 95% CI, 0.57–2.04), and no excess was observed for cancers of the colon, liver, or pancreas.

Pukkala et al. (2014) presented a more comprehensive set of results from a census linkage of 15 million people (the NOCCA cohort) from all five Nordic countries (1961–2005). A total of 16 422 men reported their occupation as firefighter. With the Nordic general population as the referent, there were modest excesses of pancreatic cancer (SIR, 1.17; 95% CI, 0.94–1.45) and colon cancer (SIR, 1.14; 95% CI, 0.99–1.31), and a larger excess of gallbladder cancer (SIR, 1.45; 95% CI, 0.86–2.29). The risks of cancers of the oesophagus, stomach, rectum, and liver were similar to those expected.

Sritharan et al. (2022) investigated cancer incidence in a cohort of 13 642 firefighters compared with other members of a large cohort of 2 368 226 workers and with a subset of police officers in the cohort in Ontario, Canada. The study group was enumerated using information from an occupational injury and disease claims database and linkage to the provincial tumour registry and other electronic health records. There was no evidence of increased incidence of cancers of the oesophagus, stomach, or liver among firefighters compared with either the cohort overall or police officers. There were relatively precise excesses of both colon (HR, 1.39; 95% CI, 1.19–1.63; 152 cases) and pancreatic (HR, 1.34; 95% CI, 1.02–1.76; 53 cases) cancer

in firefighters compared with all other workers, but not compared with police. There were also excesses of rectal cancer (HR compared with other workers, 1.18; 95% CI, 0.93–1.51; and HR compared with police, 1.19; 95% CI, 0.85–1.68; 66 cases) and lip cancer (HR compared with other workers, 1.61; 95% CI, 0.89–2.92; and HR compared with police, 1.35; 95% CI, 0.57–3.22; 11 cases).

Harris et al. (2018) conducted the CanCHEC study using the 1991 Canadian census. The cohort included 1.1 million employed men, of whom 4535 reported their occupation as firefighter, who were followed up for cancer incidence through 2010. Elevated but imprecise risks were observed for cancers of the oesophagus (HR, 1.31; 95% CI, 0.68–2.51) and pancreas (HR, 1.38; 95% CI, 0.83–2.29) in firefighters compared with other employed people who participated in the census, whereas no evidence of an excess was seen for cancers of the stomach, colon, rectum, or liver. [The Working Group noted that parallel analyses were also conducted of police and members of the armed forces, who were chosen because they share some characteristics with firefighters. Colon cancer was elevated in police, but no other excess of cancers of the digestive tract were observed in either group.]

Lee et al. (2020) used records for 1972–2012 from the office of the Florida State Fire Marshal, USA, to identify cancer cases in male and female firefighters linked to the state cancer registry. No excess was observed for cancers of the oesophagus, stomach, colon, rectum, pancreas, or liver among men, although excesses of cancers of the stomach (OR, 1.85; 95% CI, 0.46–7.49) and rectum (OR, 2.02; 95% CI, 0.90–4.58) were observed for women, both based on fewer than 10 cases. A subanalysis identified a somewhat increased risk of late-stage diagnosis for cancers of the oesophagus, colon, and liver among male firefighters. A subsequent paper by the same group (McClure et al., 2021) demonstrated that relying on cancer registry data for occupational information was prone to errors that can cause bias in either direction. For cancers of the digestive system, similar ORs were obtained when firefighters were ascertained using only the registry data (OR, 0.96; 95% CI, 0.84–1.10) and when using the data from the office of the Fire Marshall (OR, 0.93; 95% CI, 0.85–1.03), even though the latter data identified twice as many cancers in firefighters.

Muegge et al. (2018) used death certificates from the state of Indiana, USA, for a mortality study of firefighters. Four non-firefighters per firefighter, matched on year of death, age at death, sex, and race/ethnicity, were randomly chosen as the comparison population. An increased risk of mortality from pancreatic cancer was observed (OR, 1.45; 95% CI, 1.01–2.06; 46 deaths) among firefighters, although no results for other specific cancer sites in the digestive tract were presented. [The Working Group noted that the major limitation of such studies is the reliance on death certificates to identify both occupation and cancer, which is likely to result in misclassification of both firefighting and cancer and has the potential for selection bias.]

Tsai et al. (2015) used data from the California Cancer Registry, USA, 1988–2007, to identify 3996 male firefighters, including wildland firefighters. An excess of oesophageal cancer was observed (OR, 1.59; 95% CI, 1.20–2.09), attributable to adenocarcinoma (OR, 1.85; 95% CI, 1.34–2.55), and was observed in White firefighters and in firefighters with other races/ethnicities (among non-White firefighters, the OR was 2.14; 95% CI, 0.81–5.65). Modestly elevated risks were also observed for cancers of the colorectum (OR, 1.10; 95% CI, 0.93–1.31), liver (OR, 1.07; 95% CI, 0.75–1.53), and pancreas (OR, 1.10; 95% CI, 0.83–1.46), whereas no excess was observed for stomach cancer. Bates (2007) conducted a similar study with the California Cancer Registry, USA, in 1988–2003, but these data were included in the study conducted later by Tsai et al. (2015) with data from 1988–2007.

Kang et al. (2008) conducted a study that relied on records from the state cancer registry in Massachusetts, USA, from 1987 through 2003 to identify usual occupation as well as cancer. A total of 2125 cancers were identified among White male firefighters. Twenty-five cancer types of concern for firefighters were evaluated, and the remaining cancers were the controls. SMBORs were adjusted for age and smoking status. Firefighters had an increased risk of colon cancer when compared with police (SMBOR, 1.36; 95% CI, 1.04–1.79) and, although reduced, when compared with other occupations (SMBOR, 1.15; 95% CI, 0.93–1.43), and colon cancer risk increased with age. Firefighters also had a somewhat increased risk of liver cancer when compared with police (SMBOR, 1.15; 95% CI, 0.55–2.41) or with all other occupations (SMBOR, 1.19; 95% CI, 0.69–2.06), but these estimates were less precise. No excesses of cancers of the oesophagus, stomach, rectum, or pancreas were observed when firefighters were compared with police or with all other occupations. Sama et al. (1990) conducted an earlier study that also relied on records from the state cancer registry in Massachusetts, USA, and used the same design as Kang et al. (2008) but had a substantially shorter (but non-overlapping) follow-up period (1982–1986) and did not adjust for smoking. Only men were included, and the risks for nine cancer sites were assessed, with the remaining sites acting as controls. This study observed excesses of cancers of the colon (SMBOR, 1.20; 95% CI, 0.80–1.82) and rectum (SMBOR, 1.35; 95% CI, 0.84–2.19) among firefighters compared with the general population, but not with the police. In contrast, an excess of pancreatic cancer (SMBOR, 3.19; 95% CI, 0.72–14.15) was observed compared with the police, but not with the general population; however, all estimates were imprecise.

Ma et al. (1998) used death certificates from 24 states of the USA as the sole source of both occupation and underlying cause of death in 1984–1993. Among White male firefighters, modestly elevated risks were observed for cancers of the pancreas (MOR, 1.2; 95% CI, 1.0–1.5), stomach (MOR, 1.2; 95% CI, 0.9–1.6), liver (MOR, 1.2; 95% CI, 0.9–1.7), and rectum (MOR, 1.1; 95% CI, 0.8–1.6), whereas no evidence of an excess was observed for cancers of the oesophagus or colon. Among Black male firefighters, excesses were observed for cancers of the colon (MOR, 2.1; 95% CI, 1.1–4.0), pancreas (MOR, 2.0; 95% CI, 0.9–4.6), and stomach (MOR, 1.4; 95% CI, NR; 4 deaths), based on much smaller numbers (no deaths from cancers of the rectum or liver were observed). In an earlier report, Burnett et al. (1994) used data from 27 states for a proportionate mortality analysis of White male firefighters in 1984–1990. An excess of rectal cancer was identified (PMR, 1.48; 95% CI, 1.05–2.05), which was substantially higher among firefighters who died before age 65 years (PMR, 1.86; 95% CI, 1.10–2.94). No other results for cancers of the digestive tract were reported. Of the 27 states reported, 24 were the same as those reported by Ma et al. (1998) for a somewhat longer time period.

(ii) Cancers of other sites

Other cancer sites, not considered in previous sections, were also examined in some studies, and results for cancers of the lip, oral cavity, pharynx, soft tissue sarcoma/connective tissue, bone, and breast are discussed here. Zhao et al. (2020) reported an increased risk of oropharyngeal (MRR, 1.34; 95% CI, 0.81–2.21; 18 deaths), breast (MRR, 3.04; 95% CI, 0.42–21.78; 1 death), and bone cancer (MRR, 1.11; 95% CI, 0.16–7.92; 1 death) among Spanish firefighters. Sritharan et al. (2022) reported a similar risk of breast cancer among female firefighters compared with all other workers (HR, 0.97; 95% CI, 0.46–2.03) and with police (HR, 0.78; 95% CI, 0.36–1.71). In the NOCCA study, Pukkala et al. (2014) reported a greater than expected number of soft tissue cancers (SIR, 1.16; 95% CI, 0.69–1.84) among Nordic firefighters, but the incidence rates of cancers of the lip, oral cavity, and pharynx

were at or below expected rates. Harris et al. (2018) found a higher rate of lip cancer among firefighters (HR, 2.09; 95% CI, 0.87–5.06) than among others, but the incidence of oral cavity cancer was as expected. Lee et al. (2020) reported results separately for men and women for cancers of the oral cavity and pharynx combined (OR for men, 0.85; 95% CI, 0.72–0.99; and OR for women, 1.26; 95% CI, 0.47–3.40), soft tissue (OR for men, 0.93; 95% CI, 0.65–1.34; and OR for women, 0.69; 95% CI, 0.10–4.95), bone (OR for men, 0.72; 95% CI, 0.36–1.44; and OR for women, 3.90; 95% CI, 0.97–15.71). They reported a deficit of breast cancers among female firefighters. Langevin et al. (2020) reported no association between ever-employment or duration of employment as a firefighter and cancers of head and neck (all combined), oral cavity, oropharynx (SCC), or hypopharynx (SCC), although there were very few firefighters as cases or controls in the study.

Muegge et al. (2018) reported an increased risk of cancers of the oral cavity and pharynx combined (OR, 2.15; 95% CI, 1.19–3.79) and of connective tissue (OR, 2.50; 95% CI, 1.01–5.86) for the death certificate study in Indiana, USA. Tsai et al. (2015) reported unremarkable results, mainly based on very small numbers, for cancers of lip, pharynx, and soft tissues for the California registry-based study. Kang et al. (2008) reported below-null, close-to-null, or highly imprecise results for cancers of the lip, oral cavity, and pharynx, soft tissue sarcoma, and male breast for firefighters compared with either police or with other occupations in the Massachusetts registry-based study. Ma et al. (1998) reported mortality findings for cancer of the pharynx among Black firefighters (OR, 7.6; 95% CI, 1.3–46.4) and, among White firefighters, for cancers of the lip (MOR, 5.9; 95% CI, 1.9–18.3), soft tissue sarcoma (MOR, 1.6; 95% CI, 1.0–2.7), and bone (MOR, 1.0; 95% CI, NR). [The Working Group noted that findings were not consistently provided for these cancers and estimates were often based on small numbers.]

2.6 Cancer of all sites combined

2.6.1 Studies reporting occupational characteristics of firefighters

See Table S2.11 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Studies first described in Section 2.1.1 are described in less detail in the present section.

The Working Group identified 26 occupational and population-based cohort studies that had investigated the relationship between occupational exposure as a firefighter and risk of cancer of all sites combined (Feuer & Rosenman, 1986; Vena & Fiedler, 1987; Demers et al., 1992a, 1994; Giles et al., 1993; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Bates et al., 2001; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014, 2015; Ahn & Jeong, 2015; Glass et al., 2016a, b, 2017, 2019; Kullberg et al., 2018; Petersen et al., 2018a, b; Bigert et al., 2020; Pinkerton et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a, b). Two of these studies were from Asia, seven were from Europe, twelve were from North America, and six were from Oceania. [The Working Group noted that, although analysis of all cancers combined enhances the statistical power to observe an effect because of increased case numbers, interpretation of the results is seriously limited by the very heterogenous etiology and pathology of cancers at the different sites.]

Ahn & Jeong (2015) conducted a cohort mortality study among 33 442 professional [career] emergency responders in the Republic of Korea. Emergency responders had been employed between 1980 and 2007, and mortality follow-up took place from 1992 through 2007. In the subcohort of firefighters (n = 29 453, 88% of the total cohort) compared with the male population of the Republic of Korea, the SMR for cancer of all sites combined was lower than expected overall (SMR, 0.58; 95% CI, 0.50–0.68) and in all

categories of duration of employment (< 10 years, 10–20 years, and ≥ 20 years). Internal analyses of employment duration, for which firefighters employed for < 10 years and other emergency responders served as reference groups, showed age- and calendar-year ARR [adjusted rate ratio] estimates of 1.54 (95% CI, 1.02–2.31) for firefighters employed for ≥ 20 years. [The Working Group noted the young average age at end of follow-up (41.3 years), which strongly indicated a downward selection bias from a healthy-worker hire effect.]

In the same cohort as above, Ahn et al. (2012) conducted a cancer incidence study among professional [career] emergency responders with cancer incidence follow-up from 1996 through 2007 in the Republic of Korea. National cancer incidence rates for men served as the referent, and analyses were conducted overall and by duration of employment (< 10 years versus ≥ 10 years). Risk of cancer of all sites combined was not different from that for the general population (SIR, 0.97; 95% CI, 0.88–1.06) or, in the internal analyses, for the non-firefighter emergency responders (SRR, 0.83; 95% CI, 0.59–1.16). No increased risk with duration of employment (< 10 years versus ≥ 10 years) was seen.

Marjerrison et al. (2022a, b) investigated cancer incidence and mortality in a cohort of 3881 male professional [career] firefighters in Norway compared with the male general population. The cohort included mostly full-time firefighters employed between 1950 and 2019 with past or present employment in positions entailing active firefighting duties. The follow-up period for both cancer incidence and mortality analyses was from 1960 through 2018. Among those ever employed as a firefighter, the SIR for all cancer sites combined was 1.15 (95% CI, 1.07–1.23). Increased risks were seen for firefighters with longer duration of employment (SIR for ≥ 30 years, 1.19; 95% CI, 1.09–1.30), for those first employed before 1950 (SIR, 1.29; 95% CI, 1.15–1.44), and for those with ≥ 40 years since first employment (SIR, 1.18; 95% CI, 1.08–1.29). For mortality, the overall SMR for all cancers combined was 1.08 (95% CI, 0.97–1.20). In the earliest follow-up period (to the end of 1984), an SIR of 1.21 (95% CI, 1.02–1.43) and SMR of 1.25 (95% CI, 1.00–1.55) was observed. Elevated incidence and mortality were also seen in the age group ≥ 70 years (SIR, 1.23; 95% CI, 1.11–1.36; and SMR, 1.20; 95% CI, 1.05–1.38).

Bigert et al. (2020) investigated cancer incidence in a cohort of 8136 male firefighters in Sweden. Employment information was ascertained from national decennial censuses between 1960 and 1990. Cancer incidence data were ascertained from the Swedish Cancer Registry with follow-up from 1961 through 2009. With the national male general population as the referent, risk of all cancers combined did not deviate from the expected value overall (SIR, 1.03; 95% CI, 0.97–1.09) or by duration of employment ($P = 0.19$).

A cancer incidence study in a cohort of 1080 male firefighters in Stockholm, Sweden, provided information on the risk of all cancers combined (Kullberg et al., 2018). Firefighters were identified through annual enrolment records from 15 fire stations and had worked for ≥ 1 year between 1931 and 1983. As an update to a previous study (Tornling et al., 1994), this study added 26 years of cancer incidence follow-up from 1958 through 2012 in the Swedish Cancer Registry. With the male general population of Stockholm County as the referent, the overall SIR for all cancers combined was lower than expected (0.81; 95% CI, 0.71–0.91). In stratified analyses, there were statistically significant trends of increasing overall SIR for cancer with increasing age (P for trend, < 0.01), longer employment duration (P for trend, 0.03), and earlier period of hire (P for trend, < 0.01), although there was no excess of cancer overall in any stratum.

In the original analysis of this cohort, Tornling et al. (1994) investigated both cancer mortality and incidence. Follow-up for mortality

was from 1951 through 1986 and for cancer incidence from 1958 through 1986. Comparisons were made with the male regional general population. For each firefighter, exposure to fire events was assessed using reports of fires fought by the Stockholm fire brigade between 1933 and 1983. Mortality from cancer of all sites was equal to that expected. In stratified analyses, SMRs above 1.00 were seen for the highest age category (SMR, 1.09; 95% CI, 0.85–1.39), the longest employment duration (SMR, 1.09; 95% CI, 0.79–1.46), and the highest number of fire responses (SMR, 1.20; 95% CI, 0.90–1.57). SIRs did not vary with the number of fire responses. [The Working Group noted that the exposure assessment method was a strength and that trend tests were not performed.]

Petersen et al. (2018a) studied cancer incidence in a cohort of 9061 male full-time, part-time, and volunteer firefighters in Denmark. Follow-up was from 1968 through 2014, and three external comparison groups were used: the general population of Denmark, a sample of the working population, and a cohort of military employees. Additional analyses by employment type (e.g. full-time, other), era of first employment, job function (e.g. regular, specialized), age at first employment, and duration of employment were performed with the general population as referent. For cancer of all sites combined, overall estimates varied very little with choice of referent, with the SIR using the general population as the reference group being 1.02 (95% CI, 0.96–1.09). Risks were modestly elevated for employment before 1970 (SIR, 1.12; 95% CI, 1.02–1.22), specialized firefighters (SIR, 1.12; 95% CI, 0.88–1.39), age < 25 years at first employment (SIR, 1.12; 95% CI, 1.03–1.22), and for duration of employment of < 1 year (SIR, 1.14; 95% CI, 1.02–1.27).

Cancer mortality was investigated in the same cohort of firefighters in Denmark described above (Petersen et al., 2018b). An expanded study population of 11 775 male firefighters was followed for mortality in the Danish national death registry from 1970 through 2014. External comparisons were made with a sample of the working population and with a cohort of military employees. The overall SMR for all cancers combined was not elevated compared with that for either of the reference groups; however, with restriction to full-time firefighters the SMR was 1.12 (95% CI, 1.00–1.26) compared with the military referent. Overall cancer mortality decreased monotonically with longer duration of employment, with an SMR of 1.18 (95% CI, 0.99–1.40) for a duration of < 1 year. [The Working Group noted that a trend test was not performed.]

Webber et al. (2021) investigated cancer incidence in a cohort of 10 786 male firefighters from the FDNY and exposed to the WTC disaster site. Comparisons were made with the US male general population and with 8813 presumed non-WTC exposed firefighters employed during the same period from the CFHS (which included firefighters from San Francisco, Chicago, and Philadelphia). Cancer follow-up was from 11 September 2001 through 2016. With the US general population as the referent, the overall SIR for all cancers combined was elevated among the FDNY WTC-exposed firefighters (SIR, 1.15; 95% CI, 1.08–1.23) but not among the CFHS firefighters (SIR, 1.05; 95% CI, 0.98–1.12). To adjust for potential medical surveillance bias because of free and routine health examinations in the WTC-exposed FDNY cohort, additional analyses with the diagnosis date of select cases delayed by 2 years were performed. With this adjustment, the SIR for the FDNY firefighters was attenuated (SIR, 1.09; 95% CI, 1.02–1.16). Internal comparison regression analyses with the CFHS cohort as the referent, with and without adjustment for potential surveillance bias, yielded RRs of 1.07 (95% CI, 0.96–1.18 and 1.13 (95% CI,1.02–1.25), respectively. [The Working Group noted the importance of investigating potential surveillance bias attributable to enhanced screening in this firefighter cohort. Although increased medical attention would tend to elevate risk

estimates, results indicated that the effect on cancer of all sites combined was present, but modest. The opposite contributions of healthy-worker bias and surveillance bias complicated interpretation of results from this cohort.]

In a previous follow-up of cancer incidence among WTC exposed firefighters, Zeig-Owens et al. (2011) compared exposed and unexposed person-time in the FDNY cohort, which included 9853 male FDNY firefighters. Cancer incidence follow-up was conducted in state cancer registries from 1996 through 2008. With the US male general population as the referent, exposure at the WTC site was associated with higher incidence of all cancers combined (SIR, 1.10; 95% CI, 0.98–1.25) than was no exposure (SIR, 0.84; 95% CI, 0.71–0.99), with a ratio of SIRs of 1.32 (95% CI, 1.07–1.62). Sensitivity analyses with different cohort restrictions and inclusion of multiple primary cancer diagnoses did not meaningfully change the ratio of SIRs. No difference was seen by calendar period of follow-up (before or after 31 December 2004). [The Working Group noted that the SIR ratio is not a standard epidemiological effect measure.]

Three studies of both cancer mortality and incidence have been conducted among municipal career firefighters in the CFHS who were employed at fire departments in San Francisco, Chicago, and Philadelphia, USA. Most recently, Pinkerton et al. (2020) updated previous analyses by Daniels et al. (2014) with cancer mortality follow-up from 1950 extended through 2016. With the US general population as the referent, the overall SMR for all cancers combined was elevated in the full cohort (SMR, 1.12; 95% 1.08–1.16) and specifically among firefighters in the Chicago subcohort (SMR, 1.20; 95% 1.15–1.26). Significant heterogeneity between the fire department subcohorts was noted (heterogeneity *P* value, < 0.01). Stratified analyses showed that SMRs were lower than expected (SMR, 0.79; 95% CI, 0.68–0.93) among non-White firefighters and higher than expected among White firefighters (SMR, 1.14; 95% CI, 1.10–1.18) and firefighters aged ≥ 65 years (SMR, 1.22; 95% CI, 1.17–1.27). In internal regression analyses, the choice of regression model had little impact on estimates for all cancers combined, but covariate adjustment for duration of employment generally produced estimates that were higher than those without adjustment. Comparing hazard rates at the 75th and the 25th percentile of the exposure distributions, the fully adjusted model gave adjusted hazard ratios of 1.14 (95% CI, 1.00–1.31) for number of exposed days, 1.02 (95% CI, 0.94–1.11) for fire-runs, and 1.08 (95% CI, 0.96–1.21) for fire-hours.

An earlier study of a subset of 19 309 firefighters from the same CFHS cohort examined both cancer mortality and incidence and reported internal exposure–response associations with follow-up to the end of 2009 (Daniels et al., 2015). Methods were similar to those used in Pinkerton et al. (2020); however, results in the present study were not adjusted for employment duration. Results showed no evidence of an association for cancer of all sites combined with any of the exposure metrics of number of exposed days, fire-runs, or fire-hours.

An additional study of the CFHS cohort investigated cancer incidence among 29 993 municipal career firefighters and reported external and internal comparison analyses with follow-up to the end of 2009 (Daniels et al., 2014). The methods were similar to those in the study by Pinkerton et al. (2020). Cancer incidence follow-up was conducted in state cancer registries relevant to each department to the end of 2009, with start years varying between 1985 and 1988. For the incidence of all cancers combined (including all primary cancers), slightly increased risk was observed in firefighters (SIR, 1.09; 95% CI, 1.06–1.12) compared with the US general population. In Caucasian [White] men, an excess risk was observed (SIR, 1.10; 95% CI, 1.07–1.13), whereas non-White men had an SIR slightly below unity (SIR, 0.92; 95% CI, 0.81–1.05).

Among women, overall cancer incidence was modestly elevated, but imprecise (SIR, 1.24; 95% CI, 0.89–1.69).

Cancer incidence was studied in a cohort of 2447 male firefighters who had been employed for ≥ 1 year between 1945 and 1979 in the cities of Seattle and Tacoma, Washington, USA (Demers et al., 1994). Follow-up was conducted in a regional cancer registry for the period 1974–1989. There was no evidence of an overall excess risk of cancer of all sites combined, with comparisons with local county rates and local police rates yielding similar results. Risk also did not increase with duration of exposed employment or time since first employment.

In an earlier cohort study, Demers et al. (1992a) investigated cancer mortality in 4401 male municipal firefighters from the cities of Seattle and Tacoma, Washington, and Portland, Oregon, USA. Mortality follow-up was from 1944 through 1989. SMRs for all cancers combined were at unity when compared with US national mortality rates and with mortality rates for police officers from the same cities.

Vena & Fiedler (1987) studied mortality in a cohort of 1867 White male firefighters employed in Buffalo, USA, during 1950–1979. Mortality follow-up was from 1950 through 1979, and comparisons were made with mortality rates among US White men in the general population. Overall cancer mortality was similar to that expected (SMR, 1.09; 95% CI, 0.89–1.32) but was increased in firefighters with an employment duration of ≥ 40 years (SMR, 2.20; 95% CI, [1.5–3.1]). Mortality from all malignant neoplasms also tended to increase with increasing latency of time since first employment.

Feuer & Rosenman (1986) conducted a PMR study that included 263 deceased firefighters from New Jersey, USA, who died during 1974–1980. Comparisons were made with the US White male and New Jersey White male general populations, as well as New Jersey White police officers. With US White males as the referent, the PMR for all cancer sites combined was 1.15 (95% CI, [0.90–1.45]). Estimates were closer to unity when using the two alternative reference groups. Stratified analyses by duration of employment showed a higher estimate for those employed for > 25 years (PMR, 1.09; 95% CI, [0.77–1.51]) than for those employed ≤ 20 years (PMR, 0.91; 95% CI, [0.53–1.47]).

Aronson et al. (1994) investigated cancer mortality among a cohort of 5414 male career firefighters employed for ≥ 6 months in Toronto, Canada. Firefighters had been employed between 1950 and 1989, and mortality follow-up was conducted in a national mortality database from 1950 through 1989. With the male general population of Ontario as the referent, the SMR for all malignant neoplasms combined was 1.05 (95% CI, 0.91–1.20), and the highest mortality was seen among those with the shortest time since first employment (< 20 years) and shortest duration of employment (< 15 years).

Guidotti (1993) examined cancer mortality in a cohort of 3328 firefighters employed and followed-up from 1927 through 1987 in Edmonton and Calgary, Canada. External comparisons were made with the general male population of Alberta. SMRs were stratified according to employment characteristics, and an exposure index (with values of 0, > 0 to < 1, 1–9, and ≥ 10) was created on the basis of years of firefighter service weighted by an estimate of the relative time spent in proximity to fires according to job classification. With the general population as the referent, the overall SMR for all cancers combined was 1.27 (95% CI, 1.02–1.55). No clear pattern with latency period of first employment was observed, but SMRs were higher with 40–49 years (SMR, 1.76; 95% CI, [1.15–2.61]) or ≥ 50 years since first employment (SMR, 1.44; 95% CI, [0.82–2.36]) than with first employment in more recent times. The SMR was 1.67 (95%: [0.73–3.31]) for those in the lowest exposure index category and 1.96 (95% CI, [1.09–3.27]) in the second lowest exposure category. Stratified

analyses of exposure index by time since first employment showed no clear association with mortality from all cancers combined. [The Working Group noted the low number of cases in stratified analyses.]

In a large cohort of Australian female paid [career] (n = 1682) and volunteer (n = 37 962) firefighters, Glass et al. (2019) investigated both mortality and cancer incidence. Cancer incidence follow-up was conducted in a national cancer registry from 1982 through 2010. The general female population of Australia served as the reference group in external comparison analyses. Information on the number of incidents attended was ascertained from personnel records and categorized in tertiles by type of incident. Among the subset of career firefighters, the SIR for all cancers combined was 1.15 (95% CI, 0.80–1.67). Among volunteer firefighters, there was no excess of all cancers combined using either incidence or mortality outcomes. In internal regression analyses of cancer incidence, there was a modest elevation in the rate of cancer among volunteer firefighters in the highest tertile of the number of total incidents attended compared with firefighters who had never attended incidents (RIR [equivalent to rate ratio], 1.14; 95% CI, 0.93–1.38). Trend tests did not suggest positive trends in the rate of cancer with increasing tertile for any incident type.

Using the same methods as those in the study of female firefighters, cancer incidence was also investigated in a parallel cohort of 163 094 male volunteer firefighters in Australia (Glass et al., 2017). With the male general population of Australia as the referent, overall cancer mortality and incidence were similar and lower than expected in all volunteers and the subset who had attended incidents, respectively (SMR, 0.59; 95% CI, 0.57–0.62; and SIR, 0.86; 95% CI, 0.84–0.88). Internal regression analysis showed decreasing mortality with longer duration of service ($P < 0.01$). With more incidents attended, relative mortality ratios (RMR) [rate ratios] for all cancers combined were consistently above unity, specifically for attendance at structure fires (RMR, 1.38; 95% CI, 1.00–1.91) and vehicle fires (RMR, 1.29; 95% 1.00–1.66) among firefighters in the intermediate tertile of exposure. For overall cancer incidence, associations with the number of incidents attended were more attenuated than for mortality, with the highest risk estimate being an RIR [equivalent to rate ratio] of 1.20 (95% CI, 1.01–1.42) for attendance at structure fires among those in the intermediate tertile group. In the subset of volunteer firefighters who attended incidents, the RIR for duration of service of 10–20 years was 1.09 (95% CI, 1.00–1.20; $P = 0.25$) compared with < 10 years of service.

Using similar methods as those in the two studies of volunteer firefighters, mortality and cancer incidence were studied in a cohort of 30 057 paid full-time and part-time male firefighters in Australia (Glass et al., 2016a). Included firefighters had worked between 1976 and 2003 and were primarily municipal or semi-metropolitan firefighters. Cancer incidence and mortality follow-up were conducted in national registries to the end of 2010 and 2011, respectively. For all cancer sites combined, mortality was lower than expected (SMR, 0.81; 95% CI, 0.74–0.89), but incidence was higher than expected (SIR, 1.09; 95% CI, 1.03–1.14) among firefighters overall compared with the male general population of Australia. Stratified results were similar for full-time and part-time firefighters. In internal regression analyses, no trend was seen with increasing duration of employment. Among full-time firefighters, increasing attendance at all incidents and all fire incidents was positively associated with the incidence of all cancers combined, specifically for landscape fires in the second tertile of the number of incidents attended (SIR, 1.54; 95% CI, 1.18–1.99) and for vehicle fires (SIR for second tertile, 1.48; 95% CI, 1.13–1.93; and SIR for third tertile, 1.34; 95% 1.04–1.71; $P = 0.04$).

Glass et al. (2016b) studied cancer incidence and mortality in a small cohort of 614 firefighter trainers and firefighters who attended a fire-training facility in Australia. Cancer incidence follow-up was conducted from 1982 through 2012 and mortality follow-up from 1980 through 2011. Participants were grouped into risk categories of low, medium, and high chronic exposure (to smoke and other hazardous agents) on the basis of job assignment. For all cancers combined, the SMR was 1.47 (95% CI, 0.54–3.19; 6 deaths) among firefighters in the "high risk of chronic exposure" group compared with the male general population of Victoria. The SIR for cancers of all sites combined was low in the "low risk of chronic exposure" group (SIR, 0.40; 95% CI, 0.15–0.87) and elevated in the "high risk of chronic exposure" group (SIR, 1.85; 95% CI, 1.2–2.73). Sensitivity analyses differentiating between paid [career] and volunteer firefighters in the medium-risk group or using different sources for start date, did not change estimates for mortality, but had a larger impact on the incidence estimates. In the high-risk group, selection of an alternative source for start date elevated the SIR to 2.06 (95% CI, 1.32–3.06).

Bates et al. (2001) investigated cancer incidence and mortality in a cohort of 4305 paid [career] and volunteer New Zealand firefighters who had been employed as a career firefighter for ≥ 1 year and between 1977 and 1995. The cohort included 84 female firefighters who were excluded from analysis. Follow-up for cancer mortality and incidence was conducted in a national data source to the end of 1995 (for mortality) or 1996 (for incidence). External comparisons were made with the male general population of New Zealand. No excess incidence or mortality among firefighters was seen for all cancer combined in the overall analysis or, for incidence, after stratification by calendar period of follow-up. For career and volunteer service combined, 11–20 years of service gave an SIR of 1.75 (95% CI, 1.2–2.5), which was reduced to near-unity with > 20 years of service (SIR, 1.04; 95%: CI, 0.8–1.4). For duration of career service only, all estimates were closer to unity.

Giles et al. (1993) conducted a cancer incidence study of 2865 male operational firefighters employed by the fire brigade in Melbourne, Australia, between 1917 and 1989. Cancer incidence follow-up was from 1980 through 1989, and comparisons were made with the general population of the state of Victoria as the reference group. The overall SIR for all cancers combined was 1.13 (95% CI, 0.84–1.48). The SIR was specifically elevated among those aged ≥ 65 years (SIR, 2.14; 95% CI, 1.32–2.37). Decreasing SIRs were seen with increasing time since first employment, and no trend test was reported. With duration of employment, the highest SIR was seen among firefighters with employment of 15–29 years (SIR, 1.39; 95% CI, 0.85–2.15).

2.6.2 Studies only reporting having ever worked as a firefighter

(a) Occupational cohort studies

Studies first described in Section 2.1.2(a) are described in less detail in the present section.

See Table S2.12 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Altogether, nine occupational cohort studies in firefighters reported on risk of cancer of all sites combined (Mastromatteo, 1959; Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Deschamps et al., 1995; Ide, 1998; Ma et al., 2005, 2006; Amadeo et al., 2015). [One of these studies, Ide (1998), investigated a highly selected group of 505 firefighters aged 20–54 years who died (n = 17) or retired from service because of ill health (n = 488). This study was not considered informative and is therefore not further considered here.] Cancer incidence was evaluated only in Ma et al. (2006), whereas the remaining studies provided estimates for mortality as

SMRs (Mastromatteo, 1959; Musk et al., 1978; Deschamps et al., 1995; Ma et al., 2005; Amadeo et al., 2015), PMRs (Grimes et al., 1991), or both (Eliopulos et al., 1984). None of the studies had, or used, information on duration of employment, and analyses were based on registration as a firefighter at a single time-point, in some studies with a qualifier of duration of employment for ≥ 1, 3, or 5 years (Musk et al., 1978; Grimes et al., 1991; Deschamps et al., 1995, respectively). Periods of follow-up were generally long, ranging from 13 (Grimes et al., 1991) to 39 years (Eliopulos et al., 1984).

Amadeo et al. (2015) investigated all-cancer mortality in a cohort comprising 10 829 firefighters employed in 1979 and covering 93% of the population of France. Follow-up was through 2008 and comparisons were made with the male general population of France. The SMR for all cancer sites combined was near the expected value (SIR, 0.95; 95% CI, 0.88–1.02).

Deschamps et al. (1995) reported on mortality in a cohort comprising 830 male firefighters in Paris, France, with a minimum of 5 years of service on 1 January 1977. Follow-up was until 1 January 1991 (14 years). With the male general population of France as the referent, the SMR for all cancer sites combined was 0.89 (95% CI, 0.53–1.40).

Ma et al. (2006) examined cancer incidence in a cohort of 34 796 male and 2017 female career firefighters certified since 1972 in Florida. Linkage was performed with the state-wide Florida cancer registry, and comparisons were made with Florida state cancer rates. Risk of cancer of all sites was lower among male firefighters (SIR, 0.84; 95% CI, 0.79–0.90) and was elevated among female firefighters (SIR, 1.63; 95% CI, 1.22–2.14), with 970 and 52 cancer cases, respectively, compared with the general population.

In a mortality study of the same cohort as described above (Ma et al., 2005), follow-up was from 1972 through 1999. In male firefighters, stratified analyses were also made for those certified between 1972 and 1976, among whom most cases occurred. The mortality rate from cancer of all sites combined was below that expected among males and was similar in the restricted cohort and the full cohort (SMR in the full cohort, 0.85; 95% CI, 0.77–0.94). Among women, the all-cancer mortality rate was as expected.

Grimes et al. (1991) conducted a proportionate mortality analysis of causes of death during 1969–1988 among 205 deceased firefighters employed by the city and county of Honolulu, Hawaii, USA. The firefighters had been employed for ≥ 1 year, and comparisons were made with mortality rates for the male general population in Hawaii. PMRs were modestly elevated for cancers of all sites combined (overall PMR, 1.19; 95% CI, 0.96–1.49), and were somewhat higher for Hawaiian than for Caucasian [White] firefighters.

Musk et al. (1978) conducted a cohort mortality study among 5655 firefighters with ≥ 3 years of service in Boston, USA, during 1915–1975. Firefighters were identified from employment records. Information on cause of death came from death certificates, which were lacking for 194 confirmed deaths (7.9%). Mortality for cancer of all sites combined was below unity in the total cohort (SMR, 0.86; 95% CI, [0.77–0.95]) and among active firefighters (SMR, 0.73; 95% CI, [0.60–0.89]) when compared with that in Massachusetts men.

Mastromatteo (1959) conducted a cohort mortality study of all 1832 active and retired firefighters employed by the city fire department of Toronto, Ontario, Canada, from 1918 to 1954. A total of 325 firefighters (31%) were lost to follow-up after termination of work and were censored at that time. Comparison was made with mortality rates among male residents in Ontario (1921–1953) and with specifically calculated mortality rates among men in urban areas of Ontario (1937–1959). Mortality from cancer of all sites combined was moderately elevated, but

imprecise, in firefighters compared with Ontario men, and similar to that in men in urban areas of Ontario. [The Working Group noted the large loss to follow-up in this study, which rendered the result less informative.]

Eliopulos et al. (1984) studied cancer mortality from 1939 through 1978 among 990 firefighters in Western Australia compared with the male general population of Western Australia. The SMR for all cancer sites was close to that expected (SMR, 1.09; 95% CI, 0.74–1.56).

(b) Population-based studies

Studies first described in Section 2.1.2(b) are described in less detail in the present section.

See Table S2.12 (Annex 2, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.fr/615).

Altogether, eight population-based studies reported on risk of cancer of all sites combined among firefighters, including five cohort studies (Hansen, 1990; Pukkala et al., 2014; Harris et al., 2018; Zhao et al., 2020; Sritharan et al., 2022) and three studies based on death records (Burnett et al., 1994; Ma et al., 1998; Muegge et al., 2018).

Zhao et al. (2020) followed 9.5 million employed men aged 20–64 years, identified from the 2001 Spanish census, for a period of 10 years via data linkage to a national mortality registry. There was no evidence of increased risk of all cancers combined (MRR, 1.00; 95% CI, 0.89–1.12) among 27 365 firefighters compared with all other occupations. [The Working Group noted that the major limitations of this study were the lack of information on duration or other exposure-related information and the minimal information on potential confounding factors. In addition, the short follow-up time limited the power of this study. The main strength of the study was the use of national census data, which allowed the identification of all firefighters in 2001.]

Pukkala et al. (2014) in the NOCCA study conducted a census linkage of 15 million people from all five Nordic countries (1961–2005). A total of 16 422 males reported their occupation as firefighter. With the Nordic general population as the referent, a small excess of all cancers combined (excluding non-melanoma skin cancer) was observed (SIR, 1.06; 95% CI, 1.02–1.11). [The Working Group noted that the major limitations of this study were the lack of information on duration or other exposure related information and minimal information on potential confounding factors. The major strengths of this study were its use of high-quality tumour registry data and the use of national census data, which allowed the identification of all firefighters at the census time-points.]

Sritharan et al. (2022) investigated cancer incidence in a cohort of 13 642 firefighters employed in Ontario, Canada, compared with other members of a large cohort of 2 368 226 workers and separately with 22 595 police from the same cohort. The study group was enumerated and followed-up using information from an occupational injury and disease claims database and linkage to the provincial tumour registry and other electronic health records. An increased risk of overall cancer incidence was observed in firefighters compared with all other workers in the cohort (HR, 1.23; 95% CI, 1.17–1.29) but not with police (HR, 1.03; 95% CI, 0.96–1.09).

Harris et al. (2018) conducted the CanCHEC study, which was similar to the study carried out by Pukkala et al. (2014) using the 1991 Canadian census, although Harris and colleagues adjusted for education level in addition to age and geographical region. The cohort included 1.1 million employed men, of whom 4535 reported their occupation as firefighter, with follow-up to the end of 2010. The overall cancer incidence was similar to that for other employed men (HR, 1.04; 95% CI, 0.96–1.14). [The Working Group noted that the major limitations of this study were the lack of information on duration or other

exposure-related information and the minimal information on potential confounding factors. Its major strengths were the use of tumour registry data and the use of national census data, which allowed the identification of all firefighters in 1991.]

Muegge et al. (2018) used death certificates from Indiana, USA, for a mortality study using a case–control analysis among firefighters. Four non-firefighters per firefighter, matched on year of death, age at death, sex, and race/ethnicity, were randomly chosen as the comparison population. An increased risk of overall cancer mortality was observed (OR, 1.19; 95% CI, 1.08–1.30) based on 857 cancer deaths among firefighters. [The Working Group noted that the authors used non-standard analytical methods similar to the MOR analysis proposed as an alternative to the PMR. Another major limitation of this study was the reliance on death certificates to identify both occupation and cancer (which is likely to result in misclassification of both), and the lack of information on duration or other exposure-related information, which limits the ability to draw conclusions regarding causality. This study also had minimal information on potential confounding factors, other than sex and race.]

Ma et al. (1998) used death certificates from 24 states in the USA as the sole source of both occupation and underlying cause of death in 1984–1993. There were 1817 cancer deaths observed among White male firefighters (MOR, 1.1; 95% CI, 1.1–1.2) and 66 among Black firefighters (MOR, 1.2; 95% CI, 0.9–1.5). In an earlier report, Burnett et al. (1994) used data from 27 states for a proportionate mortality analysis of White male firefighters in 1984–1990. An excess of all cancers combined was identified (PMR, 1.10; 95% CI, 1.06–1.14). Twenty-four of the 27 states were the same as those reported by Ma et al. (1998) for a somewhat longer time period. [The Working Group noted that the major limitations of these studies were the reliance on death certificates to identify both occupation and cancer, which is likely to result in misclassification of both. Results may also be biased if the cancer sites chosen as controls are associated with firefighting. In addition, death certificates lack information on duration or other exposure-related information, which limits the ability to draw conclusions regarding causality. These studies also had no information on potential confounding factors, other than sex and race.]

2.7 Case reports

Twelve case reports or series describing the occurrence of cancers of any site in individuals occupationally exposed as a firefighter were reviewed (Bates & Lane, 1995; Cucchi, 2003; Bianchi et al., 2007; Wolfe et al., 2012; Cormack, 2013; Schrey et al., 2013; Sugi et al., 2013; Antoniv et al., 2017; Landgren et al., 2018; Geiger et al., 2020; Brinchmann et al., 2022; Park et al., 2022). The Working Group determined that seven of these reports were not informative to this review as they did not provide information on occupational exposures other than the patient's occupation as a firefighter. These publications included four reports that each presented a brief clinical description of a rare tumour in a firefighter: a benign clavicular neoplasm (Sugi et al., 2013); a diffuse mesothelioma of the pericardium (Cucchi, 2003); a peritoneal mesothelioma (Cormack, 2013); and an extramedullary head and neck tumour (Schrey et al., 2013). Also included in this group of publications was a report describing 99 cases of pleural mesothelioma diagnosed in residents of Trieste province, Italy, one of whom was a firefighter (Bianchi et al., 2007); a description of the clinical course of Chernobyl-exposed patients with laryngeal cancer (Antoniv et al., 2017); and a clinical description of mycosis fungoides among eight people exposed to flame-retardant clothing (with no description of the patient's occupation) (Park et al., 2022). The five case reports and case series reviewed provided detailed descriptions of risk factor information relevant to the

occurrence of cancer at sites reported in epidemiological studies reviewed in the present monograph: metastatic melanoma (Brinchmann et al., 2022); renal cell carcinoma (Geiger et al., 2020); multiple myeloma (Landgren et al., 2018); testicular cancer (Bates & Lane, 1995); and SCC of the skin (Wolfe et al., 2012). One of these case reports further provided support for non-burning heat exposure as a mechanism for SCC in wildland firefighters (Wolfe et al., 2012).

Brinchmann et al. (2022) described a case of metastatic melanoma (primary site unknown) in a male firefighter with 33 years (1973–2006) of occupational exposure as a firefighter. The patient had worked as a structural [municipal] firefighter in an industrial urban environment and had responded to diverse types of fires, including industrial, residential, vehicular, and brush. He also oversaw departmental trainings. The discussion noted probable occupational exposure to solar radiation and polychlorinated biphenyls (PCBs), both of which are considered by IARC to be carcinogenic agents with *sufficient* evidence in humans for melanoma (Lauby-Secretan et al., 2013). [The Working Group did not find the report informative for the review because no exposures unique to firefighting were discussed and no direct evidence of exposure to PCBs or solar radiation was provided.]

Geiger et al. (2020) reported on a case series of four firefighters in Washington state, USA, who were diagnosed with kidney cancer found incidentally on imaging. Cases were identified by a retrospective review of electronic healthcare records from a single clinic in a search for patients with a history of a firefighting career who had been diagnosed with renal cell carcinoma between 2014 and 2019. Abstracted information included duration of firefighting employment, as well as known risk factors for renal cancer, including age and BMI at diagnosis, smoking history, and family history of renal cancer. Career firefighting tenure among cases ranged from 8 to 40 years. Among the firefighters, age at diagnosis ranged from 31 to 59 years and three patients were aged < 40 years, whereas the authors noted that in the general population less than 5% of renal cancers are diagnosed in patients aged 20–40 years. None of the cases had a reported history of smoking [causally associated with renal cancer] and BMI ranged from 28 to 31 kg/m^2. [The Working Group noted that few agents associated with occupational exposure have been identified by the *IARC Monographs* programme with *sufficient* evidence of carcinogenicity for renal cancer: these include trichloroethylene and X- and gamma-radiation. The strengths of this case series included information on duration of career firefighting experience and a set of behavioural and medical risk factors. The limitations included that smoking history and lifetime occupation may be underreported or misclassified in medical records. Interpretation was clouded by the lack of description of the clinic source population. The reporting of BMI at the time of diagnosis (as opposed to a considerable time before diagnosis) was also a limitation since body-weight loss may result from renal cancer.]

Landgren et al. (2018) described the clinical characteristics of 16 patients with multiple myeloma among FDNY WTC-exposed firefighters. The cases were diagnosed between 11 September 2001 and 1 July 2017 and identified from the 11 959 non-Hispanic White male firefighters in the FDNY cohort who consented to participate in the research. The diagnosis of multiple myeloma was confirmed by linkage with population-based cancer registries and a review of FDNY WTC Health Program records. Cohort members of ethnicity other than non-Hispanic White (n = 959) were not included in this case series. The median age at diagnosis was 57 years (range, 38–76 years), and the median time between 11 September 2001 and diagnosis was 12 years (range, 1–16 years). Of the cases of multiple myeloma, fourteen had peripheral blood samples evaluated and light-chain proteins were detected in seven (50%; 95%

CI, 27–73%). [The Working Group noted that a strength of this case series was its robust case-finding approach. Limitations included that WTC disaster exposure was not described for the cases, and no additional information was given on other firefighting or occupational exposures. The authors also conducted serological screening for monoclonal gammopathy of undetermined significance (MGUS, the precursor state for most multiple myeloma diagnoses) and light-chain MGUS (LC-MGUS) among 781 FDNY firefighters. However, this serological analysis was not reviewed in the present section as it was beyond the scope of a case series. The Working Group noted that investigation of MGUS and LC-MGUS, as precursors of multiple myeloma, may reveal common causal pathways; however, this cross-sectional survey was not reviewed elsewhere in the present monograph because of the descriptive nature of the analysis.]

In a case report, Wolfe et al. (2012) described SCCs of the skin on the lower extremities diagnosed in 2005 in a 65-year-old Caucasian [White] man with 28 years occupational experience as a wildland firefighter in Florida, USA. The patient had incurred chronic heat exposure to the lower extremities and reported 15-hour workdays with daily exposure of an hour (4 feet [1.2 m] or less from the fire line). PPE included wildfire protective trousers and boots. The patient had a history of 13 SCCs below the knee in the 4 years preceding the current diagnosis; in the next 3 years he developed 28 SCCs between the ankle and midthigh. All SCCs developed on the heat-exposed front and side of the legs and none on the back of the legs. The authors noted that in the 1970s wildland firefighting teams began prioritizing controlled burns, which can result in longer and more proximate heat exposure than the previously prioritized wildfire suppression activities. They hypothesized that changes in the epithelium attributable to lifetime chronic non-burning heat exposure, as well as to solar radiation, may have predisposed this wildland firefighter to SCC formation. [The Working Group noted that this single case report was of interest since it points to chronic non-burning heat exposure as a potential mechanism for SCC of the skin among wildland firefighters. Limitations included that, although cumulative heat exposure to the lower extremities was quantified, the methods used to do so were not described. Similarly, although type of PPE used was described, frequency of use was not.]

Bates & Lane (1995) reported on an investigation of four cases of testicular cancer diagnosed among firefighters employed in Wellington, New Zealand. The cases were found incidentally when the Wellington fire department was used as a comparison group for another study of occupational exposure in firefighters after an industrial fire in December 1984. Three cases of testicular cancer were identified among Wellington firefighters during that study period, December 1984 to December 1988. The fourth case was diagnosed in January 1989. Information about the cancer diagnosis (e.g. date, laterality) and risk factors for testicular cancer (e.g. age, ancestry, family history of cancer, occupational history, injuries, and cryptorchidism) was gathered by medical record review and through interviews with the patients. All cases were histologically confirmed as germ cell testicular cancer. Age of diagnosis ranged from 24 to 59 years. The cases were full-time firefighters employed for 6–19 years (mean, 13 years) and all had been exposed to smoke. No common risk factors for testicular cancer were reported. [The Working Group concluded that this systematically conducted case investigation was minimally informative for the present monograph since it lacked details of firefighting exposures. However, a retrospective cohort study that compared testicular cancer incidence and mortality among all paid [career] firefighters in New Zealand in 1977–1996 with that in the general population is reviewed in Section 2.2.2 (Bates et al., 2001).]

2.8 Meta-analyses

2.8.1 Meta-analyses of cancer risk among firefighters

Seven meta-analyses investigating the association between occupational exposure as a firefighter and risk of cancer were available to the Working Group (Howe & Burch, 1990; LeMasters et al., 2006; Youakim, 2006; Sritharan et al., 2017; Jalilian et al., 2019; Soteriades et al., 2019; Casjens et al., 2020). Three of the available meta-analyses were published before the previous evaluation of firefighting by the *IARC Monographs* programme (Volume 98) in October 2007 (IARC, 2010). The Working Group for Volume 98 conducted a separate meta-analysis that showed increased meta-relative risks for cancer of the testis (1.47; 95% CI, 1.20–1.80; fixed effects, 6 studies), prostate (1.30; 95% CI, 1.12–1.51; random effects, 16 studies), and NHL (1.21; 95% CI, 1.08–1.36; fixed effects, 7 studies). One of the more recent meta-analyses focused on only prostate cancer (Sritharan et al., 2017). Further, an overview of systematic reviews of cancer incidence and mortality was available; this overview included 104 original studies, of which some overlapped, that were published between 1959 and 2018 (Laroche & L'Espérance, 2021). All meta-analyses overlapped concerning included studies, outcome (incidence and mortality), and the cancer sites evaluated. For the present review, the Working Group considered in detail two meta-analyses (Jalilian et al., 2019; Casjens et al., 2020) that included as many of the most relevant and recent studies as possible, in addition to the meta-analysis of only prostate cancer (Sritharan et al., 2017). A fourth recently published meta-analysis was considered less informative because it only included studies published until 2007 (Soteriades et al., 2019).

The meta-analysis of only prostate cancer incidence and mortality included 26 studies of firefighters published from 1980 to 2017 (Sritharan et al., 2017). Meta-risk estimates were calculated based on random effects models and were similar for incidence (1.17; 95% CI, 1.08–1.28, I^2 = 72%) and mortality (1.12; 95% CI, 0.92–1.36, I^2 = 50%). [The Working Group noted that the similarity between incidence and mortality estimates provided evidence against a strong medical surveillance bias. The heterogeneity variance estimator was not reported.]

A meta-analysis of cancer incidence and mortality studies published before 1 January 2018 combined information from 48 case–control and cohort studies using random effects meta-analysis models (Jalilian et al., 2019). Only results for male firefighters or male and female firefighters combined were included. Studies were largely conducted in the USA (41% of incidence studies and 54% of mortality studies). Case ascertainment periods were from 1950 to 2014 for incidence studies and from 1921 to 2011 for mortality studies. Studies of volunteer and trainee firefighters were excluded. Included studies used predominantly national, regional, or local external comparison populations. [Studies from the Nordic countries may have had overlapping study populations with cases included more than once in meta-estimates.] For all cancers combined, both the overall summary of incidence risk estimate (SIRE) (12 studies) and summary of mortality risk estimate (SMRE) (22 studies) among firefighters were at unity: 0.99 (95% CI, 0.93–1.05) and 0.99 (95% CI, 0.92–1.06), respectively. Small increased risks were seen for incidence of cancer of the colon (SIRE, 1.14; 95% CI, 1.06–1.23; 10 studies), rectum (SIRE, 1.09; 95% CI, 1.00–1.20; 10 studies), prostate (SIRE, 1.15; 1.05–1.27; 17 studies), bladder (SIRE, 1.12; 95% CI, 1.04–1.21; 14 studies), and thyroid (SIRE, 1.22; 95% CI, 1.01–1.48; 10 studies), and for melanoma (SIRE, 1.21; 95% CI, 1.02–1.45; 11 studies). The SIREs were over 1.3 for only two cancer sites: cancer of the testis (SIRE, 1.34; 95% CI, 1.08–1.68; 9 studies) and cancer of the pleura (mesothelioma) (SIRE, 1.60; 95% CI, 1.09–2.34;

5 studies). For cancer mortality, only the estimates for rectal cancer (SMRE, 1.36; 95% CI, 1.18–1.57; 12 studies) and NHL (SMRE, 1.42; 95% CI, 1.05–1.90; 8 studies) were elevated. [The Working Group noted that results from cohort and case–control studies were pooled into one meta-effect estimate, which may have biased results. The heterogeneity variance estimator was not reported.]

The most recent meta-analysis included 25 cohort studies of both incidence and mortality outcomes (Casjens et al., 2020) published during 1959–2018. Only cohort studies of cancer in male career full-time firefighters that included the general population as the referent in external comparisons were included. Studies of exposure to catastrophic events (e.g. the WTC responders) were excluded. Meta-risk estimates for incidence and mortality outcomes were calculated separately and based on inverse-variance random effect models. Models were fitted using the Paule–Mandel heterogeneity variance estimator. [Some of the studies in the Nordic countries may have had overlapping study populations with cases included more than once in meta-estimates.] The meta-estimates for the incidence (meta-standardized incidence ratio, meta-SIR, 1.00; 95% CI, 0.93–1.07; 9 studies) and mortality (meta-standardized mortality ratio, meta-SMR, 0.97; 95% CI, 0.89–1.05; 17 studies) of all cancers combined were similar to the general population. [The Working Group noted that a high proportion of the estimates for specific cancers, 18 of 37 cancer sites for incidence and 13 of 30 mortality sites, were based on a small number of studies and estimates were statistically imprecise.] Elevated risks were found for incidence of colon cancer (meta-SIR, 1.11; 95% CI, 1.00–1.21; 6 studies), bladder cancer (meta-SIR, 1.18; 95% CI, 1.01–1.34; 6 studies), and mesothelioma (meta-SIR, 1.46; 95% CI, 1.01–1.90; 2 studies). For mortality, increases were seen for cancers of the rectum (meta-SMR, 1.35; 95% CI, 1.12–1.59; 9 studies) and bladder (1.72; 95% CI, 1.05–2.38; 7 studies). Finally, stratification of risks by three calendar periods (related to potential differences in exposure and the use of personal protective equipment) and three geographical regions was provided. [The Working Group noted that information on the proportion of full-time career firefighters within the included cohorts was not available for all studies. This meta-analysis only included results using a general population referent, which were more prone to bias because of the healthy-worker hire effect and surveillance bias than were results using other uniformed service workers as the referent. Stratified estimates were based on small numbers of studies.]

2.8.2 Working Group meta-analysis

The Working Group conducted a meta-analysis of the most recently available epidemiological studies on the association between occupational exposure as a firefighter and cancer. The methods, analysis, and results of this work are described in detail in a stand-alone publication (DeBono et al., 2023). Briefly, the objective was to conduct a meta-analysis of the association between ever-employment and duration of employment as a firefighter and cancer incidence and mortality. Information was abstracted from studies published until 13 June 2022. Studies were evaluated for the influence of key biases on results. Random-effects meta-analysis models were used to estimate associations with 12 selected cancer sites. The impact of bias was explored in sensitivity analyses.

The overall results are presented in Table 2.13, and results for selected cancer sites are also illustrated using forest plots in Fig. 2.1, Fig. 2.2, Fig. 2.3, Fig. 2.4, Fig. 2.5, Fig. 2.6, Fig. 2.7, Fig. 2.8, and Fig. 2.9. There was evidence of positive associations between occupational exposure as a firefighter and cancer incidence for several cancer types, including cancers of the urinary bladder, testis, prostate, thyroid, and colon, and mesothelioma, NHL, and melanoma. Associations for

Table 2.13 Meta-rate ratios for selected cancers in male career firefighters compared with a general, uniformed service, or working population referent

Outcome	No. of studies[a]	Meta-rate ratio[b] (95% CI)	I^2 [c] (%)	Q *P* value	τ^2
Incidence (SIR, RR, HR)					
All cancers (C00–C95)	14	1.05 (0.99–1.11)	87	< 0.01	0.008
Stomach (C16)	12	1.00 (0.87–1.15)	33	0.12	0.002
Colon (C18)	10	1.19 (1.07–1.32)	37	0.11	0.007
Lung (C33–C34)	14	0.85 (0.75–0.96)	78	< 0.01	0.032
Melanoma (C43)	12	1.36 (1.15–1.62)	83	< 0.01	0.062
Mesothelioma (C45)	7	1.58 (1.14–2.20)	8	0.36	0.009
Prostate (C61)	14	1.21 (1.12–1.32)	81	< 0.01	0.015
Testis (C62)	11	1.37 (1.03–1.82)	56	0.01	0.084
Kidney (C64–C66)	12	1.09 (0.92–1.29)	55	0.01	0.035
Bladder (C67–C68)	10	1.16 (1.08–1.26)	0	0.71	0
Brain and nervous (C47, C70–C72)	11	1.01 (0.86–1.18)	5	0.40	0.003
Thyroid (C73)	10	1.28 (1.02–1.61)	40	0.09	0.055
Non-Hodgkin lymphoma (C82–C85)	13	1.12 (1.01–1.25)	0	0.51	0.007
Mortality (SMR, RR)[d]					
All cancers (C00–C95)	18	0.96 (0.88–1.06)	87	< 0.01	0.026
Stomach (C16)	13	1.05 (0.87–1.28)	41	0.06	0.045
Colon (C18)	9	1.03 (0.78–1.37)	63	< 0.01	0.079
Lung (C33–C34)	12	0.96 (0.86–1.06)	55	0.01	0.008
Melanoma (C43)	4	1.05 (0.48–2.30)	0	0.43	0.093
Mesothelioma (C45)	3	1.75 (0.83–3.69)	0	0.56	0
Prostate (C61)	11	1.07 (0.95–1.20)	30	0.16	0
Kidney (C64–C66)	9	1.10 (0.66–1.83)	53	0.03	0.199
Bladder (C67–C68)	9	1.22 (0.70–2.11)	67	< 0.01	0.267
Brain and nervous (C47, C70–C72)	11	1.33 (0.98–1.79)	53	0.02	0.098
Thyroid (C73)	4	1.90 (0.36–10.00)	58	0.07	0.671
Non-Hodgkin lymphoma (C82–C85)	5	1.20 (1.03–1.40)	0	0.74	0

CI, confidence interval; HR, hazard ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

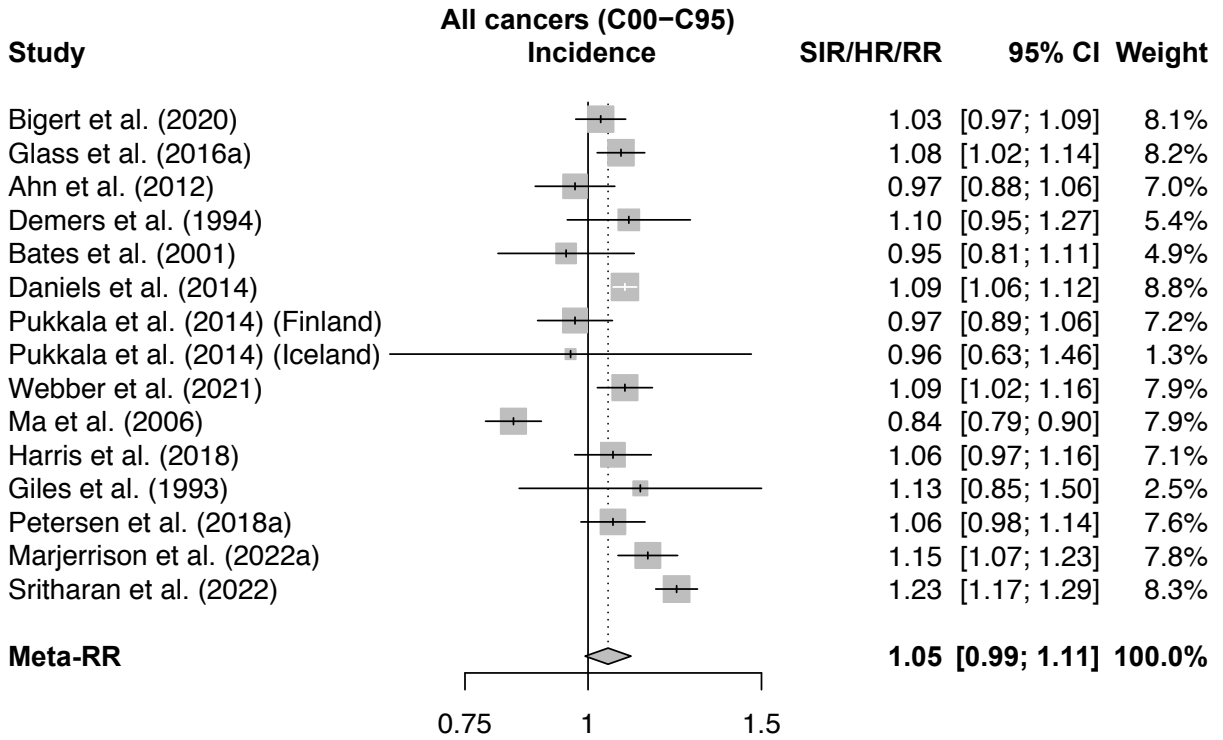
[a] Results from the studies by Daniels et al. (2014) and Pinkerton et al. (2020) included a small number of women. Petersen et al. (2018a) included part-time/volunteer firefighters for cancers of the kidney, stomach, thyroid, and brain, and for mesothelioma. Some results from overlapping study populations were excluded.

[b] Random-effects models were used with between-study variance estimated using the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction (using wider confidence intervals) were used to calculate confidence intervals.

[c] See Figure 1 in DeBono et al. (2023) for individual study results and generic inverse-variance meta-analysis statistics. The variance of individual study estimates was based on the reported confidence interval bounds and may differ from estimates obtained using exact methods when there are few cases.

[d] Outcomes with fewer than three available studies were not meta-analysed.

Fig. 2.1 Forest plot of individual study results and meta-rate ratios for incidence of all cancers in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.0079$, $P < 0.01$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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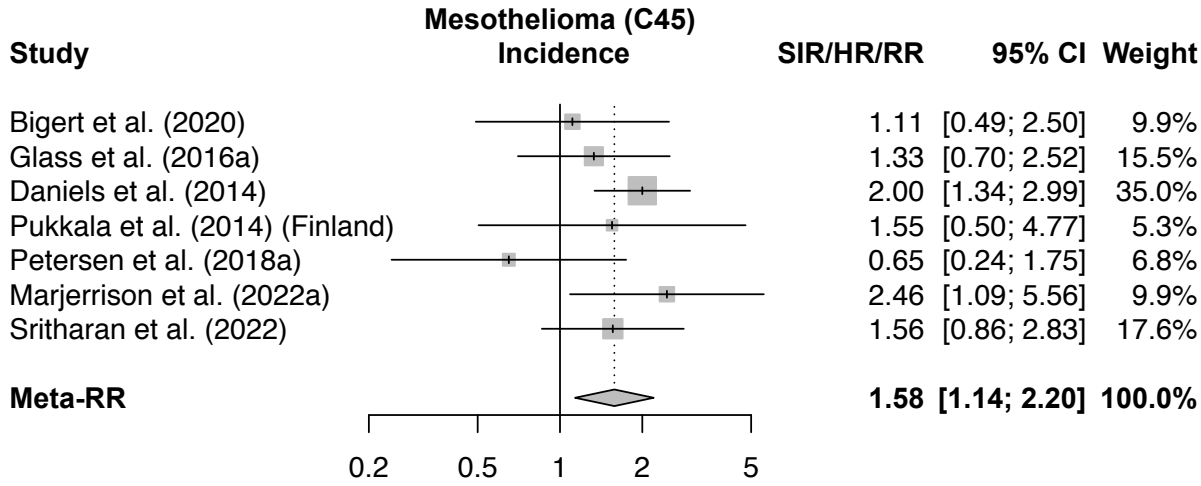
bladder cancer and NHL were modest in magnitude. For mortality outcomes, associations were attenuated compared with incidence outcomes for cancers of the prostate and colon and melanoma, whereas they were similar or greater in magnitude for cancers of the bladder and lung, NHL, and mesothelioma. Since the most recent meta-analysis on cancer in firefighters (Casjens et al., 2020), three new cohort studies (Marjerrison et al., 2022a, b; Sritharan et al., 2022; Zhao et al., 2020) and two cohorts with extended follow-up (Bigert et al., 2020; Pinkerton et al., 2020) have been published that were included in the Working Group's meta-analysis. Our results from comparable analyses were consistent with those previously reported and suggested more strongly positive associations for the incidence of testicular, colon, and prostate cancer, and for mesothelioma and melanoma. Applying a causal interpretation to our findings requires additional considerations regarding the influence of bias and the plausibility of exposures in the occupation to cause specific cancer types over time. Results of the meta-analysis are described in detail in the evidence synthesis (Section 2.9) within the context of causal inference for cancer hazard identification in humans.

Fig. 2.2 Forest plot of individual study results and meta-rate ratios for incidence of mesothelioma in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.0093$, $P = 0.36$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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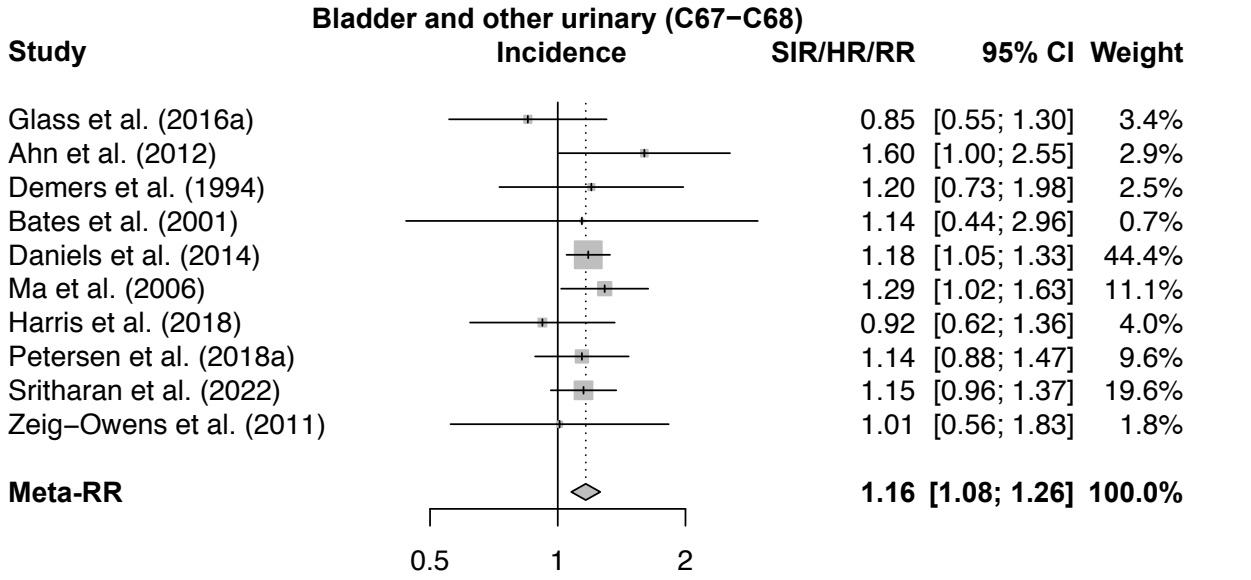
2.9 Evidence synthesis for cancer in humans

In total, 52 cohort and case–control studies (including PMR and other "event-only" studies), 12 case reports, and 7 meta-analyses were available for the evaluation of the association between occupational exposure as a firefighter and cancer incidence or mortality. Many of these studies were published since the first evaluation of firefighting by the *IARC Monographs* programme in 2007 (IARC, 2010), which included 42 studies.

2.9.1 Original studies evaluated

Many of the available studies were in occupational cohorts, which typically reported results for several different cancer types and for all cancers combined. Some of these studies provided results on cancer incidence, some on cancer mortality, and a few on both. In assessing the carcinogenicity of occupational exposure as a firefighter, the greatest weight was accorded to findings from cohort studies because of their lower potential for bias compared with other designs. In general, the cohort studies of incidence were given higher weight than studies of mortality because of the relatively poorer quality of cancer information obtained from death certificates, and lower sensitivity for identifying cases of certain cancer types with higher survivability, e.g. testicular cancer. However, the Working Group considered that mortality results may occasionally complement and inform the interpretation of incidence results for certain cancer types that may be prone to surveillance bias, such as cancers of the prostate, colon, and thyroid. The cohort studies all had retrospective designs and typically lacked information on important potential confounders apart from age, sex, and calendar period, such as tobacco smoking, alcohol drinking, sun exposure habits, and leisure time physical activity.

Fig. 2.3 Forest plot of individual study results and meta-rate ratios for incidence of cancers of the urinary bladder and other and unspecified urinary organs excluding kidney, renal pelvis, and ureter in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 0.71$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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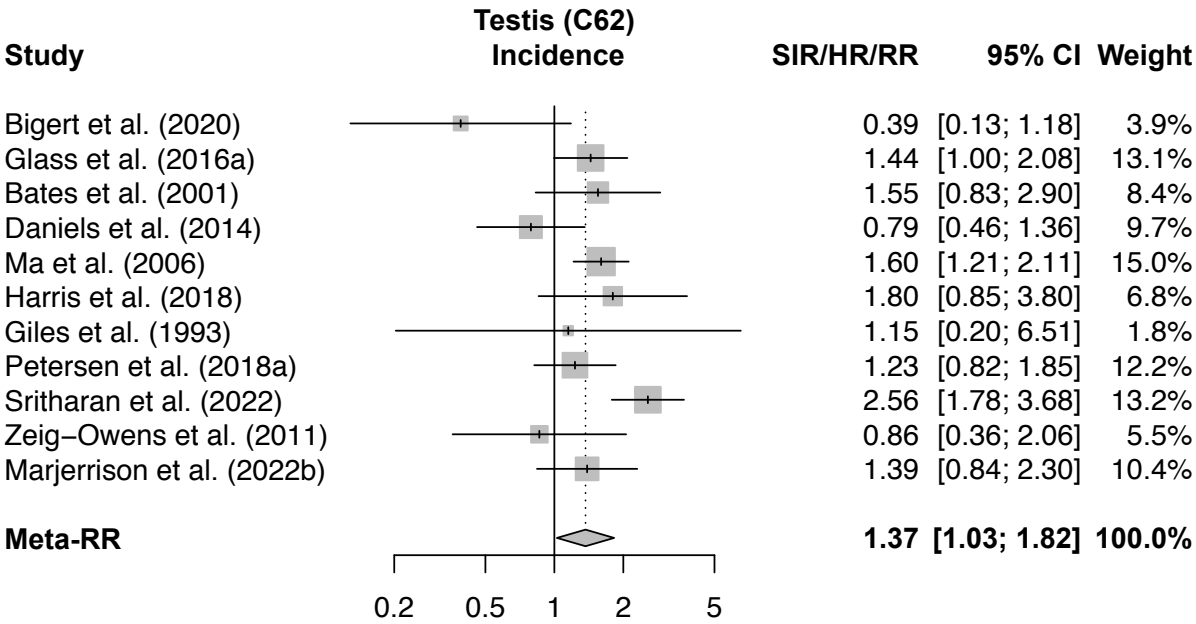
Very few case–control or "event-only" studies provided such information.

Studies based only on information from either mortality or cancer registries (e.g. proportionate mortality or other "event-only" studies) were reviewed but given little weight because of the high potential for exposure misclassification and/or selection bias. Occupational surveillance studies ($n = 36$) that did not investigate cancer in firefighters a priori were excluded from further consideration because of the potential for publication bias (e.g. selective reporting of only positive findings in the searchable abstract). [Some of these studies were included in the previous monograph on occupational exposure as a firefighter (IARC, 2010), reducing the overlap in studies evaluated in the two monographs.]

Finally, 12 case-report or case-series studies describing the occurrence of cancers of any site in individuals occupationally exposed as a firefighter were available to the Working Group. Seven were considered uninformative and were not reviewed further because they lacked information on occupational exposures outside the patient's occupation as a firefighter, and five of those reviewed by the Working Group were not considered further because they lacked details about firefighting exposures.

Some of the studies reviewed by the Working Group provided details about aspects of exposure, such as duration of work as a firefighter, full-time or part-time employment status, volunteer versus career work status, number of fire responses, and types of fires attended (e.g. structure, wildland), whereas others included only

Fig. 2.4 Forest plot of individual study results and meta-rate ratios for incidence of cancer of the testis in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 56\%$, $\tau^2 = 0.0843$, $P = 0.01$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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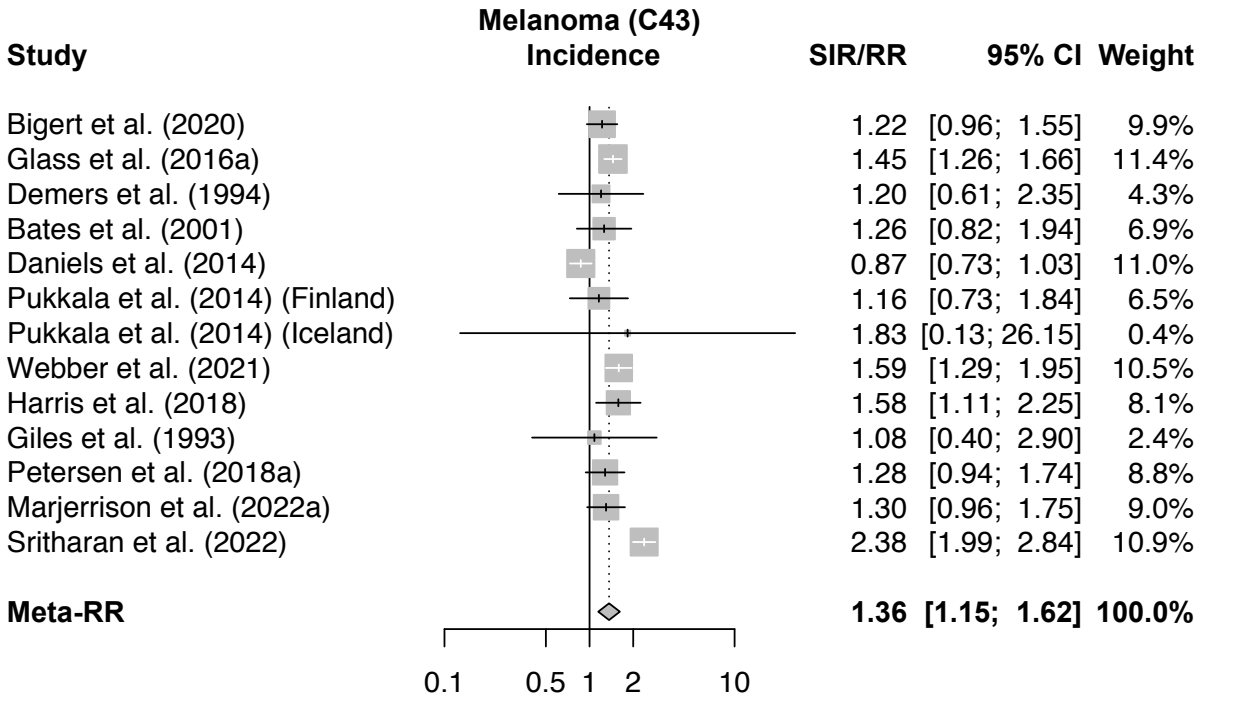
information on ever versus never having worked as a firefighter. The Working Group's critique of the quality of exposure assessment in the reviewed studies is summarized in Section 1.8.1.

A detailed definition of the agent, including various types of firefighter (e.g. career, volunteer, structure, wildland) has been described in Section 1.2. Although the work of these groups of firefighters may entail different underlying exposures, the available epidemiological data did not in general allow for making inferences by type of firefighting. Studies of firefighters included in the FDNY WTC-disaster responders cohort (Zeig-Owens et al., 2011; Webber et al., 2021) were included in the evaluation but were considered somewhat less informative, given the probable increased cancer surveillance in these firefighters compared with the reference populations used. Although some information was available on volunteer firefighters in a few studies, participants in most studies were (or were presumed to be) career firefighters. The Working Group was unable to make separate conclusions about whether the association between occupational exposure as a firefighter and cancer differed between female and male firefighters, given the paucity of data for women. Therefore, although the evaluation of the Working Group was primarily based on evidence derived from male municipal career firefighters, there was no evidence to suggest that results would not also apply to women or to other types of firefighter.

Fig. 2.5 Forest plot of individual study results and meta-rate ratios for incidence of melanoma in firefighters compared with a general, uniformed service, or working population referent

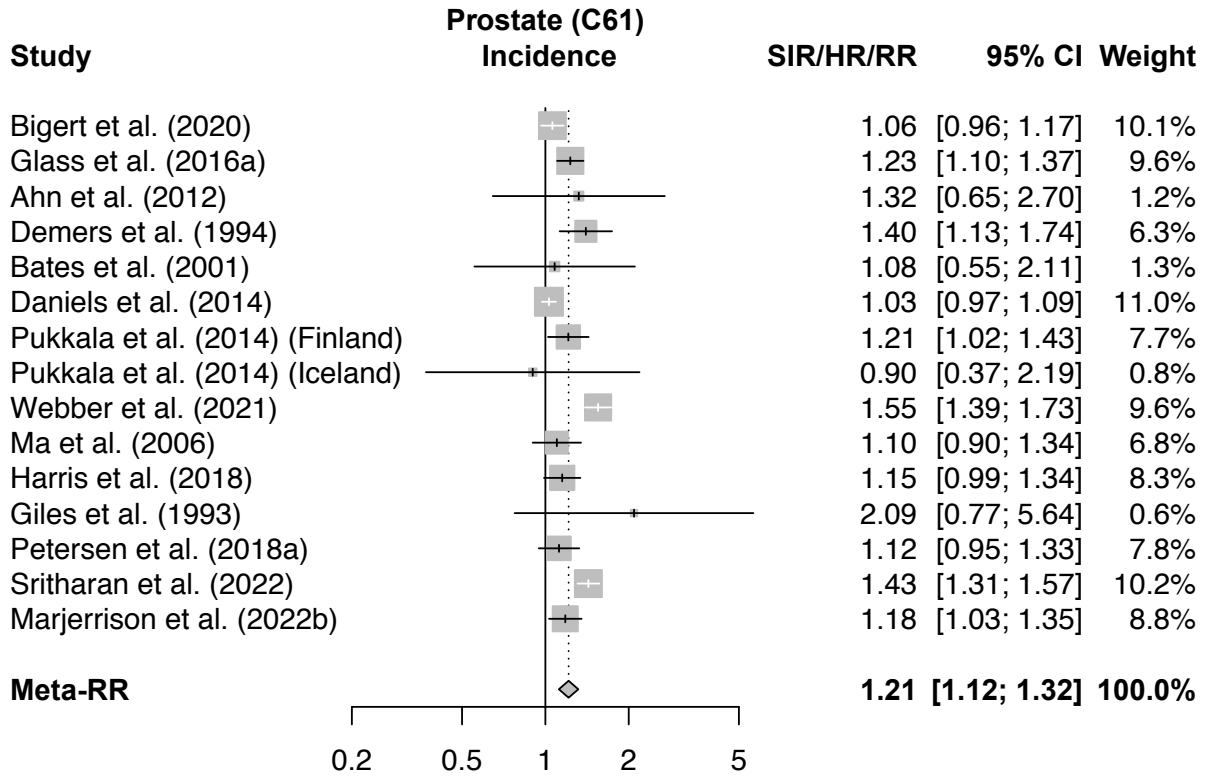


CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0619$, $P < 0.01$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
From DeBono et al. (2023), CC-BY-3.0.

2.9.2 Meta-analysis

Eight meta-analyses were available, including one performed by the Working Group in 2007 (IARC, 2010). Two were published relatively recently and captured selected studies published until 2018 (see Section 2.8.1). To improve upon some methodological approaches in these analyses, and to include the most recent studies, the Working Group performed an updated meta-analysis of studies of incidence and mortality, including cohort studies published until 13 June 2022 (DeBono et al., 2023; see Section 2.8.2). Estimates of meta-rate ratios (meta-RR) were computed for each cancer site, including I^2 and P values as estimates of residual between-study variance (heterogeneity). The following cancer types were examined: mesothelioma, urinary bladder, testis, NHL, prostate, melanoma, colon, brain, thyroid, lung, stomach, kidney, and all cancers combined. These were chosen on the basis of suggested positive findings in previous meta-analyses, findings from studies in the literature review, and the conclusions of the previous evaluation by the *IARC Monographs* programme. Other cancer sites were not considered further in the meta-analysis.

Fig. 2.6 Forest plot of individual study results and meta-rate ratios for incidence of cancer of the prostate in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.0146$, $P < 0.01$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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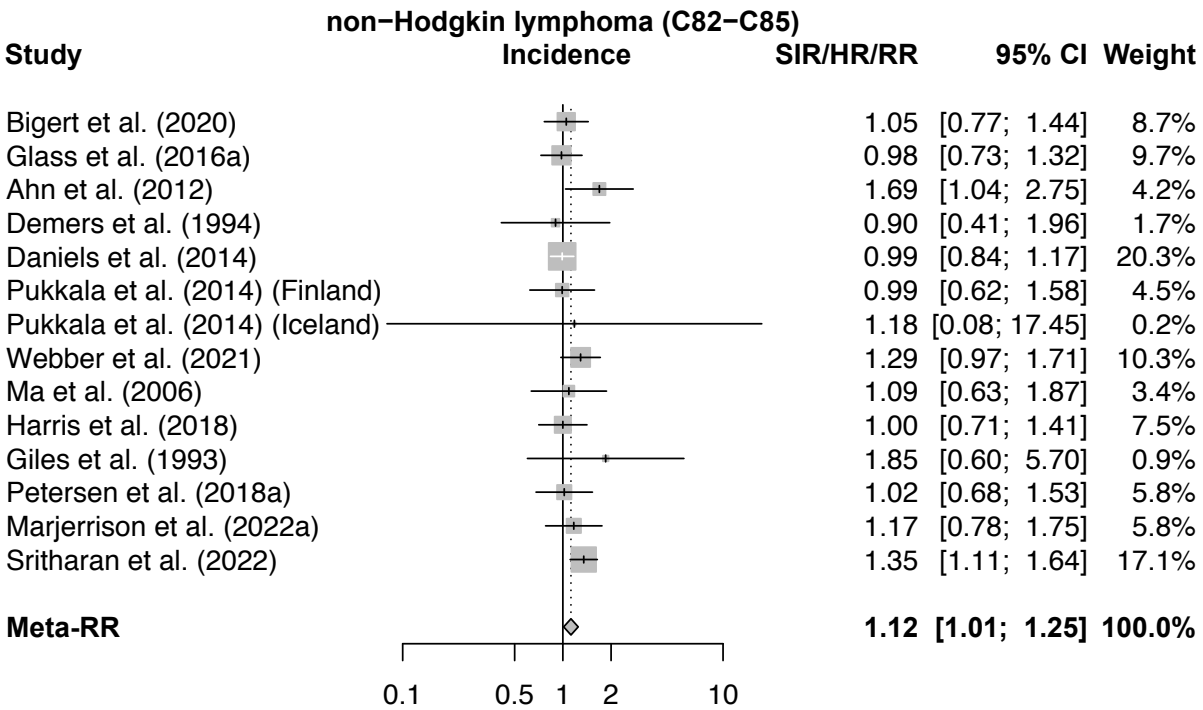
2.9.3 Exposure assessment and misclassification of exposure

As described in Section 1.8.1, many studies considered by the Working Group classified exposure on the basis of ever having worked as a firefighter, without further information on specific firefighting activities. A minority of studies captured specific job duties within fire departments, such as fire combat, fire inspection, training, or administrative positions. The number of fires and types, such as structure versus wildland, were documented only in a small number of studies. Duration of employment was the surrogate used most often for level of exposure, although a few studies used more sophisticated measures of exposure, such as number and/or types of fire responses, or duration of employment in active firefighting roles.

A challenge to assessing cancer risk among firefighters is potential exposure to a wide range of established and suspected human carcinogens

Fig. 2.7 Forest plot of individual study results and meta-rate ratios for incidence of non-Hodgkin lymphoma in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.068$, $P = 0.51$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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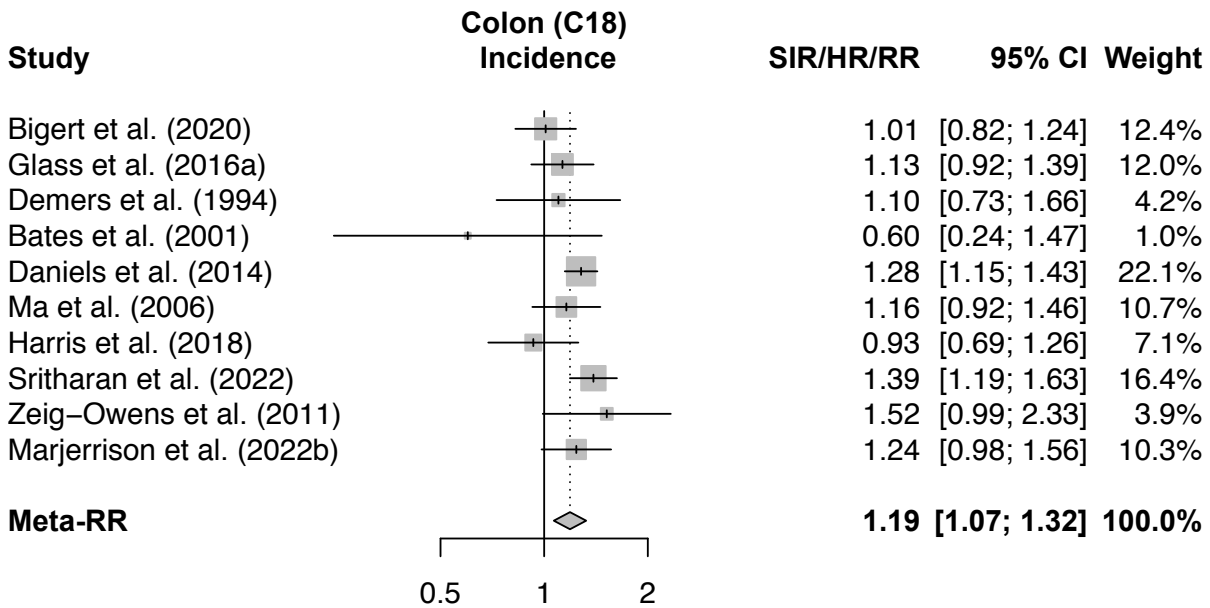
(see Section 1, Table 1.1), which may vary based on duties, types of fire being fought, calendar era, or the individual characteristics of a particular fire. Although duration of employment may be positively correlated with some firefighting exposures, it may not be closely correlated with an exposure such as fire smoke, which can vary greatly even within departments and can decline with longer employment because of diminishing front-line fire combat duties as seniority accrues. In addition, associations between cancer and duration of employment can be affected by the healthy-worker survivor bias. Information on the number and/or types of fires represents a further improvement, which may provide better surrogates of exposure to fire smoke but will still not capture specific exposures that vary by individual fire events.

In the present evaluation, the Working Group attempted to classify studies on the basis of the quality of their exposure assessment. However, there was a wide range of potential exposures to consider, and very few were well captured, even by the best surrogates. Misclassification of exposure to specific hazards was considered common in studies assessing only employment

Fig. 2.8 Forest plot of individual study results and meta-rate ratios for incidence of cancer of the colon in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 37\%$, $\tau^2 = 0.0066$, $P = 0.11$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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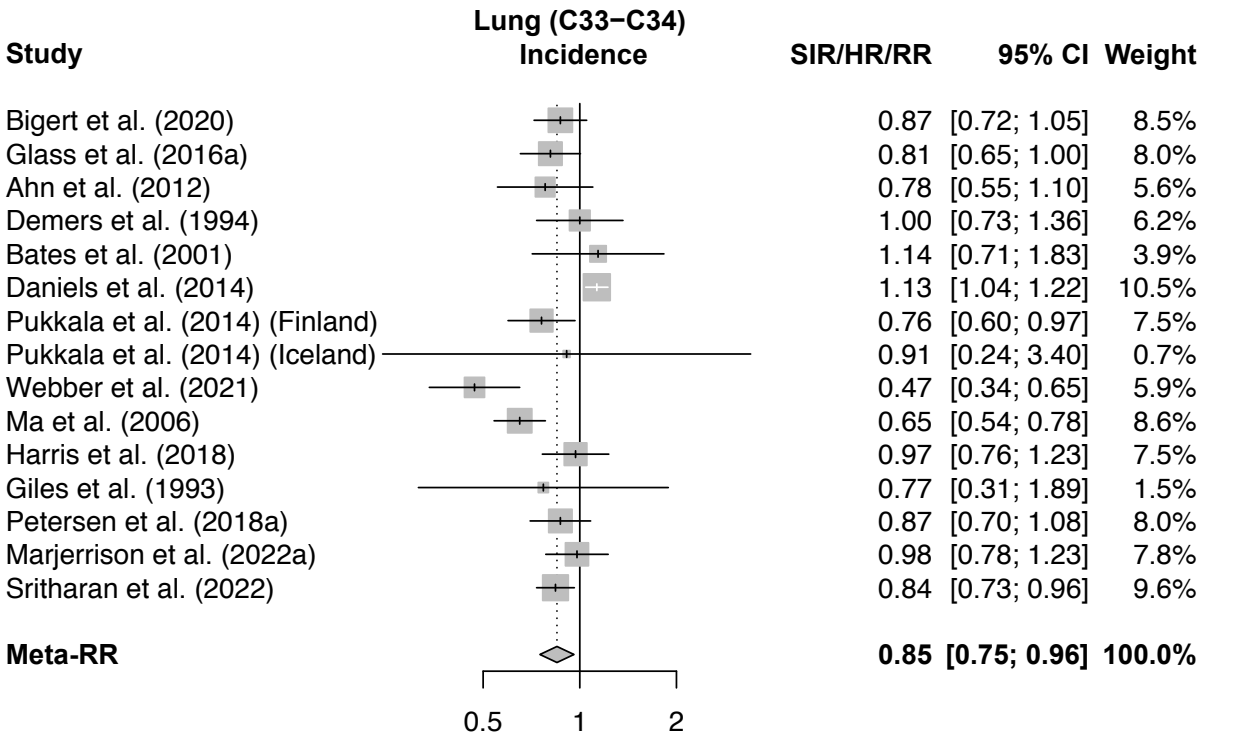
in the occupation. Assessment of exposure in almost all cohort studies would have been done independently of the eventual diagnosis of disease and should therefore be non-differential in nature, and as such may be expected to bias associations towards the null.

2.9.4 Confounding, surveillance bias, and selection bias

As "occupational exposure as a firefighter" reflects a range of different potentially carcinogenic exposures (as noted in Section 1), the Working Group defined confounders for this agent as carcinogenic exposures that occur outside of the firefighting occupation, such as chemical or other exposures from previous or concurrent occupations (e.g. asbestos exposure from construction work not related to the firefighter job). The role of confounding from such exposures is difficult to ascertain because of the potential contribution of the same exposures (e.g. physical activity, UV radiation, and asbestos) both within and outside of firefighter occupational activities.

The impact of confounding on the observed associations was somewhat unclear, since most studies did not control for confounders other than age, sex, and calendar time in analyses. The included cohort studies primarily compared cancer rates in general population groups with those among firefighters, and distributions of several potentially important risk factors may be

Fig. 2.9 Forest plot of individual study results and meta-rate ratios for incidence of cancer of the lung in firefighters compared with a general, uniformed service, or working population referent



CI, confidence interval; HR, hazard ratio; meta-RR, meta-rate ratio; RR, rate ratio; SIR, standardized incidence ratio.
Heterogeneity: $I^2 = 78\%$, $\tau^2 = 0.0319$, $P < 0.01$
Random-effects models were used with the restricted maximum-likelihood estimator. Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustments and an ad hoc variance correction were used to calculate confidence intervals for summary estimates. Calculated study intervals may differ from reported values because of differences in variance estimation methods.
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quite different in these two groups. This could be an important source of bias in some of the studies considered by the Working Group. For example, available information on smoking prevalence in firefighters compared with the general community was sparse, and was mostly for the USA, but the available published information suggested that the prevalence of smoking has been lower in firefighters than in the general population since at least the early 1990s (Haddock et al., 2011; Phan et al., 2022). This would mean that differences in smoking between firefighters and a comparison group from the general population could be a source of negative confounding for smoking-related cancers. Of note, the differences in risk factor distributions between firefighters and the comparison populations may also have changed over time, making it additionally difficult to assess the impact of this lack of information.

Notably, some confounders may be operating in opposite directions. For example, physical activity lowers the risk of several cancers, whereas chemical exposures outside of the firefighter occupation may increase risks. However, the relative importance of specific confounders

varies by cancer type. Smoking is a risk factor for many cancers, but concern about this factor as a confounder of the reported positive associations was mitigated by the observed lower risk of lung cancer among firefighters. Potential confounding from sources of chemical exposures such as benzene and diesel engine exhaust outside of the occupation as a firefighter may be most relevant for cancers such as NHL, lung, and bladder. Again, associations in opposite directions (e.g. NHL and bladder compared with lung cancer) in the same study mitigate concern about the potential impact of these confounders. Finally, as noted in Section 1.2, there was some evidence that alcohol intake is heavier in firefighters. For cancers associated with alcohol use (e.g. positively for colon cancer and inversely for NHL), alcohol use cannot be ruled out as a potential confounder (although it may create bias towards the null for NHL).

Most cohort studies relied on employment or other record linkages to enumerate their study populations. These studies are therefore less susceptible to issues related to selection into a study, and selection bias from this source should generally not be a major factor in interpretation of results from these studies.

However, other biases are of potential concern, including those related to healthy-worker biases, such as healthy-hire and healthy-worker survivor biases. Healthy-worker hire bias would tend to diminish effect estimates since at the start of employment the exposed population is generally healthier than the general population used for comparison. This might be of particular concern for occupations such as firefighting for which there are often physical requirements for employment eligibility. The majority of studies used a general population as the referent. As the healthy-worker hire bias tends to diminish with time, studies with short follow-up are most vulnerable (e.g. Giles et al., 1993; Demers et al., 1994; Bates et al., 2001; Ma et al., 2006; Ahn et al., 2012; Glass et al., 2016a; Harris et al., 2018; Webber et al., 2021). Studies that used other working populations as the referent and those that conducted internal analyses would also be less susceptible to this bias. Finally, as described in the Working Group's meta-analysis (DeBono et al., 2023), a sensitivity analysis excluding studies identified as being particularly susceptible to healthy-worker hire bias (Vena & Fiedler, 1987; Zeig-Owens et al., 2011; Ahn & Jeong, 2015; Glass et al., 2016a; Bigert et al., 2020; Webber et al., 2021) was conducted. The estimates for mesothelioma and cancers of the testis and kidney were slightly increased when these studies were excluded, suggesting that the healthy-worker hire bias may have led to underestimation of the associations for these cancers.

The healthy-worker survivor bias occurs when less-healthy workers reduce their workplace exposures through a change in employment or job tasks and would tend to diminish the magnitude of effect estimates in internal comparison analyses of cumulative exposure or employment duration (Arrighi & Hertz-Picciotto, 1994). In one mortality study that reported internal exposure–response analyses, the authors evaluated this effect by adjusting for employment duration and demonstrated some evidence of this bias for cancers of the lung and bladder, for example (Pinkerton et al., 2020).

The potential for surveillance bias in cancer incidence studies is of concern for this occupational group. Firefighters may often participate in occupational screening or cancer awareness programmes or have more access to medical care because of their employment. In this case, cancers that are detected more frequently because of heightened awareness in firefighters could lead to positive associations when compared with the general population. It is of particular concern for cancer sites at which tumours are more likely to be indolent and slow-growing (e.g. prostate, thyroid, and melanoma) and that would not be diagnosed or would be diagnosed later in the general population, in which medical

surveillance is less frequent. It is of less concern for cancer sites for which no or limited screening programmes exist, such as brain. In addition, mortality studies overall and studies on cancers with a very low rate of survival, such as lung cancer or mesothelioma, are less susceptible to this bias. In its meta-analysis (DeBono et al., 2023), the Working Group examined the potential for such bias by estimating the meta-RR for cancer sites that may be susceptible to surveillance bias and reported risk estimated using follow-up before 1990, when a strong screening bias was thought to be less influential. There was little evidence of a bias in melanoma incidence risk estimates from increasing cancer surveillance over time (see Section 2.8.2). In contrast, excess prostate cancer incidence decreased slightly after restricting follow-up to before 1990, which suggested that surveillance bias might at least partially explain the excess risk observed in the main analysis.

2.9.5 Mesothelioma

Mesothelioma is a rare cancer. It is well established that there is a dose-dependent causal association between asbestos exposure and mesothelioma, and there are positive trends in population-level risk associated with increasing exposure via asbestos production and use. The average latency period between asbestos exposure and disease occurrence is long (≥ 30 years). Other than asbestos, three agents (erionite, fluoro-edenite fibrous amphibole, and occupation as a painter) are listed by the *IARC Monographs* programme as having *sufficient* evidence for mesothelioma in humans (IARC, 2023). The examination of mesothelioma in the available occupational mortality studies of firefighters was further hampered by the lack of a cause-of-death ICD code before the late 1990s (i.e. before ICD-10).

Municipal firefighters may be exposed to asbestos during multiple activities that can disturb building materials containing asbestos, such as fire suppression, overhaul, rescue, and recovery. Exposure could also occur from resuspension of asbestos fibres from contaminated apparatus and firefighting gear (see Section 1.5.1).

There were 13 studies providing information on mesothelioma or pleural cancers among firefighters. The most informative studies were several recent (2014–2022) observational studies of municipal career firefighters compared with non-firefighter populations (Daniels et al., 2014; Pukkala et al., 2014; Glass et al., 2016a; Bigert et al., 2020; Pinkerton et al., 2020; Marjerrison et al., 2022b; Sritharan et al., 2022). Significant excess incidence of mesothelioma was observed in the meta-analysis carried out by the Working Group (meta-RR, 1.58; 95% CI, 1.14–2.20; I^2 = 8%), which combined information from seven cohort studies, including 70 mesothelioma cases from more than 1.5 million person-years of observation (DeBono et al., 2023). Among these studies, the mesothelioma SIRs ranged from 0.65 in a study of Danish firefighters (Petersen et al., 2018a) to 2.46 in a study of Norwegian firefighters (Marjerrison et al., 2022b). Only the Danish study reported less-than-expected mesothelioma risk, based on four cases. More than half of the Danish cohort comprised part-time and volunteer firefighters for whom information was not separable from that of career firefighters. Excluding that study from the meta-analysis increased the effect estimate (meta-RR, 1.70; 95% CI, 1.30–2.22) and reduced the residual heterogeneity (I^2 = 0%).

Meta-regression revealed an inverse association between mesothelioma risk and employment duration on the basis of three studies (Glass et al., 2016a; Bigert et al., 2020; Marjerrison et al., 2022a). The estimate was imprecise and strongly influenced by markedly greater risk in the lowest duration category (0–10 years). This category comprised the fewest observed cases (one to three) per study and less than one expected case each, possibly resulting in unstable estimates. Disease latency could not be addressed in

the model, although Marjerrison et al. (2022a) found that six of seven observed cases occurred 40 years after first employment (SIR, 3.47; 95% CI, 1.27–7.55).

Overall, there was consistent evidence of excess mesothelioma among municipal career firefighters compared with non-firefighter groups. The relatively new reporting of excess mesothelioma may reflect overall improvements in ascertainment, larger study sizes, longer follow-up, and increasing use of cancer registries versus death certificates. The effect size appeared strong relative to associations seen for other cancer sites. Asbestos exposure, which has been linked to municipal firefighting activities (see Section 1.1), is the primary cause of mesothelioma. Although there was an inverse association with employment duration in the meta-analysis (based on few studies), the long latent period of mesothelioma was not accounted for and may have affected regression estimates. An important limitation was the absence of information on asbestos exposures occurring outside of firefighting. For example, firefighters may have worked in previous and concurrent jobs associated with occupational asbestos exposure in the military, in construction, or elsewhere (Elbaek Pedersen et al., 2020). There were no studies available that directly examined confounding by asbestos exposures outside of firefighting. However, full occupational histories covering the period 1964–2015 were examined in the cohort of Danish firefighters, and only slightly greater prevalence of work in shipyards, construction, and as insulators was reported among part-time and volunteers than among career firefighters (Elbaek Pedersen et al., 2020). This was evidence against differential distribution of asbestos-related employment as a reasonable explanation of the risk difference observed between career fighters and part-time/volunteers or general population referents. Further, mesothelioma incidence was increased in Australian male career firefighters (Glass et al., 2016a), but not among volunteers (Glass et al., 2017), who were most likely to hold additional employment elsewhere. These findings did not support a strong bias from other sources of asbestos, but they are tempered somewhat by other potential differences, such as that volunteers may work in a predominantly rural area compared with the urban settings of most career firefighters. The Working Group concluded that there was no compelling evidence that firefighters have a greater potential for asbestos exposure outside of firefighting activities than do reference populations and concluded that, despite the lack of prior exposure information, exposures not connected to firefighting work were unlikely to fully explain the observed results. Given consistency across studies, strength of association, and an absence of other potential risk factors or sources of strong bias that could fully explain the association, chance, bias, and confounding were reasonably ruled out as explanations for the positive association seen between occupational exposure as a firefighter and mesothelioma.

2.9.6 Cancer of the urinary bladder

There were 27 studies providing information on cancers of the urinary bladder. Of these, the Working Group meta-analysis (DeBono et al., 2023) combined information from 10 good-quality (i.e. lacking potential for a strong bias) cohort studies examining cancer incidence in career firefighters (Demers et al., 1994; Bates et al., 2001; Ma et al., 2006; Zeig-Owens et al., 2011; Ahn et al., 2012; Daniels et al., 2014; Glass et al., 2016a; Harris et al., 2018; Petersen et al., 2018a; Sritharan et al., 2022). Modest but precise excess incidence of bladder cancer was observed (meta-RR, 1.16; 95% CI, 1.08–1.26), with no indication of between-study heterogeneity (I^2 = 0%; P = 0.71). Most weight (44%) was given to the large study of municipal career firefighters in the USA (SIR, 1.18; 95% CI, 1.05–1.33) (Daniels et al., 2014). The meta-analysis did not include

the cohort study of Norwegian firefighters by Marjerrison et al. (2022a) (SIR, 1.25; 95% CI, 0.97–1.25; 69 cases), which examined incidence of all cancers of the urinary tract combined (bladder, ureter, and renal pelvis) (ICD-10, C65–C68) or the cohort study of Swedish firefighters by Bigert et al. (2020) (SIR, 1.08; 95% CI, 0.89–1.31; 109 cases) using a broader case definition of ICD-10 C66–C68. Both reported similar excess risk to that reported in the meta-analysis. The meta-analysis estimate for mortality was similar in magnitude to incidence; however, the estimate was less precise because of residual between-study variance (I^2 = 67%) and fewer studies aggregated (n = 9) (Vena & Fiedler, 1987; Demers et al., 1992a; Guidotti, 1993; Aronson et al., 1994; Bates et al., 2001; Ma et al., 2005; Amadeo et al., 2015; Pinkerton et al., 2020; Zhao et al., 2020). Marjerrison et al. (2022b) reported 14% excess mortality from cancer of the urinary tract in Norwegian firefighters, based on 15 cases. Among the few studies examining cancer risk among women, excess mortality or incidence for bladder cancer was found in studies of career firefighters in the USA (Ma et al., 2006; Daniels et al., 2014). Excess incidence of urinary tract cancers was not found among Australian female volunteer firefighters (Glass et al., 2017).

Meta-regression revealed an inverse association between employment duration and bladder cancer incidence (slope = −0.017; P = 0.06), with no evidence of residual between-study variance (P = 0.75) (DeBono et al., 2023). There was no evidence of a positive exposure–response association between bladder cancer incidence and number of exposed-days, fire-runs, or fire-hours in career firefighters in the USA (Daniels et al., 2015). Similarly, there was no evidence of a positive trend in bladder cancer incidence with number or type of fire incident in internal analyses of cancer in firefighters in Australia (Glass et al., 2016a). However, Pinkerton et al. (2020) found a strong indication of confounding by employment duration in the regression model of bladder cancer and exposed-days, where the exposure–response estimate shifted from a negative to a positive association after controlling for employment duration. Thus, the Working Group concluded that time-varying confounding from a healthy-worker survivor bias may be masking a true exposure–response association.

An important consideration for bladder cancer is that firefighter exposures include both known and suspected human bladder carcinogens, e.g. PAH, soot, diesel engine exhaust (see Table 1.1 and IARC, 2023), thereby strengthening the evidence for a plausible causal association.

In summary, there was consistent evidence in good-quality longitudinal studies of a modest association between firefighter exposure and bladder cancer risk. Evidence of an exposure–response association between bladder cancer risk and exposure surrogates was lacking in most studies. However, this finding may stem from residual confounding attributable to a healthy-worker survivor bias, among other causes, therefore diminishing its weight against causality (Arrighi & Hertz-Picciotto, 1994; Stayner et al., 2003; Buckley et al., 2015). Tobacco smoking is a risk factor for bladder cancer and could therefore theoretically confound results. However, tobacco smoking is a much stronger risk factor for lung cancer than for bladder cancer, and in studies that reported on both cancer sites there was no increased risk of lung cancer, which argues against strong positive confounding, but rather suggests negative confounding attenuating the estimated bladder cancer risk. Thus, the Working Group concluded that chance, bias, and confounding could be reasonably ruled out as alternative explanations of the observed excess bladder cancer risk among firefighters.

2.9.7 Cancer of the testis

Cancer of the testis is rare, and incidence peaks at ages that are young compared with those for other cancer sites. Mortality rates have

declined sharply since the mid-1970s in high-income countries because of advancements in treatment (Purdue et al., 2005; Thun et al., 2017), which makes mortality studies less informative than incidence studies for this evaluation. Potential firefighter exposures include some compounds with *limited* evidence of human testicular carcinogenicity, e.g. perfluorooctanoic acid (PFOA) (see Table 1.1).

The evaluation included 20 studies providing information on cancer of the testis among firefighters. Of these, the most informative were 11 good- to moderate-quality cohort studies of cancer incidence published between 1993 and 2022 (Giles et al., 1993; Bates et al., 2001; Ma et al., 2006; Zeig-Owens et al., 2011; Daniels et al., 2014; Glass et al., 2016a; Harris et al., 2018; Petersen et al., 2018a; Bigert et al., 2020; Marjerrison et al., 2022b; Sritharan et al., 2022). The Working Group meta-analysis resulted in an elevated summary estimate (meta-RR, 1.37; 95% CI, 1.03–1.82) with significant heterogeneity (I^2 = 56%; P = 0.01) (DeBono et al., 2023). The model combined effect estimates ranging from 0.39 in the Swedish firefighters (Bigert et al., 2020) to 2.56 in the Canadian study of firefighters identified through workers compensation claims (Sritharan et al., 2022). All except three studies (Zeig-Owens et al., 2011; Daniels et al., 2014; Bigert et al., 2020) reported greater than expected risk. Removing the Canadian study with the highest effect estimate from the meta-analysis only slightly reduced its magnitude (meta-RR, 1.31; 95% CI, 1.04–1.64) but increased precision and reduced heterogeneity (I^2 = 26%, P = 0.20). There was no evidence of a positive association between testicular cancer incidence and employment duration (P = 0.46) from only three available studies (Bates et al., 2001; Glass et al., 2016a; Petersen et al., 2018a). There was no evidence of a positive exposure–response association between testicular cancer and any exposure proxy examined in the Australian study, although cases were few (Glass et al., 2016a). Estimates of testicular cancer incidence in studies excluded from meta-analyses, including those from exposure contrasts, were inconsistent and imprecise. Among relevant firefighting exposures, as noted above, there is *limited* evidence of an association between PFOA, which is a component in aqueous film-forming foam (AFFF) used in firefighting, and testicular cancer (IARC, 2016). However, the extent of AFFF exposure among firefighters examined in the relevant studies was unclear. Studies have examined the potential association between extreme temperature and testicular cancer; however, findings were inconsistent (McGlynn & Trabert, 2012). Standardized screening methods are not available, and most testicular cancers are found by self- or medical examination. On the basis of tumour behaviour and progression, early detection is not likely to explain the excess risk (IQWiG, 2021). Given scarce information on plausible exposures for testicular cancer, the effect size observed, heterogeneity in results among relevant studies and inconsistent findings across available exposure contrasts, chance and bias could not be reasonably ruled out as alternative explanations for the observed excess risk.

2.9.8 Melanoma

The Working Group reviewed 26 studies that reported results for incidence or mortality of cutaneous melanoma (hereafter referred to as "melanoma"). The synthesis was primarily informed by studies that were assessed as having an exposure assessment of good or satisfactory quality (see Table 1.8.1).

The Working Group's meta-analysis (DeBono et al., 2023) revealed an excess of melanoma incidence among firefighters compared with the general population (meta-RR, 1.36; 95% CI, 1.15–1.62), based on 12 studies (Giles et al., 1993; Demers et al., 1994; Bates et al., 2001; Daniels et al., 2014; Pukkala et al., 2014; Glass et al., 2016a; Harris et al., 2018; Petersen et al.,

2018a; Bigert et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a; Sritharan et al., 2022). The meta-RR was elevated similarly across categories of duration of employment as a firefighter. There was considerable heterogeneity in the meta-analysis (I^2 = 83%; P < 0.01), reducing confidence in the meta-estimate. The meta-RR for melanoma incidence was similar in a sensitivity analysis restricted to studies that were less likely to be subject to surveillance bias but was attenuated in an analysis restricted to comparisons with people in the uniformed services. Little evidence of excess melanoma mortality was seen (1.05; 95% CI, 0.48–2.30), based on four studies. This latter finding may support a role of surveillance bias, shared exposures, or non-differential misclassification by occupation.

Five cohort studies that included an exposure assessment categorized as "good" quality reported estimates for melanoma incidence. Four of these studies showed an excess risk (Glass et al., 2016a, b, 2019; Webber et al., 2021). One conducted among male volunteer firefighters in Australia (Glass et al., 2017) did not. Volunteer firefighters are more likely than career firefighters to live in rural areas and may have more sun exposure through outside jobs (e.g. farming) than people who live in cities.

Although firefighters are occupationally exposed to agents known to cause melanoma, including solar radiation (IARC, 2012) and PCBs (IARC, 2015) (see Section 1, Table 1.1), causal factors that could confound this relation were generally not controlled for in the reviewed studies, for example, early-age sunburn, non-firefighting-related sun exposure, and skin tone. For example, if the firefighter cohorts included a higher proportion of participants with light skin than did the reference population, this could be a source of positive confounding for melanoma. The race-standardized SIR from a study of municipal career firefighters in the USA showed no excess incidence of melanoma overall (Daniels et al., 2014). Further, four of the cohort studies reported incidence results for both melanoma and non-melanoma skin cancer (Kullberg et al., 2018; Petersen et al., 2018a; Bigert et al., 2020; Marjerrison et al., 2022a). Incidence at the latter site, which in contrast to melanoma has exposure to soot as an established cause, was increased in only one of the studies (Bigert et al., 2020). Given the modest effect size, the lack of information about whether exposures to some of the known causes of skin cancer (e.g. solar radiation, PCBs) were more common in firefighters than in the comparison populations hindered the interpretation of the positive findings.

Overall, the Working Group considered healthy-worker biases to be unlikely for melanoma and noted the potential for inflated risk effects because of uncontrolled confounding from UV exposure, surveillance bias, heterogeneity in results, and small numbers in some studies (resulting in unstable estimates). In summary, the Working Group concluded that, although a positive association between occupational exposure as a firefighter and incidence of melanoma is plausible, surveillance bias, confounding, and chance could not be ruled out.

2.9.9 Non-Hodgkin lymphoma

The Working Group included 26 published studies in its review of occupational exposure as a firefighter and risk of NHL. Firefighters are potentially exposed to agents that have either *sufficient* or *limited* evidence for causal associations with NHL, including exposure to PAHs in combustion products, benzene, and infections (see Section 1). The Working Group noted that the definition of NHL was not reported consistently across the studies, partly because the definition of NHL has changed over time. Therefore, the ICD codes were listed for each study to aid in interpretation. Importantly, multiple myeloma and lymphocytic leukaemia are now included in the most recent definition of NHL published by the World Health Organization (Swerdlow et al.,

2008), but none of the studies reviewed in the present monograph included multiple myeloma or lymphocytic leukaemia in their definitions of NHL. The results for multiple myeloma are described briefly below, and the results for lymphocytic leukaemia are embedded within the discussion of leukaemia as defined in previous classifications.

The cohort studies were generally considered to be the most informative, as described in Section 2.9.1. Among these, seven reported on duration of employment as a firefighter and cancer incidence. One study that was considered to have a good-quality exposure assessment (Glass et al., 2016a) reported a higher risk of NHL (ICD-10, C82–C85) with longer (10–19 years and ≥ 20 years) compared with shorter (< 10 years) duration of full-time work as a firefighter, albeit based on five cases in the reference group. Another study with an exposure assessment of satisfactory quality (Marjerrison et al., 2022a) found some evidence of a stronger SIR for NHL (ICD-10, C82–C86 and C96) with more years of employment as a firefighter, but this was not observed for the firefighters who worked the longest (≥ 30 years). The other five studies, all with exposure assessments of good or satisfactory quality, showed no evidence of duration effects: Demers et al., 1994 (ICD-9, 200–202); Ahn et al., 2012 (ICD-10, C82–C85); Glass et al., 2017 (ICD-10, C82–C85); Petersen et al., 2018a (ICD-10, C82–85 and C88.3–C88.9); and Bigert et al., 2020 (ICD-10, C83 and C85). Among studies that constructed more extensive exposure metrics (such as number of events attended, fire-hours), there was no notable evidence of exposure–response associations between proxies of firefighting exposures and NHL.

In the meta-analysis (DeBono et al., 2023), 13 cohort studies provided effect estimates for NHL incidence (Giles et al., 1993; Demers et al., 1994; Ma et al., 2006; Ahn et al., 2012; Daniels et al., 2014; Pukkala et al., 2014; Glass et al., 2016a; Harris et al., 2018; Petersen et al., 2018a; Bigert et al., 2020; Webber et al., 2021; Marjerrison et al., 2022a; Sritharan et al., 2022) and five for NHL mortality (Demers et al., 1992a; Aronson et al., 1994; Ma et al., 2005; Pinkerton et al., 2020; Marjerrison et al., 2022b). The meta-analysis showed a similar modest excess in both incidence (meta-RR, 1.12; 95% CI, 1.01–1.25), and mortality (meta-RR, 1.20; 95% CI, 1.03–1.40). The heterogeneity for both estimates was low (I^2 = 0%; P = 0.51 for incidence, and P = 0.74 for mortality). These results were also robust in analyses considering different reference groups, follow-up length, and age at follow-up, or excluding those studies with concerns about potential biases. This meta-estimate for NHL incidence was slightly weaker than, but similar to, that in the previous evaluation by the *IARC Monographs* programme in which occupation as a firefighter was reviewed (meta-RR, 1.21, 1.08–1.36; 6 studies; IARC, 2010). Notably, only three studies overlapped in the two meta-analyses because of the addition of more recent publications and the restriction to cohort studies in the current meta-analysis. Although female firefighters were largely not included in the present meta-analysis, a study of female volunteer firefighters who attended fire incidents (Glass et al., 2019) also reported a similar point estimate (SIR, 1.19; 95% CI, 0.71–1.88; 18 cases).

Although none of the studies in this review included multiple myeloma in their definition of NHL, there were 13 studies with exposure assessments of good or satisfactory quality that reported on multiple myeloma separately. Most studies reported no evidence for an association with multiple myeloma, often based on a very small number of cases (Aronson et al., 1994; Glass et al., 2016a, 2017; Petersen et al., 2018a; Marjerrison et al., 2022a). Glass et al. (2019) reported an SIR of 1.27 for all female volunteers, however, the SIR was attenuated (1.04) when restricted to volunteers who attended fire incidents, but was based on a very small number of cases. There was some evidence of an association in Bigert et al. (2020), where the overall SIR

was 1.25 and increased to 1.70 among firefighters who had worked for ≥ 30 years. One other study provided nominal support for an association (Kullberg et al., 2018), with an SIR of 1.96 based on five cases in the extended follow-up period from 1987 through 2012. Overall, the Working Group concluded that a positive association was not seen in the body of evidence for multiple myeloma.

The Working Group noted modestly positive associations between occupation as a firefighter and risk of NHL, including across several well-designed studies. The Working Group considered that the likelihood of strong surveillance bias or healthy-worker biases was low. However, inconsistency in results and the modest effect size, hovering close to the null value, clouded interpretation of the evidence for NHL. Although confounding could not be ruled out, the Working Group considered that if uncontrolled confounding were an issue, the lack of control would most probably have attenuated observed associations rather than increase them. Importantly, NHL comprises more than 40 subtypes (Swerdlow et al., 2008) with documented etiological heterogeneity for many exposures (Morton et al., 2014). This may have an impact on both the overall association with occupation as a firefighter and the importance of potential confounders. Changing definitions of NHL over time may also have led to some heterogeneity in results, particularly if there were heterogeneity in the association with occupation as a firefighter according to NHL subtype. Overall, there was a lack of consistent positive associations in the body of evidence, and chance or alternative explanations of the observed excess risk could not be ruled out.

2.9.10 Cancer of the prostate

Cancer of the prostate is a common cancer. There are no conclusive risk factors for prostate cancer apart from age. However, there is *limited* evidence for a causal association with cancer of the prostate in humans for arsenic, cadmium and night shift work (IARC, 2023), and firefighters are potentially exposed to all three hazards (see Section 1.1).

There were 34 studies that provided useable information on cancer of the prostate: 23 occupational cohort studies; six cohort studies in the general population; and five "event-only" studies of cancer end-points.

The Working Group considered that 12 cohort studies (providing 13 sets of results) with exposure assessments of good or satisfactory quality were particularly informative (Demers et al., 1992a, 1994; Tornling et al., 1994; Daniels et al., 2014; Glass et al., 2016a, 2017; Kullberg et al., 2018; Petersen et al., 2018a, b; Bigert et al., 2020; Pinkerton et al., 2020; Marjerrison et al., 2022a, b). However, the overall findings and conclusions were similar when all available studies were included.

The meta-analysis performed by the Working Group (DeBono et al., 2023) incorporating most of the cohort studies found an increased incidence of cancer of the prostate (meta-RR, 1.21; 95% CI, 1.12–1.32), but with high heterogeneity (I^2 = 81%; P < 0.01) (Giles et al., 1993; Demers et al., 1994; Bates et al., 2001; Ma et al., 2006; Ahn et al., 2012; Daniels et al., 2014; Pukkala et al., 2014; Glass et al., 2016a; Harris et al., 2018; Petersen et al., 2018a; Bigert et al., 2020; Webber et al., 2021; Marjerrison et al., 2022b; Sritharan et al., 2022), and no clear increase for mortality (meta-RR, 1.07; 95% CI, 0.95–1.20; I^2 = 30%; P = 0.16) (Vena & Fiedler, 1987; Demers et al., 1992a; Guidotti, 1993; Aronson et al., 1994; Tornling et al., 1994; Ma et al., 2005; Amadeo et al., 2015; Petersen et al., 2018b; Pinkerton et al., 2020; Zhao et al., 2020; Marjerrison et al., 2022b). For incidence, the effect estimates from the individual studies ranged from 0.90 to 2.09, with all except one of the studies having an estimate of above one. For mortality, the relative risk estimates ranged from

0.54 to 1.46, with eight of the eleven estimates being above one.

There was no consistent relationship across the studies between increased risk and any of age at diagnosis, time since employment, duration of employment, or other proxy measures of exposure. There was a consistent observation of excess prostate cancer risk at younger ages among studies with follow-up after prostate-specific antigen testing (e.g. Daniels et al., 2014; Pukkala et al., 2014; Kullberg et al., 2018; Marjerrison et al., 2022b).

All studies used the general population as the comparison population, which raised the possibility of a healthy-worker hire effect biasing the measure of effect downwards, but several studies also conducted internal analyses (Glass et al., 2016a, 2017; Pinkerton et al., 2020).

The Working Group noted evidence indicating increased medical surveillance for prostate cancer in the firefighter populations studied (Jakobsen et al., 2022). There was no clear evidence from the meta-analysis performed by the Working Group that this resulted in important bias, but such increased surveillance might be difficult to identify. For this reason, the two WTC studies (Zeig-Owens et al., 2011; Webber et al., 2021), which comprised cohorts that the Working Group considered likely to have undergone increased surveillance when compared with the reference populations used, were not considered to be among the key studies used for the evidence synthesis. These two studies were excluded from the meta-analysis in a sensitivity analysis.

Overall, the Working Group found there was evidence suggesting that the risk of cancer of the prostate is positively associated with occupational exposure as a firefighter. However, given the possibility of detection bias arising from increased medical surveillance, the lack of a consistent relation with any of the included exposure metrics, and the statistical imprecision of the estimates in many of the studies, accompanied by high heterogeneity in the meta-analysis, the Working Group concluded that chance, bias, and confounding could not be ruled out with reasonable confidence.

2.9.11 Cancer of the colon

Cancer of the colon is one of the most common incident cancers in the world (Rawla et al., 2019). Incidence rates vary by sex and are associated with several genetic, hereditary, or familial factors. A number of individual risk factors have been well established, particularly concerning physical activity, tobacco smoking, and alcohol consumption. Further, there is *limited* evidence for a causal association between night shift work and colon cancer in humans (IARC, 2023), and firefighters are exposed to this hazard (see Section 1.5.2).

In the meta-analysis performed by the Working Group (DeBono et al., 2023), a modest excess was observed for incidence of cancer of the colon (meta-RR, 1.19; 95% CI, 1.07–1.32; I^2 = 37%; P = 0.11). For mortality, the meta-RR was 1.03 (95% CI, 0.78–1.37). There was a positive association between colon cancer incidence and employment duration in meta-regression; however, the estimate was largely imprecise given that only three studies were available for aggregation. Information was insufficient to examine mortality.

Eight cohort studies of good or satisfactory exposure assessment quality including primarily career firefighters (Aronson et al., 1994; Demers et al., 1994; Bates et al., 2001; Daniels et al., 2014; Glass et al., 2016a; Petersen et al., 2018b; Bigert et al., 2020; Pinkerton et al., 2020; Marjerrison et al., 2022b) reported on overall incidence or mortality of colon cancer.

Compared with incidence rates in the general population, elevated overall SIRs for colon cancer (1.21 and 1.24) were reported by Daniels et al. (2014) and Marjerrison et al. (2022b). For mortality, SMRs in the same cohorts were

elevated by 26% and 27% (Pinkerton et al., 2020; Marjerrison et al., 2022b). Point estimates below unity were found in two studies comparing firefighters with general population reference groups (Aronson et al., 1994; Petersen et al., 2018a).

Few studies attempted to assess internal exposure–response associations. Among the most informative, consistent inverse associations between intestinal/rectal cancer and exposed-days, fire-runs, and fire-hours were observed for all models of cancer incidence and mortality in pooled studies of male career firefighters in the USA (Daniels et al., 2015; Pinkerton et al., 2020), and there was no evidence of a strong healthy-worker survivor bias that could explain these findings (Pinkerton et al., 2020). In other large studies, there was little evidence of a positive association between colorectal cancer incidence and the number and type of fire incidents attended among male career firefighters (Glass et al., 2016a) or volunteers (Glass et al., 2017) in Australia. Two earlier smaller studies found some indications of increasing incidence or mortality rates with longer employment duration, but case numbers were low, and substantial deviations from expected numbers of colon cancer cases or deaths were not seen (Demers et al.,1994; Bates et al., 2001).

Among volunteer firefighters, significant deficits in risk of incident colon cancer were observed among men (Glass et al., 2017), whereas a modest but imprecise elevation was seen among women (Glass et al., 2019).

Firefighters are required to have a high level of physical fitness to enter their profession and might, therefore, be expected to have a higher level of physical activity, which has been associated with a decreased risk of colon cancer (see Section 1.2.5) and could attenuate any association between colon cancer and occupation. However, recent survey studies from the USA and United Kingdom have indicated a higher prevalence of overweight among firefighters than in the general population (Poston et al., 2011; Munir et al., 2012) and a higher frequency of drinking five or more alcoholic beverages on an occasion (Kanny et al., 2013), but little historical information is available. In addition, there is the potential for medical surveillance bias attributable to screening, which may contribute to elevations in point estimates among firefighters compared with the general population.

Overall, the Working Group found some evidence suggesting that risk of cancer of the colon is associated with work as a firefighter. However, there was a lack of consistency among the positive results, and a potential for healthy survivor and surveillance bias. As a result, the potential for chance, bias, or confounding could not be ruled out with reasonable confidence.

2.9.12 Cancer of the brain and other cancers of the central nervous system

The Working Group synthesis for brain and other cancers of the central nervous system in humans was primarily informed by the meta-analysis of DeBono et al. (2023), as well as by studies assessed as having an exposure assessment of good or adequate quality. The meta-analysis found an excess in mortality (meta-RR, 1.33; 95% CI, 0.98–1.79; $I^2 = 53\%$; $P = 0.02$), but not incidence (meta-RR, 1.01; 95% CI, 0.86–1.18; $I^2 = 5\%$; $P = 0.40$). This was an unexpected finding given the high fatality rates of these tumours in adults. Among three cohort studies that had good exposure assessments and included mortality, one reported excess mortality (Tornling et al., 1994), and two did not (Guidotti, 1993; Pinkerton et al., 2020). Three studies with satisfactory exposure assessments reported an excess of mortality from brain and other cancers of the central nervous system (Demers et al., 1992a; Aronson et al., 1994; Marjerrison et al., 2022b); another reported a null association (Bates et al., 2001). All the individual studies reporting incidence had null findings, many of which were imprecise. Overall, the Working Group concluded that

a positive association was not seen in the body of evidence for cancers of the brain and central nervous system.

2.9.13 Cancer of the thyroid

The Working Group reviewed 21 studies that reported results for thyroid cancer incidence or mortality. The synthesis was primarily informed by studies assessed as having an exposure assessment of good or satisfactory quality (as defined in Section 1.8), as well as by the meta-analysis performed by the Working Group (DeBono et al., 2023). Of five studies with an exposure assessment considered "good" and that included incidence estimates for thyroid cancer, two studies in FDNY WTC-exposed firefighters reported an excess incidence of thyroid cancer (Colbeth et al., 2020a; Webber et al., 2021) but, as noted in Section 2.4, this finding was probably subject to a strong surveillance bias. Of three other studies with exposure assessments classified as "good," one reported slightly elevated estimates for thyroid cancer, but based on few cases (Glass et al., 2016a), and two reported null findings (Glass et al., 2017, 2019), including among female volunteer firefighters in Australia (Glass et al., 2019). In the meta-analysis performed by the Working Group, the meta-RR for thyroid cancer mortality was elevated, but based on only four studies; the meta-RR for incidence was also elevated (meta-RR, 1.28; 95% CI, 1.02–1.61; I^2 = 40%; P = 0.09). However, the meta-estimate for cancer incidence was attenuated in most sensitivity analyses, including when studies most likely to have been influenced by surveillance bias and healthy-worker effects were excluded.

The Working Group noted a lack of precision for most point estimates for thyroid cancer, and the strong possibility of overestimated associations attributable to the effect of medical surveillance bias on thyroid cancer incidence. Overall, the Working Group found little evidence that the risk of cancer of the thyroid is credibly associated with occupational exposure as a firefighter.

2.9.14 Cancer of the lung

Cancer of the lung is a common cancer, and tobacco smoking is the strongest and most important risk factor. Firefighters are potentially exposed to several known human lung carcinogens (see Table 1.1).

There were 34 studies that provided information on cancer of the lung: 28 cohort studies, five "event-only" studies, and 1 case–control study. The overall findings and conclusions were similar regardless of the exposure quality of the studies included.

The meta-analysis performed by the Working Group (DeBono et al., 2023), which incorporated estimates from most of the cohort studies, found an inverse association for lung cancer incidence (meta-RR, 0.85; 95% CI, 0.75–0.96; 14 cohort studies; I^2 = 78%; P < 0.01), and no association for mortality (meta-RR, 0.96; 95% CI, 0.86–1.06; 12 cohort studies; I^2 = 55%; P = 0.01). The relative risk estimates from the individual studies for incidence ranged from 0.47 to 1.14, with all except three of the studies having estimates below one. For mortality, the relative risk estimates ranged from 0.58 to 1.63, with all except three of the studies having estimates below one.

There was no consistent relationship across the studies between increased risk of lung cancer and age at diagnosis, time since employment, duration of employment, or other measures of exposure.

Although no increase in risk was identified, the Working Group noted several factors that clouded the interpretation of the study findings, most of which would be expected to bias the estimate of effect downwards in relevant studies: the healthy-worker hire effect, young age of included participants, short follow-up period, and potential negative confounding from smoking in studies with more recent follow-up. For many

of the studies, the participants were relatively young during much of the follow-up period, ages at which the healthy-worker effect was likely to be more evident than might be expected at older ages. Many studies also had a relatively short follow-up, providing less opportunity for cancers related to exposure to have occurred. However, restriction to studies with longer and older periods of follow-up in the meta-analysis did not indicate positive associations. Most studies did not have information about smoking for the included firefighters or the comparison population. One large pooled international case–control study with this information showed no increased lung cancer risk, either with or without smoking adjustment (Bigert et al., 2016).

Overall, the Working Group found little evidence that the risk of cancer of the lung is positively associated with occupational exposure as a firefighter.

2.9.15 Cancer of the kidney

For cancer of the kidney, the meta-analysis conducted by the Working Group (DeBono et al., 2023) found a slightly elevated risk for incidence (meta-RR, 1.09; 95% CI, 0.92–1.29; I^2 = 55%; P = 0.01) based on 12 cohort studies and for mortality (meta-RR, 1.10; 95% CI, 0.66–1.83; I^2 = 53%; P = 0.03) based on nine studies. There were four studies that evaluated duration of employment (Ahn et al., 2012; Glass et al., 2016a, 2017; Marjerrison et al., 2022a), with no patterns of increasing risk with increasing duration found in any except Glass et al. (2016a). Although there were elevations observed in some strata for other measures of exposure, inferences were limited by very small numbers and showed no consistent patterns. Overall, the Working Group found little evidence that the risk of cancer of the kidney is positively associated with occupational exposure as a firefighter.

2.9.16 Leukaemia

There were 24 cohort studies that evaluated leukaemia risk among firefighters. Nine studies reported null findings (Demers et al., 1994; Ahn et al., 2012; Ahn & Jeong, 2015; Glass et al., 2016a, 2017, 2019; Kullberg et al., 2018; Bigert et al., 2020; Marjerrison et al., 2022a), including some studies that were informative for other cancer sites. In two studies, each with six exposed cases, there was some evidence of increased risk of leukaemia with longer duration of employment (Demers et al., 1992a; Aronson et al., 1994), although there was a noted lack of precision because of small numbers. In a well-conducted study of municipal career firefighters in the USA, there was an elevated risk among 11 non-Caucasian [non-White] male firefighters (SIR, 1.90; 95% CI, 0.95–3.40) but not in 88 Caucasian [White] males (Daniels et al., 2014). In the same cohort, mortality analyses revealed no overall excess of leukaemia, although there was some evidence of an exposure–response relation for the number of fire-runs and fire-hours (Pinkerton et al., 2020). Most studies did not evaluate myeloid and lymphoid malignancies separately, and no differences were apparent. Overall, the Working Group concluded that a positive association was not seen in the body of evidence for leukaemia.

2.9.17 Other cancer sites

The Working Group also considered the evidence for a causal association between occupational exposure as a firefighter and other cancer types. For example, some studies observed an increased risk of cancers of the stomach and larynx. However, in examining the full body of evidence, few studies observed an excess risk of greater than 20%, and meta-analyses found the risk of stomach cancer among firefighters to be similar to that in the general population (DeBono et al., 2023). The six studies that examined stomach cancer risk in relation to duration

of employment found no evidence of an association. The only study to examine the relation between exposure to fire responses and stomach cancer did find a positive association (Pinkerton et al., 2020). The few studies to examine laryngeal cancer by indicators of firefighting activities, including duration of employment, showed inconsistent results based on small numbers of cases. Overall, the Working Group found little evidence that the risk of cancers of the stomach and larynx is positively associated with occupational exposure as a firefighter.

2.9.18 All cancers combined

The meta-analysis performed by the Working Group for male firefighters and all cancers combined (DeBono et al., 2023) showed little evidence of an increase in the meta-rate ratio for either incidence (meta-RR, 1.05; 95% CI, 0.99–1.11) or mortality (meta-RR, 0.99; 95% CI, 0.96–1.06). The heterogeneities of both estimates were high (I^2 = 87%). As seen above, the incidence of some of the most frequent cancers, i.e. prostate, colon, and bladder cancer, which together account for about one third of all cancers in men, was raised and may have contributed to an overall increase, which was not observed. Therefore, the Working Group found little evidence that the risk of all cancers combined is associated with occupational exposure as a firefighter.

References

Ahn YS, Jeong KS (2015). Mortality due to malignant and non-malignant diseases in Korean professional emergency responders. *PLoS One*. 10(3):e0120305. doi:10.1371/journal.pone.0120305 PMID:25756281

Ahn YS, Jeong KS, Kim KS (2012). Cancer morbidity of professional emergency responders in Korea. *Am J Ind Med*. 55(9):768–78. doi:10.1002/ajim.22068 PMID:22628010

Amadeo B, Marchand JL, Moisan F, Donnadieu S, Gaëlle C, Simone MP, et al. (2015). French firefighter mortality: analysis over a 30-year period. *Am J Ind Med*. 58(4):437–43. doi:10.1002/ajim.22434 PMID:25708859

Antoniv VF, Popaduyk VI, Antoniv TV (2017). [Ionizing radiation and laryngeal cancer]. *Vestn Otorinolaringol*. 82(2):19–23. [Russian] doi:10.17116/otorino201782219-23 PMID:28514358

Aronson KJ, Tomlinson GA, Smith L (1994). Mortality among fire fighters in metropolitan Toronto. *Am J Ind Med*. 26(1):89–101. doi:10.1002/ajim.4700260108 PMID:8074127

Arrighi HM, Hertz-Picciotto I (1994). The evolving concept of the healthy worker survivor effect. *Epidemiology*. 5(2):189–96. doi:10.1097/00001648-199403000-00009 PMID:8172994

Baris D, Garrity TJ, Telles JL, Heineman EF, Olshan A, Zahm SH (2001). Cohort mortality study of Philadelphia firefighters. *Am J Ind Med*. 39(5):463–76. doi:10.1002/ajim.1040 PMID:11333408

Barry KH, Martinsen JI, Alavanja MCR, Andreotti G, Blair A, Hansen J, et al. (2017). Risk of early-onset prostate cancer associated with occupation in the Nordic countries. *Eur J Cancer*. 87:92–100. doi:10.1016/j.ejca.2017.09.023 PMID:29132062

Bates MN (2007). Registry-based case–control study of cancer in California firefighters. *Am J Ind Med*. 50(5):339–44. doi:10.1002/ajim.20446 PMID:17427202

Bates MN, Fawcett J, Garrett N, Arnold R, Pearce N, Woodward A (2001). Is testicular cancer an occupational disease of fire fighters? *Am J Ind Med*. 40(3):263–70. doi:10.1002/ajim.1097 PMID:11598972

Bates MN, Lane L (1995). Testicular cancer in fire fighters: a cluster investigation. *N Z Med J*. 108(1006):334–7. PMID:7566760

Beaumont JJ, Chu GS, Jones JR, Schenker MB, Singleton JA, Piantanida LG, et al. (1991). An epidemiologic study of cancer and other causes of mortality in San Francisco firefighters. *Am J Ind Med*. 19(3):357–72. doi:10.1002/ajim.4700190309 PMID:2008922

Bianchi C, Bianchi T, Tommasi M (2007). [Mesothelioma of the pleura in the Province of Trieste]. *Med Lav*. 98(5):374–80. [Italian] PMID:17907531

Bigert C, Gustavsson P, Straif K, Taeger D, Pesch B, Kendzia B, et al. (2016). Lung cancer among firefighters: smoking-adjusted risk estimates in a pooled analysis of case-control studies. *J Occup Environ Med*. 58(11):1137–43. doi:10.1097/JOM.0000000000000878 PMID:27820764

Bigert C, Martinsen JI, Gustavsson P, Sparén P (2020). Cancer incidence among Swedish firefighters: an extended follow-up of the NOCCA study. *Int Arch Occup Environ Health*. 93(2):197–204. doi:10.1007/s00420-019-01472-x PMID:31463517

Brinchmann BC, Bugge MD, Nordby KC, Alfonso JH (2022). Firefighting and melanoma, epidemiological and toxicological associations: a case report. *Occup Med (Lond)*. 72(2):142–4. doi:10.1093/occmed/kqab183 PMID:35064261

Buckley JP, Keil AP, McGrath LJ, Edwards JK (2015). Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology*. 26(2):204–12. doi:10.1097/EDE.0000000000000217 PMID:25536456

Burnett CA, Halperin WE, Lalich NR, Sestito JP (1994). Mortality among fire fighters: a 27 state survey. *Am J Ind Med*. 26(6):831–3. doi:10.1002/ajim.4700260612 PMID:7892834

Casjens S, Brüning T, Taeger D (2020). Cancer risks of firefighters: a systematic review and meta-analysis of secular trends and region-specific differences. *Int Arch Occup Environ Health*. 93(7):839–52. doi:10.1007/s00420-020-01539-0 PMID:32306177

Clarivate (2022). Web of Science [online database]. Available from: https://www.webofscience.com/wos/woscc/basic-search.

Colbeth HL, Genere N, Hall CB, Jaber N, Brito JP, El Kawkgi OM, et al. (2020a). Evaluation of medical surveillance and incidence of post-September 11, 2001, thyroid cancer in World Trade Center-exposed firefighters and emergency medical service workers. *JAMA Intern Med*. 180(6):888–95. doi:10.1001/jamainternmed.2020.0950 PMID:32310290

Colbeth HL, Zeig-Owens R, Hall CB, Webber MP, Schwartz TM, Prezant DJ (2020b). Mortality among Fire Department of the city of New York rescue and recovery workers exposed to the World Trade Center disaster, 2001–2017. *Int J Environ Res Public Health*. 17(17):E6266. doi:10.3390/ijerph17176266 PMID:32872174

Cormack S (2013). Case report: malignant peritoneal mesothelioma. *Lung Cancer*. 79:S34–5. doi:10.1016/S0169-5002(13)70099-0

Cucchi G (2003). [Primary mesothelioma of the pericardium]. *Ital Heart J Suppl*. 4(3):241–3. [Italian] PMID:12784760

Dahm MM, Bertke S, Allee S, Daniels RD (2015). Creation of a retrospective job-exposure matrix using surrogate measures of exposure for a cohort of US career firefighters from San Francisco, Chicago and Philadelphia. *Occup Environ Med*. 72(9):670–7. doi:10.1136/oemed-2014-102790 PMID:26163543

Daniels RD, Bertke S, Dahm MM, Yiin JH, Kubale TL, Hales TR, et al. (2015). Exposure-response relationships for select cancer and non-cancer health outcomes in a cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950–2009). *Occup Environ Med*. 72(10):699–706. doi:10.1136/oemed-2014-102671 PMID:25673342

Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, et al. (2014). Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950–2009). *Occup Environ Med*. 71(6):388–97. doi:10.1136/oemed-2013-101662 PMID:24142974

DeBono NL, Daniels RD, Beane Freeman LE, Graber JM, Hansen J, Teras LR, et al. (2023). Firefighting and cancer: a meta-analysis of cohort studies in the context of cancer hazard identification. *Saf Health Work*. doi:10.1016/j.shaw.2023.02.003

Demers PA, Checkoway H, Vaughan TL, Weiss NS, Heyer NJ, Rosenstock L (1994). Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). *Cancer Causes Control*. 5(2):129–35. doi:10.1007/BF01830258 PMID:8167259

Demers PA, Heyer NJ, Rosenstock L (1992a). Mortality among firefighters from three northwestern United States cities. *Br J Ind Med*. 49(9):664–70. doi:10.1136/oem.49.9.664 PMID:1390274

Demers PA, Vaughan TL, Checkoway H, Weiss NS, Heyer NJ, Rosenstock L (1992b). Cancer identification using a tumor registry versus death certificates in occupational cohort studies in the United States. *Am J Epidemiol*. 136(10):1232–40. doi:10.1093/oxfordjournals.aje.a116431 PMID:1476145

Deschamps S, Momas I, Festy B (1995). Mortality amongst Paris fire-fighters. *Eur J Epidemiol*. 11(6):643–6. doi:10.1007/BF01720297 PMID:8861847

Elbaek Pedersen J, Ugelvig Petersen K, Hansen J (2020). Full employment history of Danish firefighters potentially involving additional exposures, 1964–2015. *Am J Ind Med*. 63(4):328–36. doi:10.1002/ajim.23089 PMID:31953961

Eliopulos E, Armstrong BK, Spickett JT, Heyworth F (1984). Mortality of fire fighters in Western Australia. *Br J Ind Med*. 41(2):183–7. doi:10.1136/oem.41.2.183 PMID:6722044

Elsevier (2022). Embase [online database]. Elsevier. Available from: https://www.embase.com.

Feuer E, Rosenman K (1986). Mortality in police and firefighters in New Jersey. *Am J Ind Med*. 9(6):517–27. doi:10.1002/ajim.4700090603 PMID:3488681

Geiger KW, Wright TJ, Deters L (2020). Renal cell carcinoma as an incidental finding in firefighters: a case series. *Cureus*. 12(7):e9259. doi:10.7759/cureus.9259 PMID:32821605

Giles G, Staples M, Berry J (1993). Cancer incidence in Melbourne Metropolitan Fire Brigade members, 1980–1989. *Health Rep*. 5(1):33–8. PMID:8334236

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2016b). Mortality and cancer incidence at a fire training college. *Occup Med (Lond)*. 66(7):536–42. doi:10.1093/occmed/kqw079 PMID:27371948

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2017). Mortality and cancer incidence among male volunteer Australian firefighters. *Occup Environ Med*. 74(9):628–38. doi:10.1136/oemed-2016-104088 PMID:28391245

Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR (2019). Mortality and cancer incidence among female Australian firefighters. *Occup Environ Med*. 76(4):215–21. PMID:30674605

Glass DC, Pircher S, Del Monaco A, Hoorn SV, Sim MR (2016a). Mortality and cancer incidence in a cohort of male paid Australian firefighters. *Occup Environ Med*. 73(11):761–71. doi:10.1136/oemed-2015-103467 PMID:27456156

Grimes G, Hirsch D, Borgeson D (1991). Risk of death among Honolulu fire fighters. *Hawaii Med J*. 50(3):82–5. PMID:2061032

Guidotti TL (1993). Mortality of urban firefighters in Alberta, 1927–1987. *Am J Ind Med*. 23(6):921–40. doi:10.1002/ajim.4700230608 PMID:8328477

Haddock CK, Jitnarin N, Poston WS, Tuley B, Jahnke SA (2011). Tobacco use among firefighters in the central United States. *Am J Ind Med*. 54(9):697–706. doi:10.1002/ajim.20972 PMID:21656838

Hansen ES (1990). A cohort study on the mortality of firefighters. *Br J Ind Med*. 47(12):805–9. doi:10.1136/oem.47.12.805 PMID:2271386

Harris MA, Kirkham TL, MacLeod JS, Tjepkema M, Peters PA, Demers PA (2018). Surveillance of cancer risks for firefighters, police, and armed forces among men in a Canadian census cohort. *Am J Ind Med*. 61(10):815–23. doi:10.1002/ajim.22891 PMID:30073696

Heyer N, Weiss NS, Demers P, Rosenstock L (1990). Cohort mortality study of Seattle fire fighters: 1945–1983. *Am J Ind Med*. 17(4):493–504. doi:10.1002/ajim.4700170407 PMID:2327416

Howe GR, Burch JD (1990). Fire fighters and risk of cancer: an assessment and overview of the epidemiologic evidence. *Am J Epidemiol*. 132(6):1039–50. doi:10.1093/oxfordjournals.aje.a115745 PMID:2260535

IARC (2010). Painting, firefighting, and shiftwork. *IARC Monogr Eval Carcinog Risks Hum*. 98:1–804. Available from: https://publications.iarc.fr/116 PMID:21381544

IARC (2012). Radiation. *IARC Monogr Eval Carcinog Risks Hum*. 100D:1–341. Available from: https://publications.iarc.fr/121 PMID:23189752

IARC (2015). Polychlorinated biphenyls and polybrominated biphenyls. *IARC Monogr Eval Carcinog Risks Hum*. 107:1–502. Available from: https://publications.iarc.fr/131 PMID:29905442

IARC (2016). Some chemicals used as solvents and in polymer manufacture. *IARC Monogr Eval Carcinog Risks Hum*. 110:1–276. Available from: https://publications.iarc.fr/547 PMID:31829531

IARC (2023). List of classifications by cancer sites with sufficient or limited evidence in humans, *IARC Monographs* Volumes 1–132. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf, accessed 20 March 2023.

Ide CW (1998). Failing firefighters: a survey of causes of death and ill-health retirement in serving firefighters in Strathclyde, Scotland from 1985–94. *Occup Med (Lond)*. 48(6):381–8. doi:10.1093/occmed/48.6.381 PMID:10024734

Ide CW (2014). Cancer incidence and mortality in serving whole-time Scottish firefighters 1984–2005. *Occup Med (Lond)*. 64(6):421–7. doi:10.1093/occmed/kqu080 PMID:25006097

IQWiG (2021). Testicular cancer: does routine screening for men aged 16 years and older lead to better treatment outcomes? [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG). IQWiG Reports – Commission No. HT18-01. Available from: https://www.ncbi.nlm.nih.gov/books/NBK569950/.

Jakobsen J, Veierod MB, Grimsrud TK, Fossa SD, Hammarstrom B, Kjaerheim K (2021). Early detection of prostate cancer in firefighters: a register-based study of prognostic factors and survival. *Occup Environ Med*. A8.1–A8. doi:10.1136/OEM-2021-EPI.21 PMID:34510005

Jakobsen J, Veierød MB, Grimsrud TK, Fosså SD, Hammarström B, Kjærheim K (2022). Early detection of prostate cancer in firefighters: a register-based study of prognostic factors and survival. *Occup Environ Med*. 79(3):200–6. doi:10.1136/oemed-2021-107622 PMID:34510005

Jalilian H, Ziaei M, Weiderpass E, Rueegg CS, Khosravi Y, Kjaerheim K (2019). Cancer incidence and mortality among firefighters. *Int J Cancer*. 145(10):2639–46. doi:10.1002/ijc.32199 PMID:30737784

Kang D, Davis LK, Hunt P, Kriebel D (2008). Cancer incidence among male Massachusetts firefighters, 1987–2003. *Am J Ind Med*. 51(5):329–35. doi:10.1002/ajim.20549 PMID:18306327

Kanny D, Liu Y, Brewer RD, Lu H; Centers for Disease Control and Prevention (CDC) (2013). Binge drinking - United States, 2011. *MMWR Suppl*. 62(3):77–80. [MMWR] PMID:24264494

Kullberg C, Andersson T, Gustavsson P, Selander J, Tornling G, Gustavsson A, et al. (2018). Cancer incidence in Stockholm firefighters 1958–2012: an updated cohort study. *Int Arch Occup Environ Health*. 91(3):285–91. doi:10.1007/s00420-017-1276-1 PMID:29164319

Landgren O, Zeig-Owens R, Giricz O, Goldfarb D, Murata K, Thoren K, et al. (2018). Multiple myeloma and its precursor disease among firefighters exposed to the World Trade Center disaster. *JAMA Oncol*. 4(6):821–7. doi:10.1001/jamaoncol.2018.0509 PMID:29710195

Langevin SM, Eliot M, Butler RA, McClean M, Kelsey KT (2020). Firefighter occupation is associated with increased risk for laryngeal and hypopharyngeal squamous cell carcinoma among men from the Greater Boston area. *Occup Environ Med*. 77(6):381–5. doi:10.1136/oemed-2019-106271 PMID:32107319

Laroche E, L'Espérance S (2021). Cancer incidence and mortality among firefighters: an overview of epidemiologic systematic reviews. *Int J Environ Res Public Health*. 18(5):18. doi:10.3390/ijerph18052519 PMID:33802629

Lauby-Secretan B, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. (2013). Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. *Lancet Oncol*. 14(4):287–8. doi:10.1016/S1470-2045(13)70104-9 PMID:23499544

Lee DJ, Koru-Sengul T, Hernandez MN, Caban-Martinez AJ, McClure LA, Mackinnon JA, et al. (2020). Cancer risk among career male and female Florida firefighters: evidence from the Florida Firefighter Cancer Registry (1981–2014). *Am J Ind Med*. 63(4):285–99. doi:10.1002/ajim.23086 PMID:31930542

LeMasters GK, Genaidy AM, Succop P, Deddens J, Sobeih T, Barriera-Viruet H, et al. (2006). Cancer risk among firefighters: a review and meta-analysis of 32 studies. *J Occup Environ Med*. 48(11):1189–202. doi:10.1097/01.jom.0000246229.68697.90 PMID:17099456

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA (2006). Cancer incidence in Florida professional firefighters, 1981 to 1999. *J Occup Environ Med*. 48(9):883–8. doi:10.1097/01.jom.0000235862.12518.04 PMID:16966954

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA, Lai H, et al. (2005). Mortality in Florida professional firefighters, 1972 to 1999. *Am J Ind Med*. 47(6):509–17. doi:10.1002/ajim.20160 PMID:15898094

Ma F, Lee DJ, Fleming LE, Dosemeci M (1998). Race-specific cancer mortality in US firefighters: 1984–1993. *J Occup Environ Med*. 40(12):1134–8. PMID:9871891

Marjerrison N, Jakobsen J, Demers PA, Grimsrud TK, Hansen J, Martinsen JI, et al. (2022b). A comparison of cancer incidence and mortality in the Norwegian Fire Departments Cohort, 1960–2018. *Occup Environ Med*. oemed-2022–108331. doi:10.1136/oemed-2022-108331 PMID:35589382

Marjerrison N, Jakobsen J, Grimsrud TK, Hansen J, Martinsen JI, Nordby KC, et al. (2022a). Cancer incidence in sites potentially related to occupational exposures: 58 years of follow-up of firefighters in the Norwegian Fire Departments Cohort. *Scand J Work Environ Health*. 48(3):210–9. doi:10.5271/sjweh.4009 PMID:35015085

Mastromatteo E (1959). Mortality in city firemen. II. A study of mortality in firemen of a city fire department. *AMA Arch Ind Health*. 20:227–33. PMID:14422193

McClure LA, Koru-Sengul T, Hernandez MN, Caban-Martinez AJ, Kobetz EN, Lee DJ (2021). Comparing cancer risk estimates using occupational record linkage approaches in male Florida firefighters. *Am J Ind Med*. 64(2):78–83. doi:10.1002/ajim.23205 PMID:33283309

McClure LA, Koru-Sengul T, Hernandez MN, Mackinnon JA, Schaefer Solle N, Caban-Martinez AJ, et al. (2019). Availability and accuracy of occupation in cancer registry data among Florida firefighters. *PLoS One*. 14(4):e0215867. doi:10.1371/journal.pone.0215867 PMID:31039169

McGlynn KA, Trabert B (2012). Adolescent and adult risk factors for testicular cancer. *Nat Rev Urol*. 9(6):339–49. doi:10.1038/nrurol.2012.61 PMID:22508459

Moir W, Zeig-Owens R, Daniels RD, Hall CB, Webber MP, Jaber N, et al. (2016). Post-9/11 cancer incidence in World Trade Center-exposed New York City firefighters as compared to a pooled cohort of firefighters from San Francisco, Chicago and Philadelphia (9/11/2001–2009). *Am J Ind Med*. 59(9):722–30. doi:10.1002/ajim.22635 PMID:27582474

Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, et al. (2014). Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014(48):130–44. doi:10.1093/jncimonographs/lgu013 PMID:25174034

Muegge CM, Zollinger TW, Song Y, Wessel J, Monahan PO, Moffatt SM (2018). Excess mortality among Indiana firefighters, 1985–2013. *Am J Ind Med*. 61(12):961–7. doi:10.1002/ajim.22918 PMID:30421827

Munir F, Clemes S, Houdmont J, Randall R (2012). Overweight and obesity in UK firefighters. *Occup Med (Lond)*. 62(5):362–5. doi:10.1093/occmed/kqs077 PMID:22679213

Musk AW, Monson RR, Peters JM, Peters RK (1978). Mortality among Boston firefighters, 1915–1975. *Br J Ind Med*. 35(2):104–8. doi:10.1136/oem.35.2.104 PMID:656333

NLM (2022). PubMed [online database]. Bethesda (MD), USA: National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/, accessed May 2023.

Park KE, Ramachandran V, Tran J, Joshi TP, Garg N, Duvic M (2022). Association of flame-retardant clothing with mycosis fungoides: a retrospective analysis. *Dermatol Pract Concept*. 12(2):e2022091. doi:10.5826/dpc.1202a91 PMID:35646447

Petersen KU, Pedersen JE, Bonde JP, Ebbehoej NE, Hansen J (2018a). Long-term follow-up for cancer incidence in a cohort of Danish firefighters. *Occup Environ Med*. 75(4):263–9. doi:10.1136/oemed-2017-104660 PMID:29055884

Petersen KU, Pedersen JE, Bonde JP, Ebbehøj NE, Hansen J (2018b). Mortality in a cohort of Danish firefighters; 1970–2014. *Int Arch Occup Environ Health*. 91(6):759–66. doi:10.1007/s00420-018-1323-6 PMID:29808435

Phan L, McNeel TS, Jewett B, Moose K, Choi K (2022). Trends of cigarette smoking and smokeless tobacco use among US firefighters and law enforcement personnel, 1992–2019. *Am J Ind Med*. 65(1):72–7. doi:10.1002/ajim.23311 PMID:34766643

Pinkerton L, Bertke SJ, Yiin J, Dahm M, Kubale T, Hales T, et al. (2020). Mortality in a cohort of US firefighters from San Francisco, Chicago and Philadelphia: an update. *Occup Environ Med*. 77(2):84–93. doi:10.1136/oemed-2019-105962 PMID:31896615

Poston WS, Haddock CK, Jahnke SA, Jitnarin N, Tuley BC, Kales SN (2011). The prevalence of overweight, obesity, and substandard fitness in a population-based firefighter cohort. *J Occup Environ Med*. 53(3):266–73. doi:10.1097/JOM.0b013e31820af362 PMID:21386691

Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggvadottir L, et al. (2014). Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med*. 71(6):398–404. doi:10.1136/oemed-2013-101803 PMID:24510539

Purdue MP, Devesa SS, Sigurdson AJ, McGlynn KA (2005). International patterns and trends in testis cancer incidence. *Int J Cancer*. 115(5):822–7. doi:10.1002/ijc.20931 PMID:15704170

Rawla P, Sunkara T, Barsouk A (2019). Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol*. 14(2):89–103. doi:10.5114/pg.2018.81072 PMID:31616522

Sama SR, Martin TR, Davis LK, Kriebel D (1990). Cancer incidence among Massachusetts firefighters, 1982–1986. *Am J Ind Med*. 18(1):47–54. doi:10.1002/ajim.4700180106 PMID:2378369

Schrey A, Halme E, Ventelä S, Laine J, Irjala H (2013). Extramedullary malignant tumors in the head and neck region - a case report. *Oral Oncol*. 49:S100. doi:10.1016/j.oraloncology.2013.03.263

Soteriades ES, Kim J, Christophi CA, Kales SN (2019). Cancer incidence and mortality in firefighters: a state-of-the-art review and meta-analysis. *Asian Pac J Cancer Prev*. 20(11):3221–31. doi:10.31557/APJCP.2019.20.11.3221 PMID:31759344

Sritharan J, Kirkham TL, MacLeod J, Marjerrison N, Lau A, Dakouo M, et al. (2022). Cancer risk among firefighters and police in the Ontario workforce. *Occup Environ Med*. 79(8):533–39. doi:10.1136/oemed-2021-108146 PMID:35354650

Sritharan J, MacLeod J, Harris S, Cole DC, Harris A, Tjepkema M, et al. (2018). Prostate cancer surveillance by occupation and industry: the Canadian Census Health and Environment Cohort (CanCHEC). *Cancer Med*. 7(4):1468–78. doi:10.1002/cam4.1358 PMID:29493883

Sritharan J, Pahwa M, Demers PA, Harris SA, Cole DC, Parent ME (2017). Prostate cancer in firefighting and police work: a systematic review and meta-analysis of epidemiologic studies. *Environ Health*. 16(1):124. doi:10.1186/s12940-017-0336-z PMID:29149887

Stang A, Jöckel KH, Baumgardt-Elms C, Ahrens W (2003). Firefighting and risk of testicular cancer: results from a German population-based case-control study. *Am J Ind Med*. 43(3):291–4. doi:10.1002/ajim.10178 PMID:12594776

Stayner L, Steenland K, Dosemeci M, Hertz-Picciotto I (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scand J Work Environ Health*. 29(4):317–24. doi:10.5271/sjweh.737 PMID:12934726

Sugi MT, Fedenko AN, Menendez LR, Allison DC (2013). Clavicular eosinophilic granuloma causing adult shoulder pain. *Rare Tumors*. 5(1):e8. doi:10.4081/rt.2013.e8 PMID:23772307

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors (2008). WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed., Volume 2. Lyon, France: International Agency for Research on Cancer.

Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (2017). Cancer epidemiology and prevention. Oxford University Press. doi:10.1093/oso/9780190238667.001.0001

Tornling G, Gustavsson P, Hogstedt C (1994). Mortality and cancer incidence in Stockholm fire fighters. *Am J Ind Med*. 25(2):219–28. doi:10.1002/ajim.4700250208 PMID:8147394

Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM, Calvert GM (2015). Risk of cancer among firefighters in California, 1988–2007. *Am J Ind Med*. 58(7):715–29. doi:10.1002/ajim.22466 PMID:25943908

Vena JE, Fiedler RC (1987). Mortality of a municipal-worker cohort: IV. Fire fighters. *Am J Ind Med*. 11(6):671–84. doi:10.1002/ajim.4700110608 PMID:3605104

Webber MP, Singh A, Zeig-Owens R, Salako J, Skerker M, Hall CB, et al. (2021). Cancer incidence in World Trade Center-exposed and non-exposed male firefighters, as compared with the US adult male population: 2001–2016. *Occup Environ Med*. 78(10):707–14. doi:10.1136/oemed-2021-107570 PMID:34507965

Wolfe CM, Green WH, Cognetta AB Jr, Hatfield HK (2012). Heat-induced squamous cell carcinoma of the lower extremities in a wildlands firefighter. *J Am Acad Dermatol*. 67(6):e272–3. doi:10.1016/j.jaad.2012.05.020 PMID:23158634

Youakim S (2006). Risk of cancer among firefighters: a quantitative review of selected malignancies. *Arch Environ Occup Health*. 61(5):223–31. doi:10.3200/AEOH.61.5.223-231 PMID:17891891

Zeig-Owens R, Kablanian A, Webber MP, Liu Y, Mayerson E, Schwartz T, et al. (2016). Agreement between self-reported and confirmed cancer diagnoses in New York City firefighters and EMS

workers, 2001–2011. *Public Health Rep*. 131(1):153–9. doi:10.1177/003335491613100122 PMID:26843681

Zeig-Owens R, Webber MP, Hall CB, Schwartz T, Jaber N, Weakley J, et al. (2011). Early assessment of cancer outcomes in New York City firefighters after the 9/11 attacks: an observational cohort study. *Lancet*. 378(9794):898–905. doi:10.1016/S0140-6736(11)60989-6 PMID:21890054

Zhao G, Erazo B, Ronda E, Brocal F, Regidor E (2020). Mortality among firefighters in Spain: 10 years of follow-up. *Ann Work Expo Health*. 64(6):614–21. doi:10.1093/annweh/wxaa036 PMID:32253442

3. CANCER IN EXPERIMENTAL ANIMALS

No data were available to the Working Group.

4. MECHANISTIC EVIDENCE

Overview of mechanisms for carcinogens to which firefighters are exposed

Firefighters are exposed to a heterogeneous mixture of chemicals released from fires and non-fire environments. Exposure depends not only on the fuel involved and the fire conditions but also on the firefighting roles and activities being undertaken.

There is evidence that firefighters are regularly exposed to several airborne chemical agents, primarily combustion products released from fires, motor exhaust, and emissions from other activities (e.g. vehicle accidents, hazardous material releases, building collapses, and other non-emergency events) (see Section 1.2 and Section 1.3.1). Firefighters are exposed via inhalation and dermal contact to asbestos, particulate matter (PM) (coarse, fine, and ultrafine), PM-bound metals and organic compounds, airborne volatile organic compounds (VOCs) and semi-volatile organic compounds (sVOCs), flame retardants, per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), etc. (as reported in Sections 1.4.1–1.4.4 and 1.5.1). Biomonitoring assays have also demonstrated the presence of chemical agents and/or their main metabolites on the skin and in biological fluids (e.g. urine, blood, exhaled breath) of firefighters after occupational exposure (see Section 1.4.5 and Section 1.5.1(i)). In addition, firefighters operate under conditions of extreme heat, stress, and dehydration, undertaking physical activity and night shift work.

Several of the above agents have been evaluated previously by the *IARC Monographs* programme and classified as *carcinogenic to humans* (IARC Group 1) or *probably carcinogenic to humans* (IARC Group 2A) (see Table 1.1). Their carcinogenic mechanisms as described by IARC are illustrated here. For example, asbestos, for which the primary source of exposure is structure fires or building collapse, exhibits several key characteristics of carcinogens (Smith et al., 2016) in in vitro studies; specifically, "is genotoxic"; "induces oxidative stress"; "induces chronic inflammation"; and "alters cell proliferation, cell death, or nutrient supply" (IARC, 2012a). A positive association between employment as a firefighter and mesothelioma has been observed (see Section 2.9.5).

Firefighters are exposed to PM, and the PM in outdoor air pollution has been classified as *carcinogenic to humans* (IARC Group 1). Most PM in outdoor air is a product of combustion emissions (DeMarini & Linak, 2022); as much as 25–50% of $PM_{2.5}$ (particulate matter with a diameter of 2.5 μm or less) in outdoor air in the USA originates from wildland fires (Burke et al., 2021). PM exhibits several key characteristics of

carcinogens, including "is genotoxic", "induces oxidative stress", and "induces chronic inflammation". There is strong mechanistic evidence for the genotoxicity of PM in humans (IARC, 2016).

Many known or probable human carcinogens are present in PM and are released from fires. Prominent among these are polycyclic aromatic hydrocarbons (PAHs), which have been identified in numerous exposure studies of firefighters (Section 1.4). PAHs are the chemical class most highly correlated ($r \approx 1.0$) with the mutagenicity of PM from combustion emissions (DeMarini & Linak, 2022). There is mechanistic evidence that the model PAH, benzo[*a*]pyrene (B[*a*]P), is carcinogenic to humans, exhibiting the key characteristics of carcinogens "is electrophilic or can be metabolically activated to an electrophile", "is genotoxic", "induces oxidative stress", "induces chronic inflammation", "is immunosuppressive", and "modulates receptor-mediated effects" (IARC, 2010). The only available studies were in humans exposed to mixtures of PAHs; there were no studies on exposure to B[*a*]P only. However, the finding of B[*a*]P diol epoxide–DNA adducts in humans exposed to mixtures of PAHs, together with extensive studies showing the genotoxicity of B[*a*]P in experimental systems, provided consistent and coherent mechanistic evidence for the genotoxicity of B[*a*]P in humans (IARC, 2010, 2012b).

There is mechanistic evidence, primarily electrophilicity and genotoxicity, for the carcinogenicity (IARC Group 1) of occupational exposure to complex mixtures composed predominantly of PAHs, including those encountered during coal gasification, coke production, coal-tar distillation, chimney sweeping, paving and roofing with coal-tar pitch, and aluminium production (IARC, 2010, 2012b), as well as in diesel exhaust (IARC, 2013). There is also mechanistic evidence, primarily regarding genotoxicity and electrophilicity, for the probable carcinogenicity (IARC Group 2A) of cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, dibenzo[*a,l*]pyrene, and creosotes (IARC, 2010).

Exposure studies have also shown that municipal and wildland firefighters can be exposed to acrolein (IARC Group 2A), which exhibits a variety of key characteristics of carcinogens, including "is electrophilic or can be metabolically activated to an electrophile", "is genotoxic", "alters DNA repair or causes genomic instability", and "induces oxidative stress", "is immunosuppressive", "induces chronic inflammation", and "alters cell proliferation, cell death, or nutrient supply" (IARC, 2021).

Firefighters are also exposed to carcinogenic agents classified in IARC Group 1 (Table 1.1), such as benzene (IARC, 2012b, 2018) and formaldehyde (IARC, 2006, 2012b). Both compounds exhibit the key characteristics of carcinogens "is electrophilic or can be metabolically activated to an electrophile", and "is genotoxic"; in addition, benzene also exhibits the key characteristics "alters cell proliferation, cell death, or nutrient supply", "is immunosuppressive", and "modulates receptor-mediated effects". There is strong mechanistic evidence for the genotoxicity of benzene in humans, and there is moderate mechanistic evidence for the genotoxicity of formaldehyde in humans.

Other agents to which firefighters are exposed are styrene and its related metabolite, styrene-7,8-oxide, which are classified as *probably carcinogenic to humans* (IARC Group 2A). These compounds exhibit many key characteristics of carcinogens, including "is electrophilic or can be metabolically activated to an electrophile", "is genotoxic", "alters DNA repair or causes genomic instability", "alters cell proliferation, cell death, or nutrient supply", and "modulates receptor-mediated effects" (IARC, 2019). There is strong mechanistic evidence that both styrene and styrene-7,8-oxide are genotoxic, and this mechanism can also operate in humans.

Firefighters are also exposed to fire effluents such as polychlorinated dibenzo-*para*-dioxins (PCDDs, also called dioxins) and PCBs that are released in fires only when halogen-containing fuel is present (polyvinyl chloride cables, flame retardants, etc.) (see Section 1.3.1 for further details on their release from fires). 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (2,3,7,8-TCDD) is *carcinogenic to humans* (IARC Group 1) (IARC, 1997, 2012b; Table 1.1). It exhibits several key characteristics of carcinogens, including "induces oxidative stress" and "is immunosuppressive"; and there is strong mechanistic evidence in humans for "modulates receptor-mediated effects", and "alters cell proliferation, cell death, or nutrient supply" (IARC, 1997, 2012b). Several PCB congeners (IARC Group 1) exhibit the key characteristics of carcinogens "is electrophilic or can be activated to an electrophile", "is genotoxic", and "modulates receptor-mediated effects" (IARC, 2015). There is strong mechanistic support for the carcinogenicity of dioxins: receptor-mediated effects involving activation of the aryl hydrocarbon receptor (AhR) activation induce cancer in mouse skin.

Firefighters can be exposed to various carcinogenic (IARC Group 1) metals, including chromium(VI), nickel, and cadmium (IARC, 2012a). These metals cause cancer by genotoxic mechanisms, and chromium(VI) and nickel also affect DNA repair.

Solar radiation, which is classified in IARC Group 1 and causes skin cancer in humans (IARC, 2012c), is also a component of occupational exposure as a firefighter. Solar radiation exhibits a variety of carcinogenic mechanisms, including genotoxicity, induction of DNA repair, and immunosuppression (IARC, 2012c).

Firefighters may undertake night shift work, previously classified as IARC Group 2A (IARC, 2020) (see Section 1.5.2(a) and Table 1.1). There is mechanistic evidence in experimental systems that night shift work exhibits key characteristics of carcinogens, such as "induces chronic inflammation", "is immunosuppressive", and "alters cell proliferation, cell death, and nutrient supply" (IARC, 2020). There is suggestive mechanistic evidence in humans that night shift work alters levels of estrogen, and there is robust evidence that it alters levels of melatonin.

Therefore, occupational exposure as a firefighter encompasses a wide range of agents, including physical, chemical, and/or behavioural human carcinogens and probable human carcinogens, which exhibit a variety of key characteristics of carcinogens (Smith et al., 2016).

4.1 Evidence relevant to key characteristics of carcinogens

This section reviews the mechanistic data for the key characteristics of carcinogens (Smith et al., 2016) encompassed by the agent "occupational exposure as a firefighter". The mechanistic studies were mainly conducted in humans, and the exposure assessments for these studies are reported in Table S1.30 (see Annex 1, Supplementary material for Section 1, online only, available from: https://publications.iarc.fr/615).

Evidence was available on whether occupational exposure as a firefighter exhibits the key characteristics "is genotoxic", "induces oxidative stress", "induces epigenetic alterations", "induces chronic inflammation", "is immunosuppressive", and "modulates receptor-mediated effects". Insufficient data were available for the evaluation of other key characteristics of carcinogens. Mechanistic studies in exposed humans are described in the following categories: (i) structure fires; (ii) wildland fires; (iii) employment as a firefighter; (iv) heat, mental, and/or physical challenge; and (v) catastrophic events. The "structure fires" and "wildland fires" categories were used for studies in which the authors specifically reported the type of fire to which the participants were exposed. The "employment

as a firefighter" category was used when it was unclear what type of fire the firefighters were exposed to or when firefighters may have been exposed to different fire types during the studied period. The "heat, mental, and/or physical challenge" category contains studies in which the studied effect was related to heat or mental and/or physical challenge. The "catastrophic events" category contains studies on firefighters who were exposed to specific agents while responding to a catastrophic event, such as a terrorist attack or chemical factory explosion. These types of exposure are unique events that are unlikely to apply to most firefighters. Not all sections contain all categories, depending on the studies available for each key characteristic of cancer. Within each section, the most informative studies are described first.

4.1.1 Is genotoxic

(a) Exposed humans

See Table 4.1 and Table S1.30 (see Annex 1, Supplementary material for Section 1, online only, available from: https://publications.iarc.fr/615).

(i) Structure fires

Only one study, in firefighters in Canada, examined genetic toxicity after on-shift exposure of all study participants to structure fires. In this study, 31 paired samples of urine collected pre (spot sample) and post (18-hour integrated sample) 24-hour shifts were obtained from 16 non-smoking male municipal firefighters over the course of 19 emergency fire suppression events. Samples were only collected for shifts during which emergency fire suppression events took place (Keir et al., 2017). The unexposed control group included 17 non-smoking male office workers, from whom 18 spot urine samples were collected. Study participants did not consume charbroiled foods and were not exposed to non-occupational combustion sources during the study period. Deconjugated urine extracts were assessed for urinary mutagenicity in bacteria, using the plate incorporation version of the Ames/*Salmonella* reverse mutation assay (*Salmonella typhimurium* strain YG1041 + S9, 9000 × *g* supernatant). There was a significant fold-change of 4.3 in creatinine-adjusted urinary mutagenicity in the post-fire samples compared with the pre-fire samples. There was also a significantly higher level of creatinine-adjusted urinary mutagenicity in the post-fire samples compared with the office worker controls. There was no significant difference in levels of creatinine-adjusted urinary mutagenicity between samples from the office workers and pre-fire samples (Keir et al., 2017). [The Working Group noted that this study was particularly informative because of several aspects of the study design, specifically, because confounding exposures were minimized or eliminated, all individuals participated in on-shift fire suppression events, samples were collected during a reasonable time frame for the end-point examined, and post-exposure samples were compared with pre-exposure paired samples as well as non-firefighter controls.]

DNA damage, measured by the alkaline comet assay, was assessed in peripheral blood mononuclear cells (PBMCs) collected from 12 female and 41 male non-smoking individuals undergoing a 9-month rescue-specialist educational course (Andersen et al., 2018a). Peripheral blood samples were obtained 14 days before a 3-day firefighting exercise (i.e. pre-exposure), immediately after the 3-day course (i.e. post-exposure), and 14 days post-exposure (i.e. 14-day). Firefighting exercises involved the extinction of fires started from wood fuel or from mixed fuel (i.e. wood with foam mattresses and electrical cords). There was a significant increase in DNA damage in post-exposure samples compared with 14-day samples; however, no significant difference for this end-point was found between the pre-exposure and post-exposure samples, nor when the pre-exposure and 14-day samples

Table 4.1 Genetic and related effects in exposed firefighters

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Structure fires							
Urinary mutagenicity (Ames/ Salmonella, YG1041 + S9)	Urine (creatinine-corrected)	Structural [municipal] firefighters Canada, pre/post, 31 samples collected from 16 non-smoking male municipal firefighters pre (spot sample) and post (18-h integrated sample) fire suppression events. Unexposed controls: 18 spot samples collected from 17 non-smoking male office workers. Study participants did not consume charbroiled food and were not exposed to non-occupational combustion sources throughout the study.	16 (31 paired samples, post-fire and pre-fire)	+ ($P < 0.001$)	None	Only municipal firefighter study that examined genotoxicity after on-shift exposure of all individuals to structure fire(s) Exposure assessment: appropriate personal shift PAH exposure measure; firefighting was appropriately evaluated as exposure in the pre/post design	Keir et al. (2017)
			16, 17 (31 post-fire samples from 16 firefighters and 18 control samples from 17 office workers)	+ ($P < 0.001$)			
			16, 17 (31 pre-fire samples from 16 firefighters and 18 control samples from 17 office workers)	–			

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA damage (alkaline comet assay)	PBMC	Training Denmark, pre/post, 53 (12 women and 41 men) non-smoking participants undergoing a 9-month rescue specialist educational course. Firefighting exercises involved extinction of fires from wood fuel or from mixed fuel (i.e. wood with foam mattresses and electrical cords). Samples obtained 14 days before a 3-day firefighting exercise (i.e. pre-exposure), immediately after exposure (i.e. post-exposure), and 14 days post-exposure (i.e. 14-day).	53 (paired samples, post-exposure, and 14 days after)	+ ($P < 0.01$) DNA damage (DSB) frequency was found to be positively correlated with urinary 1-OHP concentration ($P < 0.001$), skin pyrene concentration ($P < 0.001$), and with skin total PAH concentration ($P < 0.001$)		Comet scoring carried out by visual classification into 5 classes rather than by digital image analysis	Andersen et al. (2018a)
			53 (paired samples, post-exposure and pre-exposure)	–		Collection window of 3 days for the post-exposure samples may have been too long to be able to detect some of the exposure-induced DNA damage, potentially resulting in a reduced signal in those samples Pre-exposure samples were collected 2 wk before exposure	
			53 (paired samples, 14-day and pre-exposure)	–			
			53 (paired samples, post-exposure and mean of pre-exposure and 14-day)	–		Pre-exposure samples were collected 2 wk before exposure. Exposure assessment: appropriate personal shift PAH and 1-OHP exposure measures; firefighting was appropriately evaluated as exposure in the pre/post design	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Wildland fires							
Urinary mutagenicity (Ames/ Salmonella, YG1041 + S9)	Urine	Prescribed burns (wildland firefighters) USA, 2015–2018, pre/ post, 19 healthy wildland firefighters (17 men, 2 women) taking part in prescribed burn practices. Samples collected immediately before (pre-shift), immediately after (post-shift), and the morning following (next morning) their shifts. Sampling took place for both prescribed burn (burn day) and regular (non-burn day) work shifts.	19 (27 paired samples, post-shift and pre-shift, 7 burn days)	Crude urine: + ($P < 0.01$) Creatinine-corrected urine: – Cross-shift change in creatinine-corrected urinary mutagenic potency significantly associated with length of smoke exposure ($P = 0.01$)	Burn day participants only	Burn day average shift length, 4.98 ± 1.34 h Number of days between studied shift and previous shift not reported (applies to all entries for this study) No non-firefighter controls (applies to all entries for this study) A significant negative correlation was reported between pre-shift to next-morning creatinine-adjusted urinary mutagenic potency and the concentration of black carbon (as measured using a personal sampler) in wildland fire smoke emissions during the prescribed burn ($P = 0.04$); this result suggested that personal exposure measurements may not be reflective of internal dose among exposed firefighters Exposure assessment: Appropriate personal shift $PM_{2.5}$ and black carbon exposure measures; firefighting was appropriately evaluated as exposure in the pre/post design	Wu et al. (2020a)
		Prescribed burns (wildland firefighters)	19 (27 paired samples, next morning and pre-shift, 7 burn days)	Crude urine: – Creatinine-corrected urine: –	Burn day participants only	Burn day average shift length, 4.98 ± 1.34 h	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Urinary mutagenicity (Ames/ Salmonella, YG1041 + S9) (cont.)		None (wildland firefighters)	19 (14 paired samples, post-shift and pre-shift, 3 non-burn days)	Crude urine: – Creatinine-corrected urine: –	Non-burn day participants only	On non-burn days, firefighters worked at the forest office, with few exceptions Non-burn day shift length not reported	Wu et al. (2020a) (cont.)
		None (wildland firefighters)	19 (10 paired samples, next morning and pre-shift, 3 non-burn days)	Crude urine: – Creatinine-corrected urine: –	Non-burn day participants only	On non-burn days firefighters worked at the forest office with few exceptions Non-burn day shift length not reported	
Urinary mutagenicity (Ames/ Salmonella, YG1041 + S9)	Urine	Prescribed burns (wildland firefighters) USA, 2015, pre/post, 12 healthy non-smoking wildland firefighters (9 men, 3 women) taking part in prescribed burn practices. Samples collected immediately before (pre-shift), immediately after (post-shift) and the morning following (next morning) their shifts. Sampling took place for both prescribed burn (burn day) and regular (non-burn day) work shifts.	12 (48 paired samples, post-shift and pre-shift, 7 burn days)	Crude urine: – Creatinine-corrected urine: – Mean cross-shift changes in urinary mutagenicity were routinely higher for burn day samples, in comparison with non-burn day samples Significant positive associations were observed between the cross-shift change in creatinine-corrected urinary mutagenicity for all study participants and the concentration of urinary MDA ($P = 0.0010$), as well as with urinary 1-OHP ($P = 0.0001$)	Burn day participants only	Pilot study, had small sample size Number of days between last prescribed burn shift and burn day work shift ranged from 1 to > 30; no non-firefighter controls No respiratory protection Exposure assessment: Appropriate personal shift, light-absorbing carbon of $PM_{2.5}$ measured as a surrogate for black carbon, and 1-OHP exposure measures; firefighting was appropriately evaluated as exposure in the pre/post design	Adetona et al. (2019)

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Urinary mutagenicity (Ames/ Salmonella, YG1041 + S9) (cont.)	Urine (crude)		12 (40 paired samples, next morning and pre-shift, 7 burn days)	Crude urine: – Creatinine-corrected urine: –	Burn day participants only		Adetona et al. (2019) (cont.)
	Urine	None (wildland firefighters)	8 (19 paired samples, post-shift and pre-shift, 3 non-burn days)	Crude urine: – Creatinine-corrected urine: –	Non-burn day participants only	Pilot study, had small sample size Number of days between last prescribed burn shift and non-burn day work shift ranged from 3 to 30; no non-firefighter controls On non-burn days, participants reported occupational exposures to vehicle exhaust, diesel, dust, or possible exposures to smoke from nearby smouldering fires	
	Urine		8 (16 paired samples, next morning and pre-shift, 3 non-burn days)	Crude urine: – Creatinine-corrected urine: –	Non-burn day participants only		
DNA damage (alkaline comet assay)	PBMC	None (wildland firefighters) Portugal, cross-sectional, 60 volunteer wildland firefighters with ≥ 1 yr experience and 63 office-worker controls matched on age, gender, and smoking habits.	60, 63	+ ($P < 0.05$)	No significant effects of gender or smoking habits	No specific exposure event Includes current smokers Exposure assessed on the basis of duration of firefighting PPE use unknown; variable was excluded due to small number of responses to this question on questionnaire; PPE misuse is common while fighting wildland forest fires Exposure assessment: no information on specific exposures	Abreu et al. (2017)

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA damage (alkaline comet assay) (cont.)		The study population was stratified into 3 age groups: < 29 yr, 29–38 yr, > 38 yr	20, 19 (< 29 yr), 20, 24 (> 38 yr)	–	No significant effects of gender or smoking habits		Abreu et al. (2017) (cont.)
			20, 20 (29–38 yr)	+ ($P < 0.05$) For exposed volunteer firefighters, level of DNA damage was higher in those aged 29–38 vs < 29 yr ($P < 0.05$)			
		Portugal, cross-sectional, 10 female and 50 male volunteer wildland firefighters with ≥ 1 yr experience and 10 female and 53 male office-worker controls matched on age, gender, and smoking habits.	10, 10 (women), 50, 53 (men)	–			
		Portugal, cross-sectional, 16 smoker and 44 non-smoker volunteer wildland firefighters with ≥ 1 yr experience and 16 smoker and 47 non-smoker office-worker controls matched on age, gender, and smoking habits.	16, 16 (smoker), 44, 47 (non-smoker)	–			

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA adducts (PAH–DNA adducts, ELISA)	PWBC	Wildland USA, 1988, repeated measurements, 37 male and 10 female non-smoking wildland firefighters. Samples obtained 8 wk apart, during early and late forest fire season.	47 (paired samples, late and early forest fire season)	– Additionally, PAH–DNA adduct levels were not associated with cumulative hours of recent firefighting activity; results unaffected when controlling for frequency of charbroiled food consumption. In a follow-up study (Rothman et al., 1995), the impacts of the *GSTM1*-null genotype and *CYP1A1* exon 7 polymorphisms on PAH–DNA adduct levels were investigated; no significant results were found. Early vs late time-points were not compared (i.e. no exposed vs control) within the genotype analysis. There was no association between the PAH–DNA adduct levels and the cumulative hrs of recent firefighting activity in *GSTM1*$^{-/-}$ participants or in those without this genotype	Measures of previous firefighting activity	Did not control for consumption of charbroiled food in late vs early season comparison No non-firefighter controls; for early and late time-points, respectively, there were means of 16 ± 3.15 h and 97.38 ± 15.26 h of self-reported firefighting activity in the 4 wk preceding blood collection Paired samples from same individuals were treated as independent; authors justified this choice by demonstrating that the correlation between repeat adduct measurements was low Exposure assessment: good approach to semiquantitative exposure estimation from questionnaire (prospectively collected activity diary – may be affected by degree of completion)	Rothman et al. (1993)

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA damage (alkaline comet assay)	PBMC	Wildland Portugal, cross-sectional, 93 non-smoking control firefighters, 48 non-smoking exposed firefighters, and 30 smoking exposed firefighters. Exposed firefighters participated in fire suppression activities within 48 h of sampling. Participants excluded if recently consumed grilled, barbecued, or smoked foods.	48 (non-smoking exposed), 93 (non-smoking control) 30 (smoking exposed), 93 (non-smoking control)	– –		No non-firefighter controls or pre/post sampling of the same individuals. All 3 groups reported long-term (i.e. median, > 10 yr) exposure to forest fire emissions Collection window of 48 h may have been too long to be able to detect DNA damage Exposure assessment: firefighting status used for comparison with controls and biomonitoring data used for correlation analysis limited because of only post-exposure collection	Oliveira et al. (2020)
Employment as a firefighter							
Micronucleus frequency	Exfoliated buccal epithelial cells	None (municipal firefighters) India, cross-sectional, 47 male firefighters with ≥ 10 yr service and 40 male office worker controls matched on age, ethnicity, food habit, smoking status, alcohol consumption, nutritional status, and the extent of indoor air pollution in their homes.	47, 40 27 (firefighters served ≥ 20 yr), 20 (firefighters served ≥ 10 to < 20 yr)	+ ($P < 0.01$) + ($P < 0.05$)	Stratified by duration of service	No specific exposure event Exposure assessment: qualitative exposure assignment based apparently on self-report; employment status probably adequate for comparisons made	Ray et al. (2005)

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA adducts (PAH–DNA adducts, ELISA)	PBL	None (municipal firefighters) USA, cross-sectional, 43 male municipal firefighters and 40 male controls matched on age and smoking status.	43, 38	–	Consumption of charbroiled foods, smoking, alcohol intake, race	No specific exposure event; exposure based on history of firefighting activities Study included current smokers and 7 controls had history of occupational exposure to mutagens PPE use was variable Exposure assessment: adequate for primary hypothesis of higher biomarker (DNA damage) levels in firefighters vs controls	Liou et al. (1989)
			37, 29	+ (OR, 3.36; 95% CI, 1.08–10.5)	Consumption of charbroiled foods plus race as White		
			6, 9	–	Consumption of charbroiled foods plus race as non-White	Small sample size	
Sister-chromatid exchange	PBL	None (municipal firefighters)	42, 38	–	Race, history of viral infections, frequency of exposure, PPE use, duration of employment	No specific exposure event; exposure based on history of firefighting activities Study included current smokers and 7 controls had history of occupational exposure to mutagens PPE use was variable Exposure assessment: adequate for primary hypothesis of higher biomarker (DNA damage) levels in firefighters vs controls	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Sister-chromatid exchange	PBL	None (municipal firefighters) Japan, 1998, cross-sectional, male municipal firefighter controls, non-smoking male general population controls matched on age; 2 control populations from the Tokyo sarin disaster study (both not exposed to sarin).	9 (non-smoker firefighter control), 11 (non-smoker general control)	+ ($P < 0.01$)	Non-smoker	No specific exposure event Age not well matched between groups (47.0 ± 2.6 vs 41.5 ± 2.8)	Li et al. (2004)
Miscarriage	NA	None (municipal and wildland firefighters) USA, 2017–2019, cross-sectional, self-reported most recent pregnancy outcome in 1041 female firefighters and 7482 female nurses.	1041, 7482	+ (aSPR, 2.33; 95% CI, 1.96–2.75)	Age	Indirect assessment of genotoxicity	Jung et al. (2021a)
DNA damage (alkaline comet assay)	PBMC	Structural or none (municipal firefighters) Denmark, pre/post, 22 male firefighters, samples collected before and after a 24-h shift.	22 (paired samples, after and before)	–		Firefighters had 3 days off between work shifts Only 14/22 firefighters reported participation in firefighting activities and/or exposure to smoke during their shift Study included current smokers Comet scoring carried out by manual visual classification rather than by digital image analysis Exposure assessment: Firefighting was appropriately evaluated as exposure in the pre/post design; other exposure measures apparently not used in effect analysis; some logistic difficulties	Andersen et al. (2018b)

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA damage (alkaline comet assay) (cont.)			14 (paired samples, after and before)	–	Participated in fire extinction activities	Small sample size	Andersen et al. (2018b) (cont.)
			8 (paired samples, after and before)	–	Did not participate in fire extinction activities	Small sample size	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Catastrophic events							
Somatic mutations (i.e. clonal haematopoiesis detected by deep targeted sequencing)	PWBC	WTC event USA, 2013–2015, cross-sectional, 429 WTC-exposed firefighters and 255 non-WTC-exposed firefighters	429, 255	+ (OR, 2.93; 95% CI, 1.52–5.65; $P = 0.0014$) Result also significant when restricted to firefighters with smoking information and controlling for smoking (OR, 2.78; 95% CI, 1.39–5.59; $P = 0.004$) In both the WTC-exposed and firefighter control populations, mutations were predominantly in *DNMT3A* and *TET2* (involved in DNA methylation control) and were also found in several cancer associated genes (i.e. *TP53*, *U2AF1*, *PTEN*, *TERT*) Most common COSMIC mutation signatures observed in the WTC-exposed firefighters were: (1) ageing; (2) DNA mismatch repair; (3) smoking; and (4) alkylating agents	Age, sex, race/ethnicity	No non-firefighter control group COSMIC mutational signatures were not reported for the non-WTC-exposed firefighters	Jasra et al. (2022)

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Sister-chromatid exchange	PBL	Tokyo sarin disaster (municipal firefighters) Japan, 1998, cross-sectional, male municipal firefighters exposed to sarin while responding to the Tokyo sarin attack, male municipal firefighters not exposed to sarin matched on age and smoking status, non-smoking male general population controls matched on age. Samples obtained 3 yr after exposure. Sarin exposure confirmed by serum ChE activity measured at the time of exposure.	27 (firefighter exposed), 18 (firefighter control)	+ ($P < 0.05$) A significant ($P < 0.05$) positive correlation was observed between the frequency of SCEs in PBLs and the rate of serum ChE activity decrease in the sarin-exposed firefighter group		Unique exposure with limited relevance to the hazards of typical firefighters Exposure assessment: adequate to establish exposed vs unexposed to one-time exposure to sarin and contaminants	Li et al. (2004)
			15 (smoker firefighter exposed), 9 (smoker firefighter control)	+ ($P < 0.05$)	Smoker	Age not well matched (43.0 ± 2.9 vs 38.8 ± 4.1)	
			12 (non-smoker firefighter exposed), 9 (non-smoker firefighter control)	–	Non-smoker	Age not well matched between groups (41.0 ± 3.3 vs 47.0 ± 2.6) Small sample size	
			27 (firefighter exposed), 11 (non-smoker general control)	+ ($P < 0.05$)		Exposed firefighter group composed of 15 smokers and 12 non-smokers, while the general controls only non-smokers	
			12 (non-smoker firefighter exposed), 11 (non-smoker general control)	(+)	Non-smoker	Result for this comparison appears significant, but this was not explicitly stated by the authors	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA strand breaks (alkaline elution)	PBMC	Chemical factory accident (municipal firefighters) Germany, 1993, cross-sectional, 16 male firefighters who worked in a contaminated area after a chemical factory accident for ~8 h without PPE. Samples obtained 19 days (+19 days) and 88 days (+88 days) after exposure; 19 male firefighter trainees (< 2 fires/month) who did not work in the contaminated area, matched on age, alcohol consumption, town of residence, and smoking intensity among smokers; 28 male unexposed non-firefighters, matched on age and smoking intensity among smokers.	16 (paired samples, +16 and +88)	+ ($P < 0.01$) Paired comparison for non-smokers only appears to be significant as well but was not explicitly reported		Unique exposure with limited relevance to the hazards of typical firefighters Exposure assessment: documents likely substantial exposure to quantified mixture of chemicals but no individual exposure measure; contamination exposure status possibly adequate for effect comparisons that were made across groups	Hengstler et al. (1995)
			16 (+19 days exposed firefighters), 19 (trainee firefighters)	+ ($P < 0.05$)	Examined effects of age and alcohol consumption but no significant correlations were observed		
			10 (non-smoking +19 days exposed firefighters), 14 (non-smoking trainee firefighters)	+ ($P < 0.05$)	Non-smoker		
			6 (smoking +19 days exposed firefighters), 5 (smoking trainee firefighters)	–	Smoker	Small sample size	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA strand breaks (alkaline elution) (cont.)			16 (+88 days exposed firefighters), 19 (trainee firefighters)	–	Examined effects of smoking, age, and alcohol consumption, but no significant correlations were observed		Hengstler et al. (1995) (cont.)
			16 (+19 days exposed firefighters), 28 (non-firefighters)	+ ($P < 0.05$)	Examined effects of age and alcohol consumption, but no significant correlations were observed	Alcohol intake and proportion of smokers to non-smokers in non-firefighters was higher than in exposed firefighter group	
			10 (non-smoking +19 days exposed firefighters), 16 (non-smoking non-firefighters)	+ ($P < 0.05$)	Non-smoker		
			6 (smoking +19 days exposed firefighters), 12 (smoking non-firefighters)	–	Smoker	Small sample size	

Table 4.1 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, date, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
DNA strand breaks (alkaline elution) (cont.)			16 (+88 days exposed firefighters), 28 (non-firefighters)	–	Examined effects of smoking, age, and alcohol consumption, but no significant correlations were observed	Alcohol intake and proportion of smokers to non-smokers in non-firefighters were higher than in exposed firefighter group	Hengstler et al. (1995) (cont.)
		Trainee municipal firefighters	19 (trainee firefighters), 28 (non-firefighters)	–		No specific exposure event; firefighters were trainees and had only participated in < 2 fires/month Alcohol intake and proportion of smokers to non-smokers in non-firefighters was higher than in trainee firefighter group	
DNA adducts (PAH–DNA adducts, ^{32}P-postlabelling)	PBMC	Kuwait oil well fire (volunteers) Kuwait, 1991, cross-sectional; 9 male American volunteers in Kuwait for 6 wk to fight oil well fires. PPE was not used, apart from particle face masks used for up to 2 h/day. Samples collected from volunteers before leaving for Kuwait (pre), and within 3 wk of returning (post) to the USA.	9 (paired samples, pre and post)	–		Small sample size Unique exposure with limited relevance to the hazards of typical firefighters Post-exposure samples obtained up to 3 wk after returning to the USA No exposure assessment. Qualitative exposure assignment based on participant recall; did not account for potentially confounding exposure before the collection of baseline samples	Darcey et al. (1992)

aSPR, age-at-pregnancy standardized prevalence ratio; 1-OHP, 1-hydroxypyrene; ChE, cholinesterase; CI, confidence interval; COSMIC, Catalogue Of Somatic Mutations In Cancer; CYP, cytochrome P450; DSB, DNA strand break; DNMT, DNA methyl transferase; ELISA, enzyme-linked immunosorbent assay; GSTM, glutathione *S*-transferase mu; MDA, malondialdehyde; PAH, polycyclic aromatic hydrocarbon; PBL, peripheral blood lymphocytes; PBMC, peripheral blood mononuclear cells; PM, particulate matter; $PM_{2.5}$, particulate matter with a diameter of ≤ 2.5 μm; PPE; personal protective equipment; PTEN, phosphatase and tensin homologue; PWBC, peripheral white blood cell; S9, 9000 × *g* supernatant; SCE, sister-chromatid exchange; TERT, telomerase reverse transcriptase; U2AF1, serine/arginine-rich splicing factor 2; vs, versus; wk, week; WTC, World Trade Center; yr, year.

[a] +, positive; –, negative; +/–, equivocal; (+), positive result in a study of limited quality.

[b] Factors considered for study quality include the methodology and design, reporting, and quality of exposure assessment.

were pooled and the results were averaged and compared with the post-exposure samples. DNA damage levels were significantly higher in samples obtained after exposure to wood-fuel fires compared with mixed-fuel fires. The level of DNA damage was found to be positively correlated with urinary 1-hydroxypyrene (1-OHP) concentration, skin pyrene concentration, and skin total PAH concentration (see Section 1.4) (Andersen et al., 2018a). [The Working Group noted that the pre-exposure samples were collected 2 weeks before the exposure. Given that all study participants were exposed to fires, and especially given the potential for reduced exposure signal, the Working Group considered the positive result for the 14-day versus post-exposure sample, as well as the significant positive association between DNA damage and PAHs and PAH metabolites, many of which are classified in IARC Group 1, 2A, and 2B, to be particularly informative.]

[The Working Group considered both structure fire studies to be especially informative because of the study design (i.e. pre/post samples and all participants attended fire events), and because both studies detected a significant increase in genotoxicity (urinary mutagenicity and DNA damage in peripheral blood). Moreover, one study demonstrated an association between DNA damage and biomarkers of exposure.]

(ii) Wildland fires

Urinary mutagenicity was evaluated in samples from a population of 19 healthy wildland firefighters (17 men, 2 women) taking part in prescribed burn practices with no respiratory protection in the midwestern region, Ohio, USA (Wu et al., 2020a). Spot urine samples were collected from each study participant immediately before (pre-shift), immediately after (post-shift), and the morning following (the next morning) their shifts. Sampling took place for both prescribed burn (burn day) and regular (non-burn day) work shifts. Burn day study participants had a mean shift length of 4.98 ± 1.34 hours. [The Working Group noted that the shift length for non-burn day study participants was not reported, nor was the interval between the previous prescribed burn shift and the studied burn day or non-burn day shift.] Three different firefighting tasks were recorded: burn day holding (i.e. holding prescribed burn fire lines); burn day lighting (i.e. lighting prescribed burns); and non-burn day (i.e. working at the forest fire office, with few exceptions). Urinary mutagenicity was determined in deconjugated urine concentrates via the plate incorporation version of the Ames/*Salmonella* reverse mutation assay (YG1041 + S9 microsomes). For the samples obtained from firefighters who participated in prescribed burns, the crude (i.e. non-creatinine-adjusted) urinary mutagenic potency in post-shift samples was 156% higher than in the pre-shift samples, but after creatinine adjustment, the change was non-significant (16%, $P = 0.09$). [The Working Group noted that although creatinine adjustment corrects for hydration status, this can be less informative for non-homogeneous study populations since the rate of creatinine excretion has been shown to be affected by gender, and the current study included both men and women. However, the Working Group considered both crude and creatinine-adjusted urinary mutagenicity results to be informative.] For the same burn-day shift participants, there was no significant difference in urinary mutagenic potency between the next-morning samples and the pre-shift samples, without or with creatinine adjustment. For the firefighters who worked a regular (i.e. non-burn day) shift, no significant difference was found in the crude or creatinine-adjusted urinary mutagenic potencies for the post-shift versus pre-shift, or the next-morning versus pre-shift comparisons. [The Working Group noted that, since the non-burn day individuals did not attend prescribed burns, the negative results for non-burn day individuals were not unexpected and demonstrated that the increase in urinary mutagenicity occurred in a

narrow time frame after fire exposure. If samples were collected after the chemicals in the exposure had been excreted, then the mutagenic signal would have been missed.] Across all samples, the cross-shift change in creatinine-adjusted urinary mutagenic potency was significantly associated with the duration of smoke exposure. A linear mixed-effects model was used to examine cross-shift changes in urinary mutagenicity between burn and non-burn days; the authors found pre-shift to post-shift changes in crude values of urinary mutagenicity: levels on burn days were 2.79-fold those on non-burn days. This comparison was no longer significant after creatinine adjustment. The effect of the fire suppression task (i.e. "holding" or "lighting") on cross-shift changes in urinary mutagenicity was also examined. Samples from wildland firefighters who were tasked with "holding" had a pre-shift to next-morning difference in creatinine-adjusted urinary mutagenicity that was 1.56-fold that in firefighters who were tasked with "lighting" during prescribed burns. For the pre-shift to post-shift samples, this comparison was not significant (Wu et al., 2020a). [The Working Group noted that a significant negative correlation was reported between pre-shift to next-morning creatinine-adjusted urinary mutagenic potency and the concentration of black carbon (as measured using a personal sampler) in wildland fire smoke emissions during the prescribed burn. This result suggested that personal exposure measurements of black carbon may not be a good surrogate measure of smoke exposure among exposed firefighters. The Working Group noted that there were no non-firefighter controls in this study.]

In a pilot study from the same group, urinary mutagenicity measured by the plate incorporation version of the Ames/*Salmonella* reverse mutation assay (YG1041 + S9 microsomes) was investigated in samples from 9 male and 3 female healthy non-smoking wildland firefighters from a south-eastern region, South Carolina, USA, taking part in prescribed burn practices with no respiratory protection (Adetona et al., 2019). Spot urine samples were collected from each study participant immediately before (pre-shift), immediately after (post-shift), and the morning following (next morning) their shift. Sampling took place for both prescribed burn (burn day) and regular (non-burn day) work shifts. The mean work shift duration for burn days was 4.5 hours (range, 1.9–9.4 hours), and for non-burn days was 6.2 hours (range, 3.9–7.8 hours). The number of days between the last prescribed burn day shift and the studied work shift was 1 to > 30 days for burn day study shifts, and 3–30 days for non-burn day study shifts. Four different firefighting tasks were recorded: burn day holding (i.e. holding prescribed burn fire lines); burn day lighting (i.e. lighting prescribed burns); non-burn day exposure (i.e. involving occupational exposures to vehicle exhaust, diesel, dust, or smoke from nearby smouldering fires); and non-burn day office (i.e. no reported occupational exposures). No significant differences in the crude or creatinine-adjusted mutagenic potencies were found between post-shift and pre-shift samples, or between next-morning and pre-shift samples for either burn day or non-burn day work shifts. However, the mean cross-shift changes in urinary mutagenicity were routinely higher for burn day samples than for non-burn day samples. There was not a significant difference in the cross-shift crude or creatinine-adjusted urinary mutagenic potency between the different firefighting tasks recorded; however, the "lighting" task consistently had the highest mean cross-shift change in urinary mutagenicity. Significant positive associations were observed between the cross-shift (pre-shift to post-shift) changes in creatinine-adjusted urinary mutagenicity and the concentration of urinary malondialdehyde (a marker of oxidative stress; $P = 0.0010$; see Section 4.1.2), as well as with urinary 1-OHP (a PAH metabolite; $P = 0.0001$); see Section 1.4) (Adetona et al., 2019). [The Working Group noted that consistent

trends in cross-shift urinary mutagenicity were observed and that biomarkers of exposure were associated with urinary mutagenicity. These were both suggestive of an effect of the exposure on urinary mutagenicity; however, this pilot study might be underpowered to obtain statistical significance because of the low sample size. Additionally, the Working Group noted the short interval (i.e. as low as 1 day) between previous burn shifts and the studied burn shifts, the occupational exposures to combustion emissions (including smouldering fire) on the non-burn day shifts, and that no non-firefighter controls were included in this study.]

In a study assessing DNA damage levels using the alkaline comet assay, peripheral blood was obtained from 60 volunteer wildland firefighters in Portugal with ≥ 1 year of experience and 63 office-worker unexposed controls matched by age, gender, and smoking habits (Abreu et al., 2017). Personal protective equipment (PPE) used by firefighters was unknown; this variable was excluded because of the poor response rate for this question on the study questionnaire. The DNA damage level in the firefighters was 76% higher than that in the unexposed controls. These data were then analysed to assess the impact of confounding factors on the level of DNA damage between groups; no significant effect of gender or smoking habits was observed. In addition, a significant positive correlation was found between DNA damage detected using the alkaline comet assay and oxidative lesions detected using the formamidopyrimidine DNA glycosylase (Fpg) version of the comet assay (i.e. Fpg-comet), demonstrating the relationship between these two end-points (see also Section 4.1.2). The study population was subdivided into three age groups to study the influence of age: < 29 years, 29–38 years, and > 38 years. A significant increase in DNA damage in the exposed group compared with the control group was only detected in the age group 29–38 years. In the exposed firefighters, those aged 29–38 years had a significantly higher level of blood DNA damage than did the exposed firefighters aged < 29 years. There was no significant difference between the age group > 38 years and the other two age groups, and no effect of age was found among the control firefighters. The effect of duration of recent firefighting activity on the frequency of DNA damage was investigated, but no significant association was observed. Finally, firefighters were stratified into three groups on the basis of years of service (i.e. < 7 years, 7–15 years, and > 15 years); no statistically significant outcomes were found (Abreu et al., 2017). [The Working Group noted that sampling did not follow a specific exposure event and that the study groups included current smokers, which may reduce the signal-to-noise ratio for genotoxicity induced as a result of wildland firefighting.]

A study in 37 male and 10 female non-smoking wildland firefighters from the USA examined PAH–DNA adduct levels in peripheral white blood cells (Rothman et al., 1993). Samples were taken 8 weeks apart, during the early and late forest fire season. For early and late time-points, respectively, there were 16.0 ± 3.2 hours and 97.4 ± 15.3 hours of self-reported firefighting activity in the 4 weeks preceding blood collection. There was no significant difference in levels of detectable PAH–DNA adducts across the season, and no association was found between the cumulative number of hours of firefighting and levels of PAH–DNA adducts (Rothman et al., 1993). [The Working Group noted that there was no control for consumption of charbroiled food in the early versus late season comparison; however, there was control for this when analysing the association between cumulative hours of recent firefighting activity and DNA adduct levels, and the results were unaffected. The Working Group noted that there were no non-firefighter controls.] In a follow-up study, the same group investigated the impact of *GSTM1* null and *CYP1A1* exon 7 genetic polymorphisms, as well as the interaction between the two polymorphisms and PAH–DNA

adduct levels; no significant results were found (Rothman et al., 1995). There was no association between PAH–DNA adduct levels and cumulative hours of recent firefighting activity either in individual who were *GSTM1* null or in those without this genotype (Rothman et al., 1995). [The Working Group noted that late versus early time-points were not compared within the genotype analysis.] [The Working Group noted that the two studies (Rothman et al., 1993, 1995) on DNA adduct induction after exposure to wildland fire were also informative for the key characteristic of carcinogens "is electrophilic or can be metabolically activated to an electrophile".]

DNA damage was assessed by the alkaline comet assay in peripheral blood collected from 48 exposed non-smoking firefighters, 30 exposed smoking firefighters, and 93 control non-smoking firefighters who did not participate in fire suppression activities, in Portugal (Oliveira et al., 2020). Exposed firefighters participated in wildland fire suppression activities within the 48 hours before sampling, for a median duration of 3 hours. All three groups reported long-term (i.e. median, > 10 years) exposure to forest fire emissions. Only firefighters who did not recently consume grilled, barbecued, or smoked foods were included. There were no significant differences between the three groups in the level of peripheral blood DNA damage detected by the alkaline comet assay. [The Working Group noted that there were no non-firefighter controls or pre-/post-exposure sampling of the same individuals, all three groups reported long-term (i.e. median, > 10 years) exposure to forest fire emissions, and the 48-hour collection window may have been too long to be able to detect DNA damage.]

[The Working Group noted that of the five studies on wildland fires, two gave positive results for genotoxicity. Both positive studies also demonstrated correlations with genotoxicity; one demonstrated a correlation between urinary mutagenicity and biomarkers of exposure, as well as firefighting task, and the other demonstrated a correlation between DNA damage detected in the alkaline comet assay and Fpg-sensitive sites (i.e. oxidative DNA damage) in the blood. Moreover, one of the studies that gave negative results was able to demonstrate a correlation between urinary mutagenicity and biomarkers of exposure, as well as firefighting task. All three of the studies with negative results had methodological issues.]

(iii) Employment as a firefighter

The frequency of micronuclei (MN) in exfoliated buccal epithelial cells obtained from 47 male municipal firefighters in India with ≥ 10 years of service; results were compared with those determined in samples obtained from 40 male office worker controls. The firefighter and control populations were comparable in age distribution, ethnicity, food habits, smoking status and frequency, alcohol consumption, nutritional status, and the extent of indoor air pollution in their homes (Ray et al., 2005). Sample collection from firefighters did not follow a specific exposure event. The frequency of MN in exfoliated buccal epithelial cells from firefighters was 2.1-fold higher than that in matched controls. A significant difference in MN frequency was also found when the firefighters were stratified into two groups by duration of service. The firefighters who had served ≥ 20 years had a mean MN frequency that was 1.4-fold higher than that in firefighters who had served < 20 years (Ray et al., 2005). [The Working Group found this study to be particularly informative because the MN frequency is a more persistent biomarker of genotoxicity than general DNA damage, as well as because of the increased MN frequency observed in firefighters with longer service.]

Peripheral blood lymphocytes obtained from municipal firefighters and matched controls were assessed for the presence of PAH–DNA adducts by quantifying levels of antigenicity for benzo[*a*]pyrene diol epoxide (Liou et al., 1989). There was not a significant increase in the

frequency of PAH–DNA adducts in the DNA of peripheral blood lymphocytes from firefighters compared with the controls before adjustment for confounders, or when adjusted for charbroiled food consumption, alcohol consumption, smoking, or race. When controlling for both charbroiled food intake and race, White firefighters had higher levels of PAH–DNA adducts than did White controls (odds ratio, OR, 3.36; 95% confidence interval, CI, 1.08–10.5; 37 firefighters, 29 controls), but this effect was not significant in non-Whites (6 firefighters, 9 controls). [The Working Group noted the low sample size for non-White study participants.] When controlling for both charbroiled food intake and race, and including an interaction term for firefighting and race, the odds ratio was slightly increased for White study participants (OR, 3.56; 95% CI, 1.04–12.12) (Liou et al., 1989). [The Working Group noted that sample collection did not follow a specific exposure event, the study included current smokers, and that seven control participants had a history of occupational exposure to mutagens. Moreover, the study investigating DNA adducts in exposed humans employed as firefighters was also informative for the key characteristic of carcinogens "is electrophilic or can be metabolically activated to an electrophile".] The study also examined the frequency of sister-chromatid exchange (SCE) in peripheral blood lymphocytes of firefighters and control participants (Liou et al., 1989). Firefighting was not associated with an increase in baseline SCE frequency versus that in controls, including when modelling incorporated the frequency of exposure (i.e. number of fires fought in the last 24 hours, month, or year), or other exposure indices, including use of PPE or duration of employment. No association was found between the frequency of baseline SCE and the frequency of PAH–DNA adducts. [The Working Group noted that sample collection did not follow a specific exposure event, the study included current smokers, and that seven control participants had a history of occupational exposure to mutagens.]

The frequency of SCE in peripheral blood lymphocytes from 9 male non-smoking municipal firefighters and 11 male non-smoking general population controls was investigated (Li et al., 2004). The male non-smoking municipal firefighters had a significantly higher baseline frequency of SCE compared with that in the male non-smoking general population controls (Li et al., 2004). [The Working Group noted that the effect may be confounded by age since the ages of these groups were not well matched (i.e. 47.0 ± 2.6 years for firefighters versus 41.5 ± 2.8 years for general population controls). [The Working Group noted that the male municipal firefighters described above served as an unexposed control group as part of a study investigating male municipal firefighters who were exposed to sarin while responding to the 1997 terrorist attack in Tokyo. The firefighter group reported above was not exposed to sarin.]

Using data gathered as part of the Health and Wellness of Women Firefighters Study, the rate of miscarriage occurring while working in the fire service was evaluated among female firefighters compared with that in age-matched female nurses in the USA (Jung et al., 2021a). Firefighters were identified as study participants if they were working in the fire service when they found out about their pregnancy. Among 1041 pregnant firefighters, 138 experienced a miscarriage (22%). Overall, the age-standardized prevalence ratio for miscarriage was 2.33 (95% CI, 1.96–2.75) in firefighters compared with women from the cohort of nurses in the USA. [The Working Group noted that this constitutes an indirect assessment of genotoxicity. The Working Group also noted study design issues, since firefighters were included in this study if they were active firefighters when they found out they were pregnant, so there was no information regarding the duration of time of active firefighting before or subsequent to finding out they were pregnant.]

In a Danish study, PBMCs were collected from 22 male municipal firefighters before and after a 24-hour work shift (Andersen et al., 2018b). Study participants had 3 days off (rest days) between their last work shift and the studied shift. There was no significant difference in levels of DNA damage, identified by the alkaline comet assay, either across the work shift or when the samples were stratified by participation in fire suppression activities during the work shift (Andersen et al., 2018b). [The Working Group noted that only 14 of the 22 firefighters reported participation in firefighting activities and/or exposure to smoke during the studied work shift, and when samples were stratified by participation in fire suppression activities, the Working Group noted the small sample size (n = 14). The Working Group also noted that the study included current smokers. Both the inclusion of current smokers and the fact that not all firefighters participated in fire suppression activities may reduce the ability to detect a DNA damage signal, given the low prevalence of exposure and that levels of DNA damage are higher in smokers than in non-smokers.]

[The Working Group noted that there were six studies in individuals employed as a firefighter. Four reported genotoxic effects, specifically somatic mutations in cancer-related genes, increased frequency of PAH–DNA adducts and SCE in the blood, together with MN frequency in buccal cells. One study provided indirect evidence of genotoxicity (i.e. miscarriage). The only study in this category that gave negative results used a more transient measure of genotoxicity (i.e. alkaline comet assay in blood), and not all study participants were exposed to fires during the study period.]

(iv) Catastrophic events

The following section describes studies in firefighters who responded to specific emergency response situations resulting from catastrophic events, including the World Trade Center (WTC) disaster on 11 September 2001, "9/11", in New York, USA. [The Working Group noted that these are not typical of firefighting responses and that exposure resulting from these events may not be generally applicable.]

As part of a study in WTC-exposed firefighters compared with non-WTC-exposed firefighters, Jasra et al. (2022) used a deep targeted sequencing approach to analyse 237 genes that are frequently mutated in haematological malignancies. In the firefighter control population (n = 255), the observed mutations were predominantly in *DNMT3A* and *TET2*, both of which are involved in regulating DNA methylation, a process that when dysregulated is known to be associated with cancer (see also Section 4.1.3). Additionally, among the most commonly mutated genes were several known to be associated with cancer (Jasra et al., 2022). [The Working Group noted that there were no non-firefighter controls for this study.]

Jasra et al. (2022) examined the rate of clonal haematopoiesis in whole blood obtained from 429 WTC-exposed firefighters compared with 255 non-WTC-exposed firefighters. Clonal haematopoiesis results from somatic mutations in blood stem cells and is associated with an increased risk of haematological cancer. Using a targeted sequencing approach, the authors analysed 237 genes that are frequently mutated in haematological malignancies. A significantly increased odds ratio of clonal haematopoiesis was found in the WTC-exposed firefighters compared with the non-WTC-exposed firefighters (OR, 2.93; 95% CI, 1.52–5.65) after controlling for age, sex, and race/ethnicity. This result was still significant when the analysis was restricted to study participants with smoking information and controlling for smoking as well as age, sex, and race/ethnicity (OR, 2.78; 95% CI, 1.39–5.59). In the WTC-exposed first responders (i.e. a pooled population of 429 firefighters and 52 emergency medical service workers), mutations were predominantly in *DNMT3A* and *TET2*,

both of which are involved in regulating DNA methylation, a process that when dysregulated is known to be associated with cancer (see also Section 4.1.3). Additionally, mutations (mainly missense) were found in several cancer-associated genes (i.e. *TP53*, *PPM1D*, *STAT3*, *KMT2D*, *U2AF1*, *PTEN*, and *TERT*). [The Working Group noted that mutations were found in many similar genes in the firefighter control group (see above).] Mutation spectrum analysis of samples from the WTC-exposed firefighters revealed enrichment for COSMIC (Catalogue Of Somatic Mutations In Cancer) mutational signatures associated with ageing, DNA mismatch repair, smoking (tobacco), and alkylating agents (COSMIC, 2022). The Working Group also noted that COSMIC mutational signatures were not reported for the non-WTC-exposed firefighters, and that there were no non-firefighter controls.]

A study investigated the frequency of SCE in lymphocytes from 27 male municipal firefighters who were exposed to sarin while responding to the 1997 terrorist attack in Tokyo, Japan, 18 male municipal firefighters (matched on age and smoking status) who were not exposed to sarin, and 11 male non-smoking general population controls (matched on age) (Li et al., 2004). Sarin exposure was confirmed by serum cholinesterase (ChE) activity measured at the time of exposure, then peripheral blood samples were taken 3 years after the Tokyo attack. The exposed firefighters had a significantly elevated frequency of SCE in comparison with both the firefighter control group and the general control group. When controlling for smoking status, the frequency of SCE was significantly higher in exposed firefighter smokers than in control firefighter smokers, but a significant difference was not observed between exposed firefighter non-smokers and the non-smoking control firefighters. [The Working Group noted that there appeared to be a statistically significantly elevated frequency of SCE in the exposed firefighter non-smokers in comparison with the general control non-smokers, but the result of this comparison was not reported by the study authors.] Finally, in the sarin-exposed firefighter group, a significant positive correlation was observed between the frequency of SCE in peripheral blood lymphocytes and the rate of serum cholinesterase (ChE) activity decrease (Li et al., 2004).

An accident in a chemical factory in Germany resulted in the release of a mixture of substances, including *ortho*-nitroanisole, *ortho*-anisidine, and *ortho*-chloronitrobenzene. Peripheral blood samples were collected from one exposed group and two reference control groups, and the alkaline elution assay was carried out on all samples to assess the level of DNA damage (Hengstler et al., 1995). The exposed group was composed of 16 male firefighters who had worked in the contaminated area for approximately 8 hours without PPE, and samples were obtained 19 days and 88 days after the exposure. The first reference group was composed of 19 male firefighter trainees who had not worked in the contaminated area, and as trainees, their previous firefighting activity was low (< 2 fires per month). The second reference group was composed of 28 male non-firefighters with no known occupational exposures to genotoxic substances (Hengstler et al., 1995). A paired analysis of the samples from the exposed firefighters revealed that the mean normalized elution rate for the 19-day samples was significantly higher than for the 88-day samples. The mean normalized elution rate for the exposed firefighters (19-day samples) was statistically higher than that for the unexposed firefighters and the non-firefighter controls. The effect of smoking status on these comparisons was also analysed: the non-smoking exposed firefighters (19-day samples) had significantly more DNA damage than the non-smoking controls in either group, whereas no statistical differences were observed for the smokers. [The Working Group noted the small sample size for the smokers-only analysis.] The normalized elution rate was not significantly different between the two reference

groups. The DNA strand breaks in the 88-day samples were not significantly higher than in either reference group. All firefighters in the exposed group were exposed for approximately 8 hours with a single exception: one individual was exposed for 40 hours. The firefighter exposed for 40 hours had the highest normalized elution rate in the exposed group, and the second highest in the study ($n = 63$) (Hengstler et al., 1995). [The Working Group noted that for the detection of alkali-labile sites, which are representative of transient DNA damage, optimal sample collection would occur within hours rather than days.]

The frequency of PAH–DNA adducts was quantified in PBMC DNA from nine male volunteers who travelled to Kuwait for 6 weeks to fight oil-well fires (Darcey et al., 1992). PPE was not used, apart from particle-filtering face masks used for up to 2 hours per day. Blood samples were collected from volunteers before departure for Kuwait, and within 3 weeks of returning to the USA. Average relative adduct labelling (RAL) was similar for pre- and post-exposure samples; however, for a single study participant, RAL in the post-exposure sample was one-fold higher than that in the pre-exposure sample (Darcey et al., 1992). [The Working Group noted the small sample size, the lack of exposure information, and the fact that post-exposure samples were obtained up to 3 weeks after volunteers returned to the USA, which was probably too long to detect an increase in DNA adducts related to participation in fire suppression in Kuwait.] [The Working Group also noted that the study investigating DNA adducts in exposed humans employed as firefighters was also informative for the key characteristic of carcinogens "is electrophilic or can be metabolically activated to an electrophile".]

(b) Human cells in vitro

See Table 4.2.

(i) Primary human cells

The frequency of SCE induced by wildfire and typical air sample extracts was investigated in lymphocytes obtained from a healthy, non-smoking, male donor aged 25 years. High-volume air samplers were used to collect airborne particles from distant wildfires blown over to the sampling location at the University of Kentucky, USA, and typical air samples were used as control (Viau et al., 1982). A significant concentration-related increase was observed in the frequency of SCE induced by both the "smoky" and "typical" samples. When concentration was expressed per cubic metre of air sampled, the potency of the "smoky" sample was 42-fold higher than that of the "typical" sample. When the concentration units were converted from cubic metres of air sampled to milligram of particles, the "smoky" sample induced approximately 20-fold more SCE than did the "typical" sample and approximately 15-fold more revertants, indicating that the higher potency of the "smoky" sample was related to both the quantity and nature of the PM (Viau et al., 1982).

On 13 September 2001, after the WTC disaster, PM was collected from five locations within 0.5 miles [0.8 km] of ground zero. Human primary lymphocytes were exposed to WTC-PM for 20 hours, and phosphorylated H2A histone family member X (γH2AX) foci accumulation, a biomarker of DNA damage, was assessed by fluorescence microscopy. The samples exposed to WTC-PM showed a statistically significant increase in the percentage of cells containing γH2AX foci in comparison with the untreated control lymphocytes (Jasra et al., 2022). Additionally, the authors examined incorporation of the thymidine analogue 5-ethynyl-2′-deoxyuridine (EdU) by click chemistry to study the effect of treatment with WTC-PM on cell cycle progression through S-phase. Lymphocytes treated with WTC-PM did not display a significant increase in the number of EdU-positive

Table 4.2 Genetic and related effects in human cells in vitro

End-point	Tissue, cell line	Test material	Results[a]		Concentration (LEC or HIC)	Comments[b]	Reference
			Without metabolic activation	With metabolic activation			
Primary human cells							
SCE	Human primary lymphocytes	Organic extracts of airborne particles from distant wildfires ("smoky" sample)	+	NT	Air, 16.4 m^3/flask [PM, 3 mg/flask]	Sample potency was 43-fold that of a control typical air sample (in SCE/cell per m^3); when the unit was converted (SCE/cell per mg PM), it was 21-fold	Viau et al. (1982)
γH2AX	Human primary lymphocytes	WTC-PM collected from 5 locations within 0.5 miles [0.8 km] of ground zero on 13 September 2001	+ ($P < 0.0001$)	NT	PM, ≤ 200 µg/mL	Only a single concentration tested Size of PM not described	Jasra et al. (2022)
Cell cycle dysregulation (EdU-incorporation)			– Accumulation of cells in mid to late S-phase was observed but no statistical test result was reported	NT			
Common fragile sites			+ ($P < 0.05$) Significantly altered replication programme, including replication pausing, increase in initiation events, and a significant increase in replication speed	NT			

Table 4.2 (continued)

End-point	Tissue, cell line	Test material	Results[a]		Concentration (LEC or HIC)	Comments[b]	Reference
			Without metabolic activation	With metabolic activation			
Human cell lines							
DNA damage (alkaline comet assay)	Human lung epithelial carcinoma, A549	PM collected in a fire house during a firefighter rescue educational course; samples collected for 7 h/day over 2 days during smoke diving exercises with combustion of standard wooden pallets in the absence or presence of foam mattresses and electrical cords	–	NT	PM, 100 µg/mL	Unwinding/electrophoresis buffer pH not reported, authors used a manual arbitrary scoring scale No metabolic activation	Ma et al. (2020)
Micronucleus frequency	Human lung epithelial carcinoma, A549	EOM from PM_{10} + aerosols collected from biomass burning during the dry season (i.e. intense burning) of 2011 in the Amazon	+	NT	EOM, 100 µg/mL		de Oliveira Galvão et al. (2018)
			+	NT	EOM, 50 µg /mL		

EdU, 5-ethynyl-2′-deoxyuridine; EOM, extractable organic material; HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested; PM, particulate matter; SCE, sister-chromatid exchange; WTC, World Trade Center.

[a]+, positive; –, negative.

[b] Factors considered for study quality include the methodology and design, and reporting.

cells. S-phase cells were further characterized as to what stage they were in (i.e. early, mid, or late S-phase). The authors reported that treatment with WTC-PM resulted in an accumulation of cells in mid to late S-phase, indicating that treatment increased the rate at which cells progress through S-phase (Jasra et al., 2022). [The Working Group noted that statistical results were not reported for this analysis, although a shift in cell populations did seem apparent.] Finally, Jasra et al. (2022) examined WTC-PM-induced effects at common fragile sites, which are genomic hotspots of replication stress. WTC-PM-treated lymphocytes showed a significantly altered replication programme, which included multiple sites of replication pausing, a significant increase in initiation events, and a significant increase in the speed of the replication fork. [The Working Group noted that PM size was not described, and it was unclear how sterility was maintained with PM exposures for 20 hours.]

(ii) Human cell lines

PM was collected using an electrostatic sampler placed in a fire house during the firefighter rescue educational course described above in the study by Andersen et al. (2018a). Samples were collected for 7 hours per day over 2 days during smoke diving exercises involving combustion of standard wooden pallets in the absence or presence of foam mattresses and electrical cords. Induced DNA damage was assessed in cultured human adenocarcinoma cells (A549) using the alkaline comet assay after a 3-hour exposure to PM. No significant treatment effects were observed for PM samples produced with either type of combustion fuel (Ma et al., 2020). [The Working Group noted that the authors did not test the PM in the presence of exogenous metabolic activation.]

Pooled extractable organic material (EOM) from PM_{10} (diameter, ≤ 10 μM) and aerosol samples collected during prescribed burns in the Amazon, Brazil, was assessed for clastogenicity using the MN assay in human A549 cells (de Oliveira Galvão et al., 2018). Samples were collected during both the dry season of 2011 (i.e. intense biomass burning) and wet season of 2011–2012 (i.e. moderate biomass burning). A concentration-dependent increase in the frequency of MN was observed for EOM samples from both the dry season (moderate) and wet season (intense) burning. There was no statistical difference between the MN responses induced by samples collected in the dry season and those collected in the wet season. [The Working Group noted that the authors did not use clean air control samples as a reference.]

(c) Experimental systems

(i) Non-human mammals in vivo

Using the WTC-PM previously described in Jasra et al. (2022), C57BL/6 mice were exposed to a single administration of either phosphate buffered saline (PBS) or 100 μg of WTC-PM (collected from five locations within 0.5 miles [0.8 km] of ground zero) in PBS by oropharyngeal aspiration, with humane killing of animals taking place after 30 days. DNA was isolated from bone marrow cells and used for whole-genome sequencing. Exposure to WTC-PM induced a significant increase in the frequencies of non-synonymous SNPs (single nucleotide polymorphisms, $P = 0.03$), deletions ($P = 0.007$), and indels (small insertions and deletions, $P = 0.046$). [The Working Group noted that the result for insertions alone was not reported; however, this did not appear to be significant unless combined with deletions (i.e. for indels).] Murine mutational signatures were determined after further analysis of the detected SNPs and were compared with the COSMIC human mutational signatures. Murine signatures in bone marrow of WTC-PM-exposed mice were closely matched to the COSMIC signatures for tobacco smoking (SBS04) and defective homologous recombination DNA damage repair (SBS03) (COSMIC,

2022). Additionally, bone marrow cells were sorted by flow cytometry to isolate haematopoietic stem cells (i.e. KSL stem cells). An expansion of the haematopoietic stem cell population was observed in the WTC-PM-treated animals, in comparison with the vehicle control group (Jasra et al., 2022). [The Working Group noted that the size of the PM was not described.]

(ii) Bacteria

See Table 4.3.

Organic extracts of combustion emissions relevant to the occupational exposure of firefighters have been evaluated in two studies using *Salmonella typhimurium* tester strains sensitive to frameshift mutations (i.e. TA98) and to base-pair substitutions (i.e. TA100). The organic extracts from the "smoky" and "typical" air samples, as described in the study by Viau et al. (1982) on wildland fires in Kentucky, USA, were assessed for mutagenicity using the plate incorporation version of the Ames/*Salmonella* reverse mutation assay. The extract from the "smoky" sample gave positive results in TA98 with and without metabolic activation (i.e. S9), and in TA100 without S9 metabolic activation. It was marginally positive in TA100 with S9 metabolic activation. In comparison with the "typical" extract, the "smoky" extract was more potent under all tested conditions, whether the dose unit was presented in terms of cubic metres of air or in terms of micrograms of particles, indicating that the observed genotoxicity was related to both the quantity and nature of the particles. For the "smoky" sample, TA98 was the more sensitive strain, indicating predominantly frameshift mutations, and testing with S9 was more sensitive for the detection of mutations than testing without, indicating that the mutagens require metabolic activation (Viau et al., 1982). Another study examined the bacterial mutagenicity of condensates produced from the oxidative pyrolysis of four polyamides and polyvinyl chloride (PVC), from various industrial areas in France (Chastagnier et al., 1991). Polyamides (also known as nylons) are used in textile, plastic, electronic, automotive, and sporting equipment industries, among others, because of their many desirable properties, which include high tensile strength, flexibility, and heat resistance. The authors found that PVC and all four tested polyamide concentrates gave positive results in the pre-incubation version of the Ames/*Salmonella* assay in both TA98 and TA100 with S9. As with the above study, TA98 was more sensitive than TA100 for all tested condensates, indicating that the mutagenic compounds induce primarily frameshift mutations, and testing with S9 was more sensitive than without, indicating that the mutagens require metabolic activation (Chastagnier et al., 1991).

The EOM from the biomass burning samples from the Amazon, Brazil, described above in the study by de Oliveira Galvão et al. (2018) was also assessed for mutagenicity in the Ames/*Salmonella* assay in both TA98 and YG1041, with and without S9. YG1041 is derived from TA98 strain but contains a plasmid carrying genes encoding nitroreductase and acetyltransferase enzymes. Positive responses were observed for all tested conditions. The EOM from the dry season samples (i.e. intense burning) was more potent than the EOM from the wet season samples (i.e. moderate burning) in both strains. The most potent response was observed in YG1041 without S9. In TA98, the response was approximately equally potent with and without S9. Taken together, the mutagenic responses observed in this study were induced by both directly and indirectly acting frameshift mutagens, and the YG1041 response indicated a contribution from directly acting nitroaromatic compounds. [The Working Group noted that de Oliveira Galvão et al. (2018) measured nitro-PAHs in the EOM samples, which corroborates this statement. The Working Group also noted that the authors did not use clean air control samples as a reference.]

Table 4.3 Genetic and related effects in bacterial experimental systems

Test system (species, strain)	End-point	Test agent	Results[a]		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA98	Reverse mutation	Organic extracts of airborne particles from distant wildfires ("smoky sample")	+	+	1.02 m^3 air/plate [PM, 188 µg/plate] without activation, 2.03 m^3 air/plate [PM, 376 µg/plate] with activation	The "smoky" extract was more potent than the "typical" air extract, up to 38-fold in rev/plate per m^3 of air (16-fold in rev/µg PM per plate)	Viau et al. (1982)
Salmonella typhimurium TA100		Organic extracts airborne particles from distant wildfires ("smoky sample")	+	(+)	4.07 m^3 air/plate [PM, 753 µg/plate] without and with activation	The "smoky" extract was more potent than the "typical" air extract, up to 18-fold in rev/plate per m^3 of air (6-fold in rev/µg PM per plate) Result with metabolic activation considered marginally positive as dose-related increase was observed but only reached 1.8-fold the control value	

Table 4.3 (continued)

Test system (species, strain)	End-point	Test agent	Results[a]		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA98 (pre-incubation)	Reverse mutation	Condensate from oxidative pyrolysis of polyvinyl chloride	+	+	NR	Potency reported but not individual test concentrations	Chastagnier et al. (1991)
		Condensate from oxidative pyrolysis of polyamide 6	+	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 6–10	–	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 11	–	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 6–6	+	+	NR	Potency reported but not individual test concentrations	
Salmonella typhimurium TA100 (pre-incubation)		Condensate from oxidative pyrolysis of polyvinyl chloride	+	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 6	–	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 6–10	–	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 11	–	+	NR	Potency reported but not individual test concentrations	
		Condensate from oxidative pyrolysis of polyamide 6–6	+	+	NR	Potency reported but not individual test concentrations	

Table 4.3 (continued)

Test system (species, strain)	End-point	Test agent	Results[a]		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA98	Reverse mutation	EOM from PM_{10} + aerosols collected from biomass burning during the dry season (i.e. intense burning) of 2011 in the Amazon	+	+	25 µg EOM/plate without activation, 12.5 µg EOM/plate with activation		de Oliveira Galvão et al. (2018)
Salmonella typhimurium TA98		EOM from PM_{10} + aerosols collected from biomass burning during the wet season (i.e. moderate burning) of 2011 in the Amazon	+	+	5 µg EOM/plate without activation, 50 µg EOM/plate with activation		
Salmonella typhimurium TA100		EOM from PM_{10} + aerosols collected from biomass burning during the dry season (i.e. intense burning) of 2011 in the Amazon	+	+	50 µg EOM/plate without activation, 250 µg EOM/plate with activation		
Salmonella typhimurium TA100		EOM from PM_{10} + aerosols collected from biomass burning during the wet season (i.e. moderate burning) of 2011 in the Amazon	+	+	250 µg EOM/plate without activation, 500 µg EOM/plate with activation		

EOM, extractable organic material; HIC, highest ineffective concentration; LEC, lowest effective concentration; PM, particulate matter; PM_{10}, particulate matter with diameter ≤ 10 µm; NR, not reported; rev, revertants.

[a] +, positive; (+), positive in a study of limited quality.

4.1.2 Induces oxidative stress

(a) Exposed humans

See Table 4.4.

A group of studies assessed the association between oxidative stress and firefighting in exposed humans, with a wide variety of end-points measured. End-points included those that are indicative of oxidative DNA damage, such as oxidized guanine species (Ox-GS), including 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG). Ox-GS are formed during oxidized DNA repair and therefore act as biomarkers for acute redox activity. Oxidative DNA damage was also assessed via the comet assay with measurement of formamidopyrimidine DNA glycosylase (Fpg), providing detail on the concentration of DNA oxidized purines. Other biomarkers measured can be formed into two categories, antioxidants and markers of free radical activity or damage, since oxidative stress is the result of an imbalance between antioxidant capacity and free radicals. Antioxidant-related biomarkers included in these studies are: catalase (CAT), glutathione (GSH), glutathione peroxidase (GSH-Px), glutathione reductase (GR), superoxide dismutase (SOD), thiol groups, total antioxidant activity, trolox equivalent antioxidant capacity (TEAC), total radical-trapping antioxidant potential (TRAP), and uric acid (UA). Reactive oxygen species (ROS) and damage markers included are: 8-isoprostane, 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF2α), advanced oxidation protein products (AOPP), receptor for advanced glycation end-products (RAGE), conjugated diene, disulfide, dichlorofluorescein (DCF), gamma glutamyl transpeptidase (GGT), oxidized glutathione (GSSG), hydrogen peroxide (H_2O_2), lipid hydroperoxides (LOOH), malondialdehyde (MDA), myeloperoxidase (MPO), 3-nitrotyrosine (3-NT), and protein carbonyls (PC).

Biomarkers of oxidative stress were investigated in relation to a variety of exposure types; these included: structure fire exposures, wildland fire exposures, firefighters with a history of unclassified exposures, and acute exercise or smoke exposure with no fire suppression activities.

(i) Structure fires

Two studies (Andersen et al., 2018a; McAllister et al., 2018) assessed structure training fire exposures, and three studies (Al-Malki et al., 2008; Keir et al., 2017; Andersen et al., 2018b) investigated the consequence of operational structure fires on oxidative stress.

PBMCs collected from trainee firefighters from Denmark 14 days before, immediately after, and 14 days after exposure during a 3-day training course revealed a significant increase in oxidative DNA damage (i.e. Fpg-sensitive sites) in samples collected immediately after exposure compared with those collected before but not 14 days after exposure. A non-significant trend was observed for increased Fpg-sensitive sites in samples collected after exposure to fires with wood fuel in comparison with mixed-fuels. The frequency of Fpg-sensitive sites was positively correlated with skin total PAH concentration, but not with urinary 1-OHP (Andersen et al., 2018a). [The Working Group noted that this study was particularly informative because of the large sample (n = 53) of non-smoking participants, pre/post design, and the significant association between oxidative DNA damage and PAH content of skin wipes from the neck. Findings may suggest that fuel type may be a contributory factor to oxidative stress occurrence.] In a study performed in the USA, training fire search and rescue (~17–20 minutes) within a heat house resulted in no association with GSSG, GSH/GSSG, or SOD levels, but caused increased CAT and decreased AOPP levels; the antioxidant supplement curcumin had no effect (McAllister et al., 2018) [The Working Group considered that

Table 4.4 End-points relevant to oxidative stress in exposed firefighters

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Structure fires						
Blood (PBMC)	Training (3-day course) Denmark, pre/post study trainee male and female firefighters, repeated measures design 14 days before, immediately post-, and 14 days post-exposures	53 (19 exposed to wood combustion, 34 exposed to wood, foam mattresses and electrical cord combustion)	↑ Fpg-sensitive sites post vs pre ($P < 0.05$) ↑ Fpg-sensitive sites immediately post vs combined pre and 14 days post ($P < 0.05$) Fpg-sensitive sites positively correlated with skin total PAH concentrations	Non-smokers, same supply of food	Limited age range of participants (18–26 yr); PPE and breathing apparatus worn; comet scoring carried out by visual classification Exposure assessment: appropriate personal shift PAH and 1-OHP exposure measures; firefighting was appropriately evaluated as exposure in the pre/post design	Andersen et al. (2018a)
Blood	Training (heat house, victim search and clear) USA, male firefighters, pre/post trial, repeated measures design, exposure with fire vs exposure without fire	10	↑ GSH greater at all time-points (including pre) with fire ($P < 0.05$) No change in GSSG, GSH/GSSG, SOD pre- to post-exposure both with and without fire ↑ CAT both with and without fire ($P = 0.005$) ↓ AOPP 30 min post exercise, both with and without fire ($P = 0.0009$)	Smoking habits, cardiovascular diseases	Randomized to job role within task; small sample size Exposure assessment: exposure to heat appropriately tested as exposure for the effects assessments that were done in the experiment	McAllister et al. (2018)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Blood (PBMC)	Multi (24-h shift included car, basement, waste container, apartment fires) Denmark, male firefighters, pre/post	22 (14 exposed, 8 non-exposed)	↓ in Fpg-sensitive sites after shift for all participants ↓ in Fpg associated with fire suppression activities	No exposure for 3 days prior; similar timing of cross-shift sample collection	Small sample size; underpowered for statistical analysis; study included smokers; comet scoring carried out by manual visual classification Exposure assessment: firefighting was appropriately evaluated as exposure (PAH, 1-OHP measures) in the pre/post design; other exposure measures apparently not used in effect analysis; some logistic difficulties	Andersen et al. (2018b)
Urine	Residential or commercial operational fire Canada, male firefighters, pre/post and comparison to office worker controls	16 (31 pre and post sample pairs), 17 (18 samples)	No change in 8-iso-PGF2α pre to post	Smoking habit, non-exposure combustion sources, age, urine dilution (creatinine adjustment)	Small sample size given possible variability in operational fire roles and exposure duration; end-point may be altered by oxygen availability via breathing apparatus Exposure assessment: appropriate personal shift PAH exposure measure; firefighting was appropriately evaluated as exposure in the pre/post design	Keir et al. (2017)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Blood	Operational fire (no other detail) Saudi Arabia, male firefighters, cross-sectional, firefighters from 2 locations vs non-exposed control	37 (28, 9), 9	No change in GGT	Cardiovascular disease, sample collection timing	GGT showed non-significant increase, but firefighter groups were not combined in the analysis, possibly underpowered; limited sample analysis detail Exposure assessment: temporality issue is somewhat handled by collection of samples among firefighters within first hour after firefighting	Al-Malki et al. (2008)
Wildland fires						
Blood	Training (wildland fire exposure as part of 2 wk pre-season training) USA, pre/post study, male and female wildland firefighters, repeated measures design, day 1 vs day 4 vs day 8 vs day 11	18 men and 3 women	↑ LOOH day 4, 8, 11 vs day 1 ($P < 0.05$) ↑ 3-NT day 8 vs day 4 ($P < 0.05$) ↓ 8-Isoprostane day 4 and 8 vs 1 ($P < 0.05$) No change in PC	Sample timing	Variability of training tasks; limited detail of fire exposure; limited detail regarding participant health (smoking habit, cardiovascular disease); no non-exposed controls Exposure assessment: Specific firefighting exposure was not evaluated but effect of involvement in firefighting appropriately tested with the study design	Gurney et al. (2021)
Exhaled breath condensate	Wildland prescribed burn USA (south-eastern), male and female wildland firefighters, pre/post, immediately post and morning after exposure compared for day type (exposure vs control)	12 (84 exposure sample sets),12 (36 non-exposure sets)	No change in 8-isoprostane pre- to post-exposure or between exposure and control at any time-point	Cardiovascular and respiratory diseases	No detail of control non-burn day activity Exposure assessment: firefighting appropriately used for analysis in the pre/post comparisons; no personal monitoring data was used in analysis	Wu et al. (2020b)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Urine	Wildland prescribed burn USA (midwest), male and female wildland firefighters, pre/post, immediately post- and morning after exposure compared for day type (exposure vs control) and work task (holding fire, lightly fire, non-burn exposure, non-burn office work)	19 (81 pre- and post-exposure sample pairs), (39 non-exposure pairs)	↑ Ox-GS next morning compared with pre with exposure ($P = 0.03$) ↑ 8-Isoprostane and Ox-GS changes greater on burn than non-burn days ($P = 0.03$ and 0.02, respectively) No change in MDA Positive correlation between change in MDA and black carbon ($P = 0.01$)	Urinary dilution (creatinine adjustments)	Non-burn exposure day tasks may lead to misclassification of exposure Exposure assessment: firefighting and shift personal exposure to $PM_{2.5}$ and black carbon appropriately used for analysis in the pre/post comparisons	Wu et al. (2020a)
Urine	Wildland prescribed burn USA (south-eastern), male and female wildland firefighters and volunteers, pre/post, immediately post- and morning after exposure compared for day type (exposure vs control) and work task (holding fire, lightly fire, non-burn exposure, non-burn office work)	12 (10 firefighter, 2 volunteers; 48 pre- and post-exposure sample pairs, 40 including morning after), 8 (19 pre- and post-non-exposure pairs, 16 including morning after)	No change in 8-isoprostane or MDA Positive correlation between MDA change and 1-OHP ($P = 0.0001$)	Chewed tobacco, age, career length, shift duration, days since last burn, urinary dilution (creatinine adjustments)	Small sample size; non-burn exposure day tasks may lead to misclassification of exposure; sample analysis blinded Exposure assessment: appropriate personal shift $PM_{2.5}$, black carbon, and 1-OHP exposure measures; firefighting was appropriately evaluated as exposure in the pre/post design	Adetona et al. (2019)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Urine	Wildland fire (2 days of 12.5 h) USA, male wildland firefighters, cross-sectional, non-exposed vs exposed from recent 5 days	20, 18	↑ 8-OHdG in exposed ($P = 0.01$), although not significant when controlled for levoglucosan ($P = 0.07$) No change in 8-isoprostane	Smoking, urine dilution (creatinine adjustment)	Asthma reported was physician diagnosed; no control for diet levoglucosan; no pre-exposure sample collection; limited detail regarding non-exposed firefighter tasks Exposure assessment: levoglucosan concentrations may not well reflect variability in exposure between firefighters	Gaughan et al. (2014b)
Blood (PBMC)	Wildland (forest) fire Portugal, firefighters, cross-sectional, non-smokers exposed vs smokers exposed vs station control	48 (non-smokers exposed), 30 (smokers exposed), 93	↑ Net-Fpg in non-smokers exposed vs control ($P < 0.001$) and smokers ($P < 0.05$) Positive correlation Net-Fpg with urinary 2-OHF and 1-OHP ($P < 0.05$)	Smoking habits, diet, cardiovascular diseases	Post samples collected at end of shift, exposure time varied from 2 to 12 h, time from end of exposure to sampling was unclear; unclear if male and/or female participants Exposure assessment: firefighting status used for comparison with controls and biomonitoring data used for correlation analysis limited because of only post-exposure collection	Oliveira et al. (2020)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Urine	Wildland prescribed burn USA (south-eastern), male and female wildland firefighters, pre/post, model analysis of end-point changes with $PM_{2.5}$ exposure, career length, and age	17 (providing 94 pre and post sample pairs)	↑ 8-OxodG pre to post with ≤ 2 yr career length ($P = 0.04$). ↓ 8-OxodG pre to post with ≥ 10 yr ($P = 0.03$) MDA: no association with age, career length, or $PM_{2.5}$	Second-hand smoke exposure, smoking, urinary dilution (creatinine adjustments)	Large variation in number of samples provided per participant; pre and post samples with different time conditions and undefined period between burn days Exposure assessment: appropriate personal shift $PM_{2.5}$ exposure measure; firefighting was appropriately evaluated as exposure in the pre/post design	Adetona et al. (2013)
Blood (PBMC)	History of wildland exposure Portugal, volunteer firefighter (male and female) and non-exposed office workers, cross-sectional	60, 63	No change in Net-Fpg Positive correlation between comet assay-detected DNA strand breaks and Net-Fpg ($P < 0.05$)	Age, gender, smoking habits, BMI, respiratory pathologies, recent exposures	Not controlled for PPE use; limited statistical analysis data presented; sample analysis blinded Exposure assessment: no information on specific exposures	Abreu et al. (2017)
Employment as a firefighter						
Urine	Operational fire (type not defined) Republic of Korea, male firefighters, cross-sectional, exposed ≥ 8 h in 5 days vs exposed < 8 h in 5 days vs non exposed	49 (13 ≥ 8 h, 36 < 8 h), 24	No change in 8-OHdG	Smoking, diet, age, BMI, urine dilution (creatinine adjustment)	No detail on type of fire Exposure assessment: misclassification of length of time unlikely, but non-consideration of intensity (amount of exposure) could be an issue	Hong et al. (2000)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Blood	History of exposure. Shift week (but type not clearly defined) Türkiye, male firefighters vs office worker controls, cross-sectional	100, 50	↑ Disulfide in firefighters ($P < 0.001$) ↑ Disulfide:thiol % ratio ($P < 0.001$)	Cardiovascular disease, antioxidant supplements, smoking habit	Samples collected at end of shift week, no control for time since recent exposure, recent exposure number, physical activity or diet; no measurement post exercise or fire exposure Exposure assessment: Employment as a firefighter possibly adequate for effects comparisons that were made; rationale for choice of arsenic uncertain	Gündüzöz et al. (2018)
Exposure to heat, mental, or physical challenges						
Blood	No fire exposure (strength, anaerobic, and aerobic fitness test) Brazil, male military firefighters, pre/post treadmill fitness test, RCT	30 (with resveratrol), 30 (without resveratrol)	No change in all parameters pre- to post-exposure fitness test	Energy intake before exercise	Unknown firefighting exposure history; no heat/live fire/PPE Exposure assessment: engagement in experimental fitness test appropriately tested as exposure for the effects assessments that were done in the experiment; compliance with taking capsule was not reported	Macedo et al. (2015)
Blood	No fire exposure (treadmill exercise in temperate environment) Republic of Korea, male volunteer firefighters, pre/post treadmill exercise in PPE vs regular clothing, 25 °C at 9 METs	12 (PPE),12 (regular clothing)	↑ Exercise in PPE increased CD ($P < 0.05$) and TRAP ($P < 0.01$) No change in SOD, GSH-Px, or CAT	Cardiovascular disease, antioxidant nutrient intake	No heat/live-fire exposure; small sample size; limited ecological validity to firefighter tasks; no detail of regular clothing; no statistical comparison between PPE and regular clothing trials Exposure assessment: PPE-wearing appropriately tested as exposure for the effects assessments that were done in the experiment	Park et al. (2016)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Blood	No fire exposure (6-week training programme) USA, male firefighters, pre/post time-restricted feeding (TRF) over 6 wk	15 (pre vs post)	↓ TRF decreased AOPP ($P = 0.02$) and AGE ($P = 0.05$)	Diet, training status, cardiorespiratory diseases	Sequential design without control group; no measurement post exercise or fire exposure Exposure assessment: firefighting-specific exposure was not assessed	McAllister et al. (2020)
Exhaled breath condensate, blood	Wood smoke (treadmill exercise in temperate environment with wood smoke) USA, male firefighters, pre/post randomized cross-over, filtered air vs wood smoke	10 (pre vs post); no control group	↓ Immediately post-exposure 8-isoprostane was lower than in filtered air ($P < 0.05$) ↑ 1 h post-exposure 8-isoprostane increased compared with filtered air ($P < 0.05$) No change in MPO or H_2O_2	Similar timing of data collection, fitness, smoking habits	No details on clothing worn; shorter duration exposure than wildland fire; small sample size Exposure assessment: the experimental exposure to different concentrations appropriate for the pre/post design	Ferguson et al. (2016)

Table 4.4 (continued)

Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments[b]	Reference
Blood	Wood smoke (treadmill exercise in temperate environment with smoke) USA, experimental RCT, clean air vs wood smoke low (250 μg/m^3) vs woodsmoke high (500 μg/m^3) $PM_{2.5,}$ pre, post, 1 h post	10 (pre vs post); no control group.	↓ UA post combined smoke exposure ($P = 0.032$) ↑ TEAC post vs pre for both clean air ($P = 0.015$) and high exposure ($P = 0.001$) and 3-NT post vs pre for combined smoke exposure ($P = 0.049$) ↓ LOOH 1 h post high smoke exposure ($P = 0.036$) ↑ 8-Isoprostane and MPO with low ($P = 0.004$, $P = 0.035$) and high ($P = 0.009$, $P = 0.019$) exposure No change in PC	Similar timing of data collection, respiratory disease, wood smoke exposure, fitness level	Some statistical comparisons to control unclear; no details on clothing worn; shorter duration exposure than wildland fire; small sample size Exposure assessment: exposure was relative to wildfire situation but exposure vs non-exposure to woodsmoke appropriately tested for the assessment of effects	Peters et al. (2018)

AGE, advanced glycated end-products; AOPP, advanced oxidation protein products; BMI, body mass index; CAT, catalase activity; CD, conjugated diene; DCF, dichlorofluorescein; Fpg, formamidopyrimidine DNA glycosylase; GGT, gamma glutamyl transpeptidase; GR, glutathione reductase; GSH, glutathione; GSH-Px, glutathione peroxidase activity; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; 8-iso-PGF2α, 8-iso-prostaglandin $F_{2α;}$ LOOH, lipid hydroperoxides; MET, maximal exercise treadmill training; MDA, malondialdehyde; MPO, myeloperoxidase; 3-NT, 3- nitrotyrosine; 2-OHF, 2-hydroxyfluorene; 8-OHG, 8-hydroxyguanosine; Ox-GS, oxidized guanine species; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; PAH, polycyclic aromatic hydrocarbon; PBMC, peripheral blood mononuclear cells; PC, protein carbonyls; PM, particulate matter; PPE, personal protective equipment; RCT, randomized controlled trial; SOD, superoxide dismutase; TEAC, trolox equivalent antioxidant capacity; TRAP, total radical-trapping antioxidant potential; TRF, time restriction feeding; UA, uric acid; vs, versus; yr, year.

[a], ↑, increase; ↓, decrease.

[b] Factors considered for study quality include the methodology, design, reporting, and quality of exposure assessment.

this small sample included firefighter participants who were healthy with consistently high levels of physical activity; consequently they may not provide a valid reflection of the general firefighter population. As noted in Section 1.2, there may be a similar or greater prevalence of obesity in firefighters compared with the general population.]

Assessment of PBMCs collected from operational firefighters from Denmark across shifts indicated a decrease in the frequency of Fpg-sensitive sites, using the Fpg-comet assay, after a 24-hour work shift and when compared with PBMCs from non-exposed firefighters on the same shifts (Andersen et al., 2018b). [The Working Group noted the small sample size (14 out of 22 participants exposed to fire) and the inclusion of current smokers as participants. These factors may have reduced the ability to detect oxidative DNA damage, given the lower prevalence of exposure and the association between smoking and increased oxidative DNA damage.] Emergency structure fire suppression has also been reported to result in no cross-shift changes in urinary 8-iso-PGF2α (Keir et al., 2017). [The Working Group highlighted the fact that 8-iso-PGF2α levels may be altered by the hyperoxic conditions resulting from breathing apparatus use.] A further assessment of operational fires revealed that post-exposure levels of serum GGT were elevated in comparison to non-exposed controls, but not significantly (Al-Malki et al., 2008). [The Working Group considered that the absence of pre-exposure samples and details of fire exposure type limited the conclusions that could be drawn from this result.]

(ii) Wildland fires

Effects on oxidative stress markers were assessed in one study on wildland fire training (Gurney et al., 2021), and a further five studies on acute wildland fire exposures (Adetona et al., 2013, 2019; Gaughan et al., 2014a; Wu et al., 2020a, b). Two additional cross-sectional studies compared wildland firefighters with non-exposed controls (Abreu et al., 2017; Oliveira et al., 2020).

Wildland fire training resulted in decreased levels of 8-isoprostane, no change in PC, and increases in levels of plasma LOOH and 3-NT (Gurney et al., 2021). [The Working Group noted that minimal exposure details were provided for the wildland training.] Cross-shift assessment and comparison of exposure with non-exposure days revealed no significant changes in urinary or exhaled breath condensate (EBC) 8-isoprostane by enzyme-linked immunosorbent assay (ELISA) analysis (Gaughan et al., 2014a; Adetona et al., 2019; Wu et al., 2020b), although Wu et al. (2020b) did report a marginal but non-significant cross-shift increase in levels of 8-isoprostane on burn days. Gaughan et al. (2014a) reported elevated levels of 8-OHdG as measured by ELISA urine analysis in firefighters after recent fire suppression activities compared with firefighters with no recent exposure; however, after adjusting for urinary levoglucosan, which is a cellulose pyrolysis product that may indicate smoke exposure, differences were no longer present. [The Working Group noted that a major contributor for levoglucosan is also diet, which was not controlled for.] Alternately, a positive correlation was noted between pre- and post-wildland exposure changes in urinary MDA levels and exposure markers (1-OHP), despite no significant change in MDA levels (Adetona et al., 2019) (see Section 4.1.1). [The Working Group noted variations in the details provided regarding tasks completed on non-exposure days and sample collection time-points; also, timing of sample collection by Wu et al. (2020b) may not have been optimal for 8-isoprostane measurement.]

A more comprehensive analysis of creatinine-corrected oxidative stress markers in urine after wildland fire exposure revealed increases in Ox-GS the morning following the burn compared with pre-exposure levels; Ox-GS and

8-isoprostane changes were also greater on burn days compared with non-burn days (Wu et al., 2020a). Biomarkers were analysed by ELISA, with Ox-GS analysed as a combined ELISA including 8-OHdG, 8-hydroxyguanosine (8-OHG), and 8-hydroxyguanine (8-OHGua). A positive correlation between pre- and post-exposure change in MDA levels and black carbon exposure was also reported; however, no significant change in MDA levels pre- to post-exposure was noted (Wu et al., 2020a). [The Working Group judged this study as particularly informative because of the large number of paired samples (n = 81 burns and n = 39 non-burns), and the significant association between MDA and an exposure marker.]

The association between oxidative stress and career duration and age has also been investigated in firefighters from a south-eastern region of the USA. Despite overall urinary MDA and 8-oxodG levels as measured by HPLC-EDC being similar before and after a wildland firefighting shift, an increased cross-shift change in 8-oxodG levels was noted in firefighters with ≤ 2 years of experience in the role, whereas firefighters with ≥ 10 years of experience had a decrease in 8-oxodG levels (Adetona et al., 2013). Change in MDA levels from pre- to post-wildland firefighting shift was not associated with age, length of firefighter career, or $PM_{2.5}$ exposure (Adetona et al., 2013). [The Working Group noted variable exposure accumulation due to sample collection across numerous work shifts, although a large number of sample pairs (n = 94) were included in the analysis. Additionally, although age was previously reported to be associated with MDA increase, the age range was small (21–44 years), and therefore the lack of correlation was not unexpected.]

Cross-sectional analysis of blood samples from non-smoking Portuguese firefighters exposed to forest fires within the last 48 hours exhibited a level of oxidative lesions (identified using the Fpg-modified comet assay) that was 316% higher than that of the non-smoking control firefighters, and 112% higher than that of the tobacco smoke- and fire-exposed firefighters (Oliveira et al., 2020). Regarding the frequency of oxidative DNA lesions, there was a positive correlation with urinary 2-hydroxyfluorene concentration and urinary 1-OHP concentration in both exposed groups, as well as a borderline significant positive correlation with urinary 1-hydroxyphenanthrene concentration in the non-smoking exposed firefighters. [The Working Group noted that the sample size was large (n = 78 exposed, n = 93 non-exposed), and the association between oxidative stress and exposure markers was informative.]

Cross-sectional comparison of baseline blood samples revealed a higher frequency of oxidative DNA damage (detected using the Fpg-modified comet assay) in Portuguese wildland firefighters than in office workers, matched for age, gender, and smoking habits, although this difference was not significant (Abreu et al., 2017). This was despite a positive correlation reported between the level of Fpg-sensitive sites and the level of DNA damage detected using the alkaline comet assay (see Section 4.1.1). An increasing level of oxidative DNA damage with longer service was noted; however, this association was not significant. [The Working Group noted the lack of information regarding sample timing in relation to firefighting tasks but did regard the non-firefighter comparison group as a strength of the study, because of the matched characteristics.]

(iii) Employment as a firefighter

Two cross-sectional studies (Hong et al., 2000; Gündüzöz et al., 2018) assessed oxidative stress in firefighters with a history of exposure. 8-OHdG levels in the urine, as measured by ELISA, were not different in firefighters with ≥ 8 hours or < 8 hours fire exposure in the previous 5 days compared with firefighters with no exposure (Hong et al., 2000). Comparison of baseline samples from firefighters with officer controls revealed increased serum disulfide

levels and disulfide:thiol percentage ratios in firefighters, with a positive correlation between disulfide and urinary arsenic levels (Gündüzöz et al., 2018). [The Working Group noted that no information was provided regarding time since last exposure or fire types. Firefighter and control (officers) groups were well matched for age and work time; however, history of exposure for officers was not detailed.]

(iv) Exposure to heat, or mental and/or physical challenge

Three studies (Macedo et al., 2015; Park et al., 2016; McAllister et al., 2020) investigated the consequence of exercise with or without PPE on oxidative stress. In firefighter fitness tests without PPE, no changes were stimulated in blood thiol groups, total plasma antioxidant activity, SOD, CAT, GR, GSH-Px, or 8-OHdG and 8-isoprostanes (measured by ELISA) (Macedo et al., 2015). In firefighters completing a 6-week exercise training programme there were reductions in AOPP and AGE in resting plasma samples (McAllister et al., 2020). Park et al. (2016) reported that in firefighters treadmill walking (20 minutes at 25 °C) while wearing PPE and breathing apparatus there were increases in plasma levels of conjugated diene but no changes in SOD, GSH-Px, or CAT. Increased total radical-trapping antioxidant potential (TRAP) was noted, possibly indicative of increased antioxidant capacity. In addition, alterations in oxidative stress markers were not exhibited when the exercise was carried out without PPE. [The Working Group noted that the exercise modalities included in these studies, combined with the ambient environmental temperatures, may limit generalizability to firefighter suppression tasks. Heightened physical strain when wearing PPE and breathing apparatus may be associated with oxidative stress, although no statistical comparison with the group wearing regular clothing was conducted.]

Two studies (Ferguson et al., 2016; Peters et al., 2018) investigated the effect of smoke exposure on oxidative stress in controlled laboratory exposures, with participants from the general population. Participants were exposed to three conditions: filtered air (as control), 250 μg/m^3 wood smoke $PM_{2.5}$, and 500 μg/m^3 wood smoke $PM_{2.5}$, during 90 minutes of treadmill exercise. Levels of 8-isoprostane (measured by ELISA) in EBC increased 1 hour after exposure to wood smoke in comparison with filtered air, although levels were greater in filtered air immediately after exposure (Ferguson et al., 2016). Peters et al. (2018) also reported increased levels of plasma 8-isoprostane via ELISA analysis after both low (250 μg/m^3) and high (500 μg/m^3) exposures, increased MPO after both exposures, increased 3-NT after combined smoke exposure, and a decrease in the antioxidant marker UA. However, numerous markers measured (H_2O_2, EBC MPO, TEAC, LOOH, PC) did not indicate oxidative stress (Ferguson et al., 2016; Peters et al., 2018). [The Working Group noted that the physiological strain and duration of wildland exposure may not have been accurately reflected because of the selected exercise task type and duration, environmental temperature, and clothing worn.]

[The Working Group noted that robust pre/post studies in humans demonstrated correlations between exposure markers and oxidative damage, and associations between occupational firefighting exposure and oxidative stress. The study design of an additional group of studies lacked rigour, with disparities in the timing of sample collections and exposure measurements; thus, these studies were considered less informative.]

(b) Human cells in vitro

See Table 4.5.

Two studies (Park et al., 2016; Ma et al., 2020) provide in vitro assessment of oxidative stress in human cells. Isolated leukocytes from firefighters from the Republic of Korea and from

Table 4.5 End-points relevant to oxidative stress in human cells in vitro

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
GSH, ROS as DCF	Human lung epithelial cell carcinoma, A549	Training, PM collection only Denmark, particles from wood smoke with and without presence of foam and electrical cords. Particle collection by electrostatic deposition		No change in GSH ↑ ROS from wood burn only ($P < 0.05$)	Exposure duration and PM dose	Authors used a manual arbitrary scoring scale	Ma et al. (2020)
DNA damage (comet assay)	Lymphocytes	No fire exposure (treadmill exercise in temperate environment) Republic of Korea, male volunteer firefighters, repeated measures design, treadmill exercise in PPE vs regular clothing, 25 °C at 9 METS Cells exposed to H_2O_2	12 (PPE), 12 (regular clothing)	Reduced resistance to H_2O_2-induced oxidative DNA damage 40 min post ($P < 0.001$)	Cardiovascular disease, antioxidant nutrient intake	No heat/live-fire exposure; small sample size; limited ecological validity to firefighter tasks; no details on regular clothing; no statistical comparison between PPE and regular clothing trials; limited details on assay characteristics	Park et al. (2016)

DCF, dichlorofluorescein; Fpg, formamidopyrimidine DNA glycosylase; GSH, glutathione; H_2O_2, hydrogen peroxide; MET, maximal exercise treadmill training; PM, particulate matter; PPE, personal protective equipment; ROS, reactive oxygen species.
↑, increase; ↓, decrease.

Denmark, respectively, after treadmill walking (20 minutes in 25 °C) while wearing PPE exhibited reduced resistance to H_2O_2-induced oxidative DNA damage (measured by the comet assay) immediately after exercise and 40 minutes after exercise (Park et al., 2016). [The Working Group noted that no statistical comparison with the regular clothing group was conducted, values post trials appeared similar (regular clothing, tail intensity, 84.8 ± 1.3%; PPE, tail intensity, 82.4 ± 1.1%).] Assessment of the influence of smoke particles on oxidative stress measured in the lung epithelial cell line A549 indicated that ROS levels generated after 3 hours of exposure to 100 µg/mL of PM from wooden pallet burn were 50% higher than those before exposure (Ma et al., 2020). However, exposure to particle matter from wooden pallets combined with foam mattresses and electrical cords resulted in no difference in ROS generation. GSH concentration was also unaffected by PM.

(c) Experimental systems

(i) Non-human mammals in vivo

See Table 4.6.

Two studies (Demling & LaLonde, 1990; Demling et al., 1994) used experimental systems in vivo to assess oxidative stress; both used a similar protocol in adult female sheep. Sheep exposed to a tidal volume of 5 mL/kg smoke for 20 breaths exhibited increased plasma MDA immediately after exposure; this returned to baseline 1 hour after exposure and was again elevated at 24 hours after exposure. No changes in lung lymph MDA or conjugated diene were detected. Increasing smoke exposure to 10 mL/kg resulted in increased levels of lung lymph and plasma conjugated diene and MDA after exposure. These variables returned to baseline levels in 4 hours, with plasma MDA peaking again 24 hours later. Liver tissue MDA level was also doubled after exposure at the higher dose (Demling & LaLonde, 1990). Sheep exposed to 5 mL/kg smoke for an extended duration of 48 breaths exhibited increased levels of liver tissue MDA, decreased liver tissue GSH, GSSG, and CAT, decreased lung tissue CAT and decreased kidney tissue GSH, compared with control sheep (Demling et al., 1994). [The Working Group noted that smoke was generated from dyed cotton towel burning, so this study was of limited relevance to firefighters.]

(ii) Non-human mammalian cells in vitro

In the third study in an experimental system, mouse peritoneal monocytes RAW 264.7 were exposed to smoke collected from wildland fire (Leonard et al., 2007). Increased levels of H_2O_2 and MDA were detected after exposure to ultrafine (0.042–0.24 µm) and fine (0.42–2.4 µm) PM compared with a control exposure to clean air. No differences were noted after exposure to coarse (4.2–24 µm) PM. In addition, assessment in an acellular system using DNA fragments (λ Hind III fragments) revealed DNA damage, identified by increased electrophoresis band smearing, with all three PM exposure types (ultrafine, fine, coarse) and co-treatment with H_2O_2, compared with controls. The induced DNA damage was inhibited by co-treatment with sodium formate, a hydroxyl radical scavenger, and the metal chelator deferoxamine. [The Working Group noted that the inhibitor experiments indicated that a transition metal reaction with H_2O_2 was involved in the hydroxyl-generated DNA damage.]

4.1.3 Induces epigenetic alterations

See Table 4.7.

DNA methylation, post-translational histone modifications, and non-coding RNAs including microRNAs (miRNAs) were considered as indicative of epigenetic alterations. Epidemiological studies assessing DNA methylation and miRNA among firefighters were identified and reported. One of the studies also investigated epigenetic

Table 4.6 End-points relevant to oxidative stress in non-human mammalian experimental system in vivo

End-point	Species, route of exposure, doses	Tissue	Results[a]	Covariates controlled	Comments	Reference
MDA, CD	Female adult sheep, low vs high exposure exposed via intubation to smoke from burning cotton towels, 5 mL/kg smoke and 10 mL/kg smoke	Blood, lung lymph, lung, and liver tissue	*5 mL/kg smoke:* ↑ Plasma MDA post exposure and 24 h post No change in lung lymph or plasma CD or lung or liver tissue MDA *10 mL/kg smoke:* ↑ Lymph and plasma MDA and CD post exposure ↑ Plasma MDA at 24 h post ↑ Liver tissue MDA No change in lung tissue MDA	Veterinary-confirmed infection free, breath number, quantity of fuel source	Smoke from cotton towelling; 24-h study period providing time-dependent response	Demling & LaLonde (1990)
MDA, CD, CAT, GSH, GSSG	Female adult sheep, exposed vs control, exposed via intubation to smoke from burning cotton towels; 5 mL/kg smoke	Blood, airway fluid, lung lymph, lung tissue, liver tissue, kidney tissue, gut tissue	↑ Plasma MDA and CD pre to 1 h post (return to normal by 2 h) ↑ Airway fluid MDA at 12 h and 24 h compared with control No change in lung lymph CD ↓ Lung lymph MDA decreased at 4 h but returned to baseline by 18 h No change in lung tissue MDA, CD, GSH, or GSSG In lung tissue, ↓ CAT In liver tissue, ↑ MDA, ↓ GSH, GSSG, and CAT In kidney tissue, ↓ GSH No change in gut tissue for any markers	Confirmed infection free, breath number, quantity of fuel source	Some statistical data unclear; smoke from cotton towelling. 24-h study period providing time-dependent response	Demling et al. (1994)

CAT, catalase activity; CD, conjugated diene; GSH, glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; vs, versus.
[a], ↑, increase; ↓, decrease; statistical significance was defined as $P < 0.05$.

Table 4.7 End-points relevant to epigenetic alterations in exposed firefighters

End-point	Biosample, tissue, or cell type	Technical details	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significant)[a]	Covariates controlled	Comments[b]	Reference
DNA methylation								
Gene-specific DNA methylation in promoter region	Peripheral blood leukocytes	Gene specific analysis in promoter region of *GSTP1*, *DUSP22*, *RAD21*, and *IFN-γ*	Employment as firefighter USA (Ohio), Fire Service and Radiation Safety in Cincinnati, cross-sectional	18 firefighters, 20 controls	↓ *DUSP22* promoter methylation; inverse correlation with years of service	None	Small sample size; included men and women, and several current smokers; the study had in vitro data that corroborated the results for *DUSP22* Exposure assessment: adequate for primary hypothesis of higher biomarker levels in firefighters vs controls	Ouyang et al. (2012)
EWAS, DNA methylation	Peripheral blood leukocytes	Infinium EPIC array, included 834 912 CpG sites Bonferroni-correction for EWAS Pathway analysis with IPA	Employment as firefighter USA (Arizona), Tucson Fire Department, cross-sectional	41 new recruits, 45 incumbents firefighters	Incumbent vs recruits EWAS: 4 CpG sites differentially methylated Prediction analysis: 11 CpG sites predicted group and 91 CpG sites predicted years of service among incumbent FF Pathway analysis of 443 genes annotated to 512 CpG differentially methylated between incumbent firefighters and new recruits, identified enrichment for cancer-related pathways	Age, ethnicity, BMI	All non-smoking men Exposure assessment: strong methodology using fire response records to quantify proxies for exposure duration and qualitative aspects of types of fires likely correlated with chemical composition of fumes (see also Jeong et al., 2018; and Jung et al., 2021b)	Zhou et al. (2019)

Table 4.7 (continued)

End-point	Biosample, tissue, or cell type	Technical details	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significant)[a]	Covariates controlled	Comments[b]	Reference
EWAS, DNA methylation	Peripheral blood leukocytes	Infinium EPIC array, included 740 842 CpG sites FDR $q < 0.05$ for significance in EWAS Pathway analysis with missMethyl	Employment as firefighter USA, firefighters from 3 states; cross-sectional	194	Hispanic firefighters vs non-Hispanic firefighters EWAS: 54 CpG sites with lower methylation and 22 with higher methylation Pathway analysis: not significant	Gender, age, batch, blood cell proportions; sensitivity analyses with smoking and years firefighting	Comparison was meant to show ethnicity difference (only Hispanic and non-Hispanic White included) and not effect from firefighting Exposure assessment: no information on individual exposure histories	Goodrich et al. (2021b)
EWAS, DNA methylation Epigenetic age biomarkers	Peripheral blood leukocytes	Infinium EPIC array, included 740 842 CpG sites $P < 9 \times 10^{-8}$ for significance DMR analysis with DMRcate Pathway analysis with missMethyl Assessed 7 epigenetic clocks	Employment as firefighter USA, firefighters from 3 states, cross-sectional	197 firefighters	EWAS: 5 CpG sites associated with serum concentrations of 1 PFAS each DMR analysis: 3 PFAS associated with DMRs Pathway analysis: results from 3 PFAS enriched in pathways including lipid transport, immune function, cell movement Epigenetic clocks: 3 PFAS associated with ↑ epigenetic age biomarkers	Age, gender, race, Hispanic ethnicity, blood cell proportions, batch	Focus on specific PFAS chemicals Exposure assessment: no unexposed controls; range of serum PFAS concentrations but source undetermined; 9 PFAS measured in serum; other exposures not assessed	Goodrich et al. (2021a)

Table 4.7 (continued)

End-point	Biosample, tissue, or cell type	Technical details	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significant)[a]	Covariates controlled	Comments[b]	Reference
EWAS, DNA methylation	Peripheral blood leukocytes	Infinium EPIC array, included 759 346 CpG sites; FDR $q < 0.05$ for significance; pathway analysis with IPA	Employment as firefighter USA (Arizona), Tucson Fire Department, pre/post	50 new recruits before training and 20–37 months later	EWAS: 680 CpG sites changed over time (292 ↑ and 388 ↓) including 60 with ≥ 5% difference; 140 of these loci associated with number of fire-runs and time spent at fires Pathway analysis: enrichment in 9 canonical pathways and 27 disease categories including 14 cancer-related	Hispanic ethnicity, estimated smoking pack years, batch, cell type proportions	98% men Exposure assessment: strong methodology using fire response records to quantify proxies for cumulative exposure including number of fire-runs and total fire-hours; limiting study to new recruits also improved accuracy of exposure estimates	Goodrich et al. (2022)
EWAS, DNA methylation	Peripheral blood leukocytes	Infinium 450K array, included 375 223 CpG sites FDR $q < 0.05$ Pathway analysis with missMethyl	Exposure index based on time, location, and tasks of WTC response USA (New York), WTC General Responder Cohort, cross-sectional	185 responders; 69 in low and 116 in high exposure groups	EWAS: no changes Pathway analysis: 21 enriched gene-sets among top 500 CpG sites between low and high, including 7 cancer-related pathways	Age, race, smoking status, blood cell proportions	Follow-up 10 yr post-WTC event with no adjustment for exposures in between; no unexposed controls Exposure assessment: well-developed index of exposure including all available detailed self-reported information on duration of exposure and exposure-related tasks, PPE, etc.	Kuan et al. (2019)

Table 4.7 (continued)

End-point	Biosample, tissue, or cell type	Technical details	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significant)[a]	Covariates controlled	Comments[b]	Reference
Somatic mutations								
Somatic mutations in epigenetic driver genes	Peripheral blood	Deep targeted sequencing of 237 genes frequently mutated in haematological malignancies	Presence as firefighter at WTC event USA (New York), FDNY First Responders Study, cross-sectional	481 WTC responders (429 firefighters, 52 EMS) and 255 current firefighters (non-responders)	Most highly mutated genes in WTC compared with non-WTC firefighters were epigenetic regulators, *TET2* and *DNMT3A* Non-synonymous mutations in *DNMT3A*, *TET2*, and *IDH2* reported in both groups	Age, race, ethnicity, sex, smoking	Follow-up 12–14 yr post WTC event for first responders; no non-firefighter control group (see Section 4.1.1 for additional results) Exposure assessment: exposure contrast was qualitative, WTC vs "normal" firefighter exposures	Jasra et al. (2022)
microRNA expression								
miRNA expression	Peripheral blood	Blood preserved in tempus RNA tubes nCounter v3 Human miRNA expression panel, 821 miRNAs Bonferroni correction miEAA for enrichment analysis	Employment as firefighter USA (Arizona), Tucson Fire Department, cross-sectional	52 incumbent firefighters, 45 new recruits before live-fire training	Incumbents vs new recruits miRNA: 6 decreased expression and 3 increased expression (fold-change, 1.5) Enrichment analysis: targets of top miRNAs enriched for stem cells, inflammation, and cancers (melanoma, Burkitt lymphoma)	Age, BMI, ethnicity, only non-smokers included	All White men; incumbent group ~14 yr older, and 2 of the 9 significant miRNAs were also associated with age Exposure assessment: qualitative exposure assignment based on employment records; enhanced validity from comparing incumbent vs recruit firefighters	Jeong et al. (2018)

Table 4.7 (continued)

End-point	Biosample, tissue, or cell type	Technical details	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significant)[a]	Covariates controlled	Comments[b]	Reference
miRNA expression	Peripheral blood	Blood preserved in tempus RNA tubes; nCounter v3 Human miRNA expression panel, 799 miRNAs; used Bonferroni correction	Employment as firefighter USA (Arizona), Tucson Fire Department pre/post	52 new recruits before training and 20–37 months later	3 miRNA replicated from Jeong et al. (2018) Full array: 5 decreased expression and 4 increased expression in association with employment duration	Age, BMI, ethnicity, batch effects (also adjusted for time since more recent fire in some analyses)	A priori marker analysis (from Jeong et al., 2018); season of sampling was potential confounder; all white men Exposure assessment: strong methodology using fire response records to quantify proxies for exposure duration and qualitative aspects of types of fires likely correlated with chemical composition of fumes (see also Jeong et al., 2018; and Goodrich et al., 2022)	Jung et al. (2021b)

AZ, Arizona; CpG, cytosine-phosphate-guanine; DMR, differentially methylated region; EMS, emergency medical service workers; EWAS, epigenome-wide association study; epigenetic age indicators, DNA methylation-based estimators of epigenetic (biological) ageing called IEAA, EEAA, Horvath, Hannum, PhenoAge, Skin-Blood, and GrimAge; IPA, Ingenuity Pathway Analysis software; miRNA, microRNAs; PAHs, polycyclic aromatic hydrocarbons; PFAS, per- and polyfluoroalkyl substances; PFNA, perfluorononanoic acid; *q*-value, *P* value adjusted for multiple comparisons via the Benjamini-Hochberg false discovery rate (FDR) method; WTC, World Trade Center.

[a] Only statistically significant result(s) reported at appropriate *P* value cut-off used by the study (either $P < 0.05$ or adjusted for multiple hypothesis testing); "no changes" means no statistically significant results reported for any end-points of interest.

[b] Factors to be considered for study quality included the methodology, design, reporting, and quality of the exposure assessment.

alterations in vitro. The association between occupation as a firefighter and alterations in DNA methylation or in miRNA expression was investigated (Ouyang et al., 2012; Jeong et al., 2018; Kuan et al., 2019; Zhou et al., 2019; Goodrich et al., 2021a, b, 2022; Jung et al., 2021b). All studies investigated DNA methylation or miRNA in peripheral blood samples. All except one study focused on employment as a municipal firefighter, and one followed up first responders to a catastrophic event, the WTC disaster. One study reported mutations in key epigenetic regulator genes in first responders to the WTC disaster and non-WTC firefighters (Jasra et al., 2022). There were no studies investigating potential epigenetic alterations in wildland firefighters or induced by specific challenges (i.e. mental or physical, including heat). Considering the availability of data, the studies reported below are grouped by end-point.

(a) DNA methylation

Alteration in DNA methylation after occupational exposure as a firefighter was investigated in different study types. Two studies followed-up municipal firefighters (Goodrich et al., 2022) or first responders to the WTC disaster (Kuan et al., 2019); two were cross-sectional studies of incumbent firefighters (Goodrich et al., 2021a, b); and two studies compared incumbent firefighters with new recruits or non-firefighter controls (Ouyang et al., 2012; Zhou et al., 2019). In five studies (Kuan et al., 2019; Zhou et al., 2019; Goodrich et al., 2021a, b, 2022), the authors explored an epigenome-wide association study (EWAS) of DNA methylation using high-dimensional DNA methylation arrays (the Illumina Infinium 450K or EPIC arrays), which provide data at thousands of loci (called CpG sites) throughout the genome. One study employed a candidate gene approach (Ouyang et al., 2012).

Goodrich et al. (2022) sampled blood (peripheral blood leukocytes) from 50 recruits in the USA before live-fire training and again approximately 2 years later. When comparing DNA methylation data, 680 CpG sites were significantly differentially methylated (388 CpG sites had lower and 292 had greater methylation at follow-up). [The Working Group noted that associations in either direction could be important since implications for gene regulation are dependent on the genomic context.] Among these loci, 140 exhibited a significant linear association with number of fire-runs and/or time spent at fires, suggesting a dose–response with cumulative fireground exposures (see Sections 1.4.1 and 1.5.1 for chemical agents that have been observed at the fireground in other studies). Enriched gene sets among these loci included pathways relevant to carcinogenesis and tumorigenesis. [The Working Group noted that enrichment in some of these pathways, namely, molecular mechanisms of cancer, colorectal and gastrointestinal cancers, overlapped with that in other studies in the present section (Goodrich et al., 2021a, b).] [The Working Group deemed this an informative study because of the pre/post design, with repeat measures taken 2 years later. Collection of proxies for cumulative exposure, including number of fire-runs and total fire exposure time, was a strength. In addition, the results indicated persistent and cumulative DNA methylation alterations in loci annotated to cancer-related genes.]

Other DNA methylation studies provided supportive data for the influence of firefighting on DNA methylation. Zhou et al. (2019) compared DNA methylation data from blood samples (peripheral blood leukocytes) of 45 incumbent and 41 new-recruit firefighters from Arizona, USA, all non-smoking men. Methylation at four CpG sites was statistically significantly associated with firefighting, with at least a 0.5-fold difference between the two groups. In prediction analyses, methylation in 11 CpG sites predicted whether a participant belonged to the incumbent or new-recruit group, and methylation in 91 CpG sites predicted years of service among incumbent

firefighters. Pathway analysis of the most differentially methylated CpG sites identified a significant enrichment of genes in pathways relevant to tumorigenesis and tumour physiology, including sirtuin signalling, molecular mechanisms of cancer, p53 signalling, AMP-activated protein kinase (AMPK) signalling, and enriched disease pathways: abdominal cancer, colon tumours, skin cancer, and lung tumours/cancers. Goodrich et al. (2021a, b) conducted cross-sectional EWAS using blood samples from approximately 200 municipal firefighters from the USA, investigating differences in DNA methylation by ethnicity (Goodrich et al., 2021b) and by serum concentrations of PFAS (Goodrich et al., 2021a), chemicals that firefighters may be exposed to (see Section 1.5.1(b)). Of the nine PFAS measured in serum, six were detected in > 70% of participants (Goodrich et al., 2021a). When examining associations between the six PFAS and all methylated loci on the array, three PFAS (linear perfluorooctanesulfonic acid, *n*-PFOS; perfluorononanoic acid, PFNA; and perfluorodecanoic acid, PFDA) were significantly associated with DNA methylation at specific loci and multisite regions. In pathway analysis of the top loci associated with *n*-PFOS, PFNA, and PFDA ranked by raw *P* value, significantly enriched gene sets included hippo signalling, and functions related to lipid transport, ion transport, cell motility, and circadian entrainment.

Epigenetic age can be estimated from DNA methylation using data from well-validated and widely replicated CpG sites that change with chronological age. Accelerated epigenetic age has been associated with risk of cancer and mortality from cancer, including when it is measured in the blood (Perna et al., 2016). When evaluating the association between serum PFAS and seven indicators of epigenetic age in blood leukocytes, perfluorohexanesulfonic acid (PFHxS), linear perfluorooctanoic acid (*n*-PFOA), and the sum of perfluoromethylheptanesulfonic acid isomers (Sm-PFOS) were each associated with accelerated epigenetic age in multiple indicators. In contrast, PFDA and perfluoroundecanoic acid (PFUnDA) were inversely associated with one indicator. [The Working Group noted that the limitations of the study by Goodrich et al. (2021a) included the inability to identify whether the source of exposure was occupational or environmental, the cross-sectional nature of the study, and the lack of other fireground exposures measured.] [The Working Group also reviewed Goodrich et al. (2021b) but deemed it to be uninformative, because it was not investigating the impact of exposure from firefighting since all participants were incumbent municipal firefighters. Results focused on differences in DNA methylation between ethnicity groups, and they may be important when considering interindividual susceptibility to cancer in the fire service.]

Ouyang et al. (2012) conducted a study in Ohio, USA, using blood samples from 18 firefighters and 20 controls (non-firefighters) using a hypothesis-driven approach. DNA methylation was quantified at the promoter region of four genes that had been previously associated with combustion by-products or smoking in other populations. *DUSP22* promoter methylation was found to be significantly lower among firefighters than among non-firefighter controls and was inversely correlated with years of service among the firefighters but not with age in the controls. [The Working Group noted the relatively small sample size. The strengths of this study were the controlled variables and the gene selection. Moreover, the Working Group noted that the gene *DUSP22* has been related to inflammation and tumour suppressor activities in several cancers (Lin et al., 2019).] Ouyang et al. (2012) also conducted an in vitro study to build upon the epidemiological results, testing whether B[*a*]P – a combustion by-product classified in IARC Group 1, *carcinogenic to humans* – reduces promoter DNA methylation at *DUSP22* and increases its expression. Human prostate epithelial cells (NPrEC) and human T-lymphocytes

(Jurkat cells) were treated for 2 weeks with either B[*a*]P (0.1, 1, or 10 nM) or a control. Treatment was associated with a dose-dependent decrease in promoter-region DNA methylation and subsequent increase in the expression of *DUSP22*.

Kuan et al. (2019) evaluated first responders (firefighters and other responders) to the WTC disaster at multiple time-points post-exposure. DNA methylation analysis was conducted > 10 years later in blood samples from male responders who were in the top or bottom 10% of exposure according to percentiles of exposure ranking indices ($n = 116$ and $n = 69$, respectively). Exposure rank was not significantly associated with DNA methylation at any individual CpG sites at a *P* value cut-off adjusted for multiple testing. A gene-set enrichment analysis was conducted on the top 500 differentially methylated CpG sites by raw *P* value. The 21 significantly enriched gene sets included broad pathways related to cancer (i.e. "pathways in cancer" and "choline metabolism in cancer"), and other pathways relevant to tumorigenesis (i.e. "MAPK signalling"). [The Working Group noted that the limitations of this study included no adjustment for exposures in the interim (i.e. work as a firefighter after 11 September 2001), the unique exposure of WTC firefighters that may not be generalizable to other firefighters, and inclusion of primarily White male participants.]

Jasra et al. (2022) (study fully described in Section 4.1.1) reported finding in blood samples of WTC responders an increase in somatic mutations in two genes (*DNMT3A* and *TET2*) that encode epigenetic drivers – an enzyme that methylates DNA and one that is involved in active demethylation, respectively. WTC responders had more mutations overall in the blood than did firefighters who were not at the WTC. *DNMT3A* and *TET2* were the most frequently mutated genes in blood samples from WTC first-responders. Both groups had non-synonymous somatic mutations in *DNMT3A*, *TET2*, and another epigenetic regulator (*IDH2*). [The Working Group noted that these data suggested a potential mechanism for broad DNA methylation alterations in either type of firefighter. Mutation in these genes were observed with ageing (Buscarlet et al., 2017). The Working Group noted that this study lacked a non-firefighter control group.]

[The Working Group noted that collectively the above studies showed alterations in DNA methylation associated with firefighting, including alterations that persist after exposure. Several tumorigenesis- and cancer-related gene pathways were common and significantly enriched in at least two studies, including hippo signalling, circadian entrainment, AMPK signalling, general molecular mechanisms of cancer, and colorectal and gastrointestinal cancer pathways. Although these data were only available in the blood, they showed persistent alterations in DNA methylation induced by firefighting.]

(b) microRNA

Two studies in the same source population from Arizona, USA, examined associations between miRNA expression and employment as a municipal firefighter. Jeong et al. (2018) conducted a comparison of 52 non-smoking, male incumbent and 45 new-recruit firefighters, the same population described in (Zhou et al., 2019). Six miRNAs were significantly downregulated (*miR-1260a*, *miR-548h-5p*, *miR-145-5p*, *miR-331-3p*, and *miR-181a-5p*) and three were upregulated (*miR-5010-3p*, *miR-374a-5p*, and *miR-486-3p*) in incumbents compared with new recruits. [The Working Group noted that the six downregulated miRNAs have tumour suppressor functions (Epis et al., 2009; Hu et al., 2014; Ma et al., 2015; Ozen et al., 2015; Zhao et al., 2016), and two of the upregulated miRNAs (*miR-374a-5p*, *miR-486-3p*) have oncogenic properties in e.g. colorectal and oesophageal cancers (Mosakhani et al., 2012; Wang et al., 2015).] In enrichment analysis, 234 differentially expressed miRNAs were significantly associated with stem cells and significantly enriched in pathways related to

inflammation, cell adhesion-related functions, general carcinoma, Burkitt lymphoma, and melanoma.

Jung et al. (2021b) conducted a follow-up study with the same new recruits (n = 52) and re-evaluated miRNA expression 20–37 months later. The nine miRNAs identified in the cross-sectional study by Jeong et al. (2018) were compared at baseline and follow-up; three miRNAs related to cancer replicated in the same direction and were also significantly associated with employment duration: *miR-1260a* (a tumour suppressor), and *miR-5010-3p* and *miR-486-3p* (linked to cancer promotion). In the discovery full-array approach, nine additional miRNAs were identified that were significantly associated with employment duration when adjusting for structure and/or all fire-runs or fire-hours. These included four downregulated tumour suppressors (*miR-422a*, *miR-26a-5p*, *miR-92a-3p*, and *let-7f-5p*) and four upregulated oncogenes (*miR-548a-3p*, *miR-556-3p*, *miR-548ad-3p*, and *miR-525-3p*). [The Working Group considered that the strength of the study was the pre/post design and assessment of proxies for chronic and acute sources of fireground exposure, including consideration of time spent at structure fires only and all fires that the workers responded to. Replication of results across two studies was also a strength. Limitations included the small sample size, which was underpowered to detect all true associations. Mutual adjustment for employment duration and cumulative fireground responses might have attenuated the effect reported here.]

4.1.4 Induces chronic inflammation

See Table 4.8.

Alterations in inflammatory markers, such as C-reactive protein, cytokines, interleukins IL-6, IL-8, and IL-10, or tumour necrosis factor alpha (TNFα), and lung function parameters, such as the forced expiratory volume (FEV) were among the end-points considered relevant to the key characteristic "induces chronic inflammation" and reported at the beginning of the present section (Section 4.1.4(a)). Symptoms of lung dysfunction and bronchial hyperreactivity, although not directly linked to the key characteristic-associated end-points, were also considered relevant to describe the mechanistic evidence in the context of occupational exposure as a firefighter; these were also reviewed and reported at the end of the present section (Section 4.1.4(b)).

(a) Exposed humans

(i) Structure fires

Eight papers available to the Working Group reported findings from structure fires, or exposure to structure training fires. All the studies reported significant changes in markers of inflammation (e.g. various interleukins, fibrinogen, P-selectin, Club cell secretory protein (CC16; alias Clara cell protein), C-reactive protein, etc.) after fire exposure. [The Working Group noted that the strength of these papers lies in the study designs, with most papers reporting results from pre/post-fire exposure (Burgess et al., 2001, 2002; Cordeiro et al., 2021), or pre/post trial studies (Watt et al., 2016; Kim et al., 2018; Smith et al., 2019; Watkins et al., 2019a). One cross-sectional study was also included in this exposure type (Gaughan et al., 2014b).]

Several studies reported significant increases in interleukin-6 (IL-6) after exposure to live-fire structure training exercises (Kim et al., 2018; Smith et al., 2019; Watkins et al., 2019a), with Watkins et al. also reporting significant leukocytosis. IL-6 concentrations were significantly higher in fire service instructors with greater exposure to live fire because of involvement in training exercises (Watkins et al., 2019a). There was also evidence that IL-6 and fibrinogen remained significantly elevated in fire instructors 24 hours after exposure (Kim et al., 2018). [The Working Group noted that increase in fibrinogen was part of the inflammatory response.]

Table 4.8 End-points relevant to chronic inflammation in exposed firefighters

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Structure fires							
FVC, FEV_1 (lung function) CC16 SP-A	Serum	Structure fire USA (Arizona), pre/post	51 pre/post samples 25 from Tucson, 26 from Phoenix	At Phoenix, ↓ lung function, ↑ CC16 ↑ SP-A ($P < 0.01$) At Tucson, ↑ CC16 ($P < 0.01$); no changes in SP-A and lung function	Baseline FEV_1, ever smoking, age, gender, race	No smoke exposure in 24 h before testing; participants asked to participate in overhaul only (where possible) and avoid prior entry/ventilation or extinguishing where possible; no difference between groups at baseline At Tucson, no SCBA used for overhaul; at Phoenix O_2 tanks removed, but facepieces/cartridge respirators remained; noting differing use of SCBA separate analyses were completed Exposure assessment: appropriate assessment of personal shift exposure measures in analysis and firefighting was appropriately evaluated as exposure in the pre/post design	Burgess et al. (2001)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-10 IL-8 TNFα Mean FVC (lung function) CC16 SP-A	Sputum Serum	Structure fire USA (Arizona), pre/post	17 male firefighters	↓ Sputum IL-10 ($P = 0.02$); no changes observed in IL-8 or TNFα ↓ Mean FVC with smoke exposure ($P = 0.02$). ↑ CC16 ($P < 0.01$); ↑ SP-A ($P = 0.03$) indicated lung permeability after smoke exposure		Well designed; blood, pulmonary function data, and induced sputum were measured at baseline, and 1 h after overhaul Exposure assessment: engagement in smoke exposure during overhaul appropriately tested as exposure in the pre/post design; inclusion of sufficiently exposure firefighters (≥ 25 min of exposure	Burgess et al. (2002)
IL-2 IL-8 IL-10 IL-12 CC16 FVC, FEV_1, FEF25–75 (lung function)	Nasal lavage fluid (for cytokines) Sputum	Structure fire [firefighter training course] Sao Paulo, Brazil, volunteer firefighters, pre/post	37:0	↑ IL-8; ↑ IL-10; ↑ IL-2; ↑ ratio of IL-12p40:IL-12p70 ($P < 0.05$) ↓ IL-2 wk 1 to wk 4 ($P < 0.05$) ↑ CC16 ($P = 0.011$) at wk 4 vs wk 1 No changes in lung function. Significant alterations in respiratory rate, heart rate and O_2 saturation after simulation		Samples taken pre/post fire exposure, and 4 wk post exposure; 2 cohorts, no statistical differences between physical characteristics of these groups All participants used SCBA Exposure assessment: engagement in fire training appropriately tested as exposure in the pre/post design; effects of exposure to combustion by-products and heat at the same time, effect of each cannot be disentangled	Cordeiro et al. (2021)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
hsCRP FVC, FEV_1 (lung function)	Venous blood	Structure fire USA, career members of midwestern fire department, cross-sectional	401:0	↑ hsCRP-associated ↓ lung function, after adjusting for confounding variables ($P < 0.05$)	Included in regression analysis: current smoker, history of pulmonary disease, BMI, maxMETs, resting blood pressure	Single time-point; methods not clear PPE use not reported Exposure assessment: no exposure data on participants	Gaughan et al. (2014b)
IL-6 Fibrinogen	Plasma Serum	Structure fire [live-fire simulation at training centre] Republic of Korea, pre/post trial	14 firefighting academy instructors: 7 suppression simulation, 7 control group	↑ IL-6; immediately after live-fire simulation and remained elevated after 24 h; ↑ fibrinogen after 24 h		Small sample size; no significant difference between general characteristics of groups; group exertion not clearly described; smokers vs non-smokers not evenly split between groups, 5:2; wearing PPE and SCBA Inconsistency of results reported in the article Exposure assessment: involvement in controlled hot working and smoke exposure conditions appropriately tested as exposure for the effects assessments that were done in the trial	Kim et al. (2018)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
CRP IL-6 ICAM-1 P-selectin MMP-9 TAC	Serum Plasma	Structure fire Illinois, USA, male firefighters. randomized controlled trial (RCT)	24 male firefighters across 4 conditions	↑ IL-6 ($P \leq 0.0001$); ↑ MMP-9 ($P < 0.0001$); ↑ P-selectin ($P = 0.001$) No change in CRP, or TAC and ICAM-1 detected		Well designed; 9 firefighters were obese; SCBA worn Exposure assessment: engagement in simulated firefighting appropriately tested as exposure for the effects assessments that were done in the trial in relation to supplement intervention	Smith et al. (2019)
CRP IL-6 Neutrophils Lymphocytes Monocytes Eosinophils *c*TnT	Whole blood plasma	Structure fire [structure fire training exercises] United Kingdom, fire service instructors, pre/post trial	16 fire service instructors (14 men, 2 women)	↓ CRP ($P < 0.048$). ↑ Neutrophils; ↑ lymphocytes; ↑ monocytes; ↑ IL-6; ↑ *c*TnT ($P < 0.001$) No changes in eosinophils	None reported	Fire type and PM not reported; PPE worn Exposure assessment: exposure to different fire exercises appropriately tested as exposure for the effects assessments that were done in the experiment	Watkins et al. (2019a)
IL-6 Neutrophils FVC, FEV_1 (lung function)		Structure fire [structure fire training exercises] United Kingdom, fire service instructors, pre/post trial	6 fire service instructors, 6 non-firefighter controls	Fire service instructors vs controls baseline levels: ↑ IL-6; ↑ neutrophils ↑ IL-6 in fire service instructors during heat exposure and fire instruction course time periods ↓ Lung function in fire service instructors over the 4-wk training course	Time since recent exposure, no additional operational exposures	Variation in exposure duration and roles conducted; small sample size Exposure assessment: inadequate since potential simultaneous exposure to smoke was not considered; the quantitative heat exposure measure that was collected was not used in exposure–response analysis	Watt et al. (2016)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Wildland fires							
IL-8 IL-4 IL-13 TNFα VEGF ECP Macrophages Neutrophils Eosinophils Lymphocytes FEV_1, FVC, FEF 25–75 (lung function) BHR	Sputum Serum BALF	Wildland (forest) fire Greece, 2008 forest fires, repeated measurements	60:0; post exposure vs off-season	Sputum: ↑ neutrophils ($P = 0.035$); ↑ eosinophils ($P = 0.05$); ↑ IL-8 ($P = 0.03$); ↑ TNFα ($P = 0.04$) BALF: ↑ neutrophils ($P = 0.043$); ↑ eosinophils ($P = 0.05$) Serum: ↑ IL-8 ($P = 0.03$); ↑ TNFα ($P = 0.03$); ↑ VEGF ($P = 0.02$) No changes in sputum: IL-4; IL-13; VEGF; ECP No changes in serum: IL-4; IL-13; ECP > 10 h continuous firefighting induced a more intense systemic inflammation compared with < 10 h exposure; serum: IL-8 ($P = 0.026$), TNFα ($P = 0.027$), and VGEF ($P = 0.021$) ↓ Lung function post exposure compared with off-season No changes in BHR off-season and post-exposure		Thorough clinical assessment; 87% current smokers with history of 9 ± 5 packs/year Exposure assessment: time away from firefighting adequately assessed	Gianniou et al. (2018)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
42 inflammatory cytokines, chemokines, and growth factors FEV_1, FVC (lung function)	Plasma	Wildland (forest) fire Fort McMurray fire, Canada, 2016, repeated measurements	160 (148 men) firefighters from 2 fire services. Samples collected 19 days of the start of the fire (early sample) and again 14–18 wk later (late sample)	25/42 inflammatory markers ↓ ($P < 0.05$) from early to late samples Second component of inflammatory markers associated with ↓ lung function ($P = 0.032$) Clustered within fire service, cumulative exposure, dehydration, and time since last deployed to a fire were all related to the second principal components late cluster scores of inflammatory markers		Unbalanced samples/ time-point; differences in tasks/roles for each group; principal components analysis conducted to reduce the dimensionality of the inflammatory marker arrays and extract uncorrelated component scores Exposure assessment: measurements on exposure levels at group level, not for individual workers, so possible exposure misclassification; possible unmeasured events before or after the fire	Cherry et al. (2021)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-6 IL-8 GM-CSF MCP-1 FEV_1 (lung function)	Serum Sputum	Wildland (forest) fire Canada, seasonal forest firefighters, pre/post	52:0 Before and after a day of firefighting	Serum: ↑ IL-8 ($P < 0.001$); ↑ IL-6 ($P < 0.02$); ↑ MCP-1 ($P < 0.02$). Sputum: macrophages containing phagocytosed particles and circulating band cells No changes in GM-CSF No changes in lung function		Pre/post 8-h shift samples Healthy non-smoking firefighters aged 17–60 yr were eligible Exposure assessment: although misclassification was possible with self-reported smoke intensity, carbon monoxide concentrations as surrogate for particulate matter exposure were used to confirm presence of smoke; firefighting shift appropriately tested as exposure for pre/post comparison	Swiston et al. (2008)
CRP IL-1β IL-8 SAA ICAM-1 VCAM-1	Dried blood spot	Wildland (forest) fire Savannah river site, USA, pre/post	12 firefighters (10 men, 2 women)	↑ IL-8 ($P = 0.0012$) Firefighters who lit the fires as opposed to other tasks had ↑ IL-8 ($P = 0.0186$). No changes in IL-1β, CRP, SAA, ICAM-1, VCAM-1	Work shift exposure to $PM_{2.5}$ and CO_2, gender, number of burns before sampling, work task, age, BMI, illness status, or allergies	Exposure assessment: appropriate personal shift $PM_{2.5}$ exposure measure; firefighting was appropriately evaluated as exposure in the pre/post design	Hejl et al. (2013)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-1β IL-2 IL-4 IL-5 IL-6 IL-7 IL-8 IL-10 IL-12p70 IL-13 IFN-γ TNFα GM-CSF	Plasma	Wildland (forest) fire Australia, pre/post	12 male CFA firefighters 2 consecutive days, 3 timepoints (pre-, post, and 2 h post-shift)	Significant change in IL-6 after exposure (within same days) and between days (repeated exposure over days) ($P = 0.037$) *Within-day*: ↑ IL-1β; ↓ IL-5, ↑ IL-7, ↓ IL-10, and ↓ TNFα (all $P < 0.01$) IL-1β and IL-7 returned towards baseline after end of shift. ↓ IL-5; ↓ IL-10 and ↓ TNFα 2 h post-shift compared with baseline ($P < 0.01$) *Between days:* Significant effect of performing repeated shifts on several inflammatory cytokines. IL-1β ($P = 0.005$), IL-7 ($P = 0.004$), IL-4 ($P = 0.048$), IL-6 ($P = 0.036$), IL-8 ($P = 0.045$), and IL-13 ($P = 0.05$) all presented with an attenuated response across the course of the second day		Standard fire-retardant personal protective clothing was worn throughout the shift as per agency guidelines, but no respiratory PPE/SCBA was used Exposure assessment: all workers were exposed; no differentiation between workers; no individual data on tasks performed at site taken into account; possible unmeasured events before or after shift	Main et al. (2013)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
13-plex cytometric bead array kit (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IFN-γ, GM-CSF, and TNFα)	Plasma	Wildland (forest) fire (suppression activities after Black Saturday natural disaster) Australia, pre/post 12-h shift of wildfire suppression, pre/post	38 male CFA volunteer firefighters; 0 controls	↑ IL-6 ($P = 0.003$); ↑ IL-8 ($P = 0.017$); ↓ IL-10 ($P = 0.021$) No changes in any other biomarker		High-sensitivity assay used Standard fire-retardant personal protective clothing was worn throughout the shift as per agency guidelines, but no respiratory PPE/SCBA Exposure assessment: all workers were exposed; no differentiation between workers; no individual data on tasks performed at site taken into account; possible unmeasured events before or after shift	Main et al. (2020)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
CRP IL-6 IL-8 sICAM-1	EBC	USA, Savannah River site, pre/post shift, and next morning, pre/post	12 healthy wildland firefighters (9 men and 3 women)	No significant changes observed across the prescribed burn shifts for any of the inflammatory markers		Data collected after 7 prescribed burn shifts (burn days), as well as 3 regular work shifts (non-burn days) Small sample size; question as to feasibility of EBC for measuring inflammatory cytokines; only 3/142 EBC samples had detectable IL-6 levels Exposure assessment: firefighting appropriately used for analysis in the pre/post comparisons; no personal monitoring data was used in analysis	Wu et al. (2020b)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Employment as a firefighter							
IL-1β IL-6 IL-8 IL-10 INF-γ TNFα FVC, FEV_1 (lung function) Serum pneumoproteins BHR	Sputum Serum	Employment as a firefighter Netherlands, repeated measurements, samples at 24 h, 1 wk and 3 months post-exposure	51:0 control 37 volunteer 8 professional [career] 6 both volunteer and professional [career]	Serum: ↑ IL-8 at 24 h ($P = 0.031$), 1 wk ($P = 0.0007$; ↑ IL-6 and ↑ IL-8 3 months after exposure ($P < 0.0001$) compared with pre-exposure Sputum: ↑ neutrophils positively associated with IL-8 ($P = 0.0023$), IL-10, ($P = 0.023$), and TNFα ($P = 0.011$) in serum within 24 h after exposure Perceived exposure was positively associated with a change in IL-8 after 1 wk ($P = 0.001$) 44% of firefighters had elevated sputum neutrophil levels (> 60%) No changes in BHR, lung function and serum pneumoprotein levels	Questionnaire assessed exposure including job history, working years, use of SCBA	Sputum was induced within 5 days of smoke exposure Exposure assessment: detailed self-reported exposure information and objective data on particle counts in induced sputum	Greven et al. (2012)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-8 ECP VEGF TNFα Macrophages Neutrophils Eosinophils Lymphocytes FEV_1, FVC (lung function)	Serum Sputum BALF Bronchial biopsies (for a subgroup of 20)	Employment as a firefighter Greece, cross-sectional	63 professional [career] firefighters with 9 ± 1 yr in service; 29 trainees with 1 ± 0.1 yr; 18 healthy controls	Professionals vs trainees Sputum: ↑ eosinophils ($P < 0.05$); ↑ IL-8 ($P = 0.04$); ↑ ECP ($P = 0.02$); ↑ VEGF ($P = 0.04$); ↑ TNFα ($P = 0.02$) Serum: ↑ IL-8 ($P = 0.04$); ↑ TNFα ($P = 0.03$) BALF: ↑ eosinophils ($P < 0.05$) Trainees vs controls Serum and sputum: ↑ IL-8; ↑ TNFα Duration of the occupation in service correlated with higher number of cells in sputum and BALF, higher percentage of eosinophils, neutrophils, and lymphocytes No significant differences in lung function between groups	Comparison were adjusted for age, smoking pack-years and pre-existing diagnosed asthma	Exposure assessment: employment categories used for effects comparisons likely adequate; potential confounding of career length with age	Gianniou et al. (2016)
CRP IL-6 IL-1β Neutrophils	Venous whole blood Plasma	Employment as a firefighter United Kingdom, cross-sectional	57 firefighters; 53 fire service instructors	Fire service instructors vs firefighters ↑ Neutrophils; ↑ IL-6; ↑ IL-1β; ↑ CRP ($P < 0.05$) Multiple regression analysis revealed 18.8% of IL-6; 24.9% of IL-1β, 29.2% of CPR could be explained by the number of heat exposures/month		Fire exposures, and health complaints self-reported Exposure assessment: self-reported frequency prone to misclassification	Watkins et al. (2021)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-6 IL-1β Neutrophils Eosinophils CRP	Whole blood Plasma	Employment as a firefighter United Kingdom, fire service instructors, pre/post trial	11 fire service instructors: 11 controls	↑ Neutrophils; ↑ IL-6, ↑ IL-1β, ↑ CRP, after heat exposure irrespective of group ($P < 0.05$) Fire service instructors vs controls: Resting ↑ IL-6; ↑ IL-1β ($P < 0.05$)	None reported	40 min walk test (6 W/kg) in climate chamber at 50 °C ± 1.0 °C; PPE worn Exposure assessment: number of self-reported fires may be misclassified; heat exposure was under controlled condition	Watkins et al. (2019b)
CRP FVC, FEV_1 (lung function) SAA ICAM-1 VCAM-1	Plasma	Employment as a firefighter Denmark, pre/post 24-h shift sample pairs, pre/post	22 men	↓ Lung function; ↑ VCAM-1 ($P < 0.05$) No changes in ICAM-1, SAA, and CRP IL-6 and IL-8 below LOD		Small sample size; only 3 days without work may have resulted in elevated levels of biomarkers pre-shift; the biological effective dose may not have been sufficiently large in present study to elicit expected responses Exposure assessment: firefighting was appropriately evaluated as exposure in the pre/post design; other exposure measures apparently not used in effect analysis; some logistic difficulties	Andersen et al. (2018b)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-1RA Macrophages FVC, FEV_1 (lung function)	Sputum	Employment as a firefighter USA (Arizona), cross-sectional	67 firefighters (64 men, 3 women) Average service, 16.6 yr (range, 3–32 yr)	↑ IL-1RA ($P = 0.025$); ↑ macrophage count ($P = 0.002$) associated with a slower rate of FEV_1 decline	Ethnicity, sex, age, baseline FEV_1, ever-asthma, ever smoker, weight change	Participants provided ≥ 4 pulmonary function tests in 7 yr Exposure assessment: genetic polymorphism was the "exposure" of interest; self-reported occupational/ firefighting-related exposure information collected, but not used	Josyula et al. (2007)
Exposure to heat, mental or physical challenges							
PTX3	Plasma and EBC	[Wildland] wood smoke, mimicking wildland firefighter activities USA, pre/post trial	10:0 Exposed to 3 doses of wood smoke $PM_{2.5}$ (filtered-air, 250 µg/m³, and 500 µg/m³) while exercising on a treadmill	Plasma ↑ PTX3 immediately post-exposure, ($P = 0.048$) and 1 h post-exposure ($P = 0.012$) No changes in PTX3 concentration in EBC		Exposure assessment: the controlled exposure to different concentrations appropriate for the pre/post design	Ferguson et al. (2016)
Leukocytes Neutrophils TNFα IL-6 IL-10 CRP	Serum	Heat, mental, physical challenges [repeated work protocol in heat chamber (100 ± 5 °C)] Australia, purpose-built climate chamber (100 °C ± 5 °C), pre/post trial	42 urban firefighters	*Pre/post:* ↑ TNFα; ↑ IL-6 ($P < 0.05$); ↑ leukocytes; ↑ neutrophils ($P < 0.01$), *After 24 h:* ↓ TNFα; ↓ IL-6 ($P < 0.01$) No change in CRP		Exposure assessment: exposure to heat appropriately tested as exposure for the effects assessments that were done in the trial	Walker et al. (2015)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Leukocytes TNFα CRP		Heat, mental, physical challenges [repeated work protocol in heat chamber (100 ± 5 °C)] Australia, pre/post trial	Same cohort as above	Higher baseline leukocytes observed for high body fat ($P = 0.002$) and low mean mass ($P = 0.023$) Significant lower values for TNFα with high lean mass at all time-points	None reported	Similar data set as Walker et al. (2015) Exposure assessment: exposure to heat appropriately tested as exposure for the effects assessments that were done in the trial	Walker et al. (2017)
IL-6 IL8 IL-1β TNFα IL-4 IL-10	Finger prick plasma	Heat, mental, physical challenges Australia, CFA volunteers, pre/post trial	18 controls; 17 sleep-restricted	IL-6 diurnal values above normal levels in both groups Across days: ↑ IL-6 ($P < 0.05$) Within days: ↑ IL-6; ↑ IL-4; ↓ IL-1β; ↓ TNFα; ↓ IL-8 ($P < 0.05$) IL-8 higher in firefighters who received 8 h sleep ($P < 0.05$) No changes in IL-10		Controlled study design with a control group investigating impact of restricted sleep on firefighters when performing simulated wildfire suppression tasks PPE worn but no SCBA Linear mixed models with restricted maximum likelihood Exposure assessment: longer sleep opportunity does not automatically result in more sleep; authors did present the actual hours slept, which was significantly different between groups	Wolkow et al. (2015a)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-6 IL8 IL-1β TNFα IL-4 IL-10	Finger prick plasma	Heat, mental, physical challenges Australia, CFA volunteers, pre/post trial	18 controls; 17 sleep-restricted	Morning ↑ IL-6 related to ↑ cortisol ($P < 0.05$) in sleep-restricted firefighters	Age, BMI, sex	Controlled study design with a control group investigating impact of restricted sleep on firefighters when performing simulated wildfire suppression tasks; PPE worn but no SCBA; 3 days of simulated wildfire suppression tasks ± restricted sleep Exposure assessment: longer sleep opportunity does not automatically result in more sleep; authors did present the actual hours slept, which was significantly different between groups	Wolkow et al. (2015b)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-6 IL8 IL-1β TNFα IL-4 IL-10	Finger prick plasma	Heat, mental, physical challenges [3 days of simulated wildfire suppression tasks ± restricted sleep] Australia, CFA volunteers, pre/post trial	Control, 18 (mild temperatures); 19 (hot temperatures)	Mild vs hot temperatures ↑ IL-4 ($P < 0.05$) Significant condition × time interaction IL-1β, which was consistently lower in hot conditions ($P = 0.011$) Significant day × time interaction for IL-1β in hot conditions, which were higher on D1 vs D3 at 06:15 ($P < 0.05$) and 11:30 ($P < 0.01$). indicating a decrease in IL-1β across days Significant fixed effect of time on IL-6, increasing across time-points ($P < 0.001$); significant day × time effect for IL-6 ($P < 0.05$) showed Il-6 increased from day 1 to 2 Fixed effect of time for TNFα ($P < 0.02$) and IL-8 ($P < 0.04$) indicating a decrease across time Morning IL-6 positively correlated with elevated cortisol ($P < 0.024$)		Controlled study design with a control group investigating impact of heat exposure on firefighters when performing simulated wildfire suppression tasks; ambient temperature for hot condition was 33 °C; PPE worn but no SCBA Exposure assessment: exposure to 2 different temperatures appropriately tested as exposure for the effects assessments that were done in the trial	Wolkow et al. (2017)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
CRP IL-6 TNFα	Whole blood Serum IL-6 and CRP Plasma TNFα	Heat, mental, physical challenge [strenuous work (physical activity) in the heat (with or without humidity to simulate impact of PPE)] Ottawa, Canada, firefighters, pre/post trial	12 older firefighters (age, 49.8 ± 1.1 yr); 12 non-firefighters age-matched (age, 51.7 ± 1.5 yr); and 6 younger firefighters (age, 26.7 ± 0.8 yr) and 6 age-matched (age, 24.8 ± 1.4 yr) non-firefighters	IL-6: showed group × time × condition effect. IL-6 significantly higher post warm/humid conditions vs warm/dry for non-firefighters ($P < 0.05$) but not firefighters; IL-6 also significantly higher in non-firefighters post warm/humid than in firefighters ($P < 0.05$) CRP: significantly decreased with time pre to post in both groups and conditions ($P < 0.05$) TNFα: no significant changes within or between groups, or over time	Age, humidity [not included as true covariates but examined within the analysis]	20 min baseline, HR monitor worn, performed 4 × 15 min cycling at 400 W (~45% of VO_{2peak}) in dry or humid conditions: 35 ± 0.1 °C and 20 ± 1.5 RH (warm/dry) vs 35 ± 0.1 °C and 60 ± 1.0 RH Exposure assessment: exposure to different humidity conditions appropriately tested as exposure for the effects assessments that were done in the trial	Wright-Beatty et al. (2014)
IL-6 Et-1 TXB_2	Plasma	Heat, mental, physical challenges [physical challenge (bike ergometer) ± dual FSTD mental challenge USA, professional [career] firefighters, pre/post trial	12 professional [career] firefighters 11.58 ± 7.52 yr experience	No differences between conditions for IL-6, Et-1 or TXB_2 Positive correlation between cortisol, IL-6, Et-1, and TXB_2 Negative correlation between IL-6 and TXB_2	NR RMANOVAs used with paired samples *t*-tests for between conditions analyses	Well controlled Exposure assessment: exposure to exercises or mental challenge appropriately tested as exposure for the effects assessments that were done in the trial	Webb et al. (2011)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
IL-2 IL-6	Plasma	Heat, mental, physical challenges USA, exercise with and without FSTD, pre/post trial	9 professional [career] male firefighters	Significant condition × time interaction for IL-2 ($P < 0.05$) NS change over time for IL-6 under either condition		Dual task challenge using computer decision-making FSTD while exercising; low workload selected to limit stimulating markers of inflammation because of prolonged high-intensity training Exposure assessment: engagement in controlled drill exercise appropriately tested as exposure for the effects assessments that were done in the trial	Huang et al. (2010a)
Catastrophic events							
WTC-lung injury CRP FEV_1 (lung function) Apo-AII MIP-4 sVCAM MPO	Serum	WTC firefighting, WTC-exposed firefighters, nested case–control study	124/171 subcohort controls, 68/100 WTC-LI (lung injury) resistant cases, and 66/100 WTC-LI susceptible	WTC-LI susceptible cases had higher Apo-AII, CRP, and MIP-4 Resistant WTC-LI cases had significantly higher sVCAM and lower MPO			Weiden et al. (2013)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Macrophages Neutrophils Lymphocytes Eosinophils MMP-9	Induced sputum	WTC firefighting, cross-sectional study	39 highly exposed firefighters (FDNY-FF); Control groups of 12 Tel-Aviv firefighters (TA-FF) and 8 Israeli health care workers not exposed to WTC dust	FDNY-FF vs TA-FF vs controls ≥ 10 days work at WTC associated with significantly higher percentage of neutrophils ($P = 0.046$); and eosinophils ($P = 0.038$) Trend for higher MMP-9 in FDNY-FF vs TA-FF Both firefighter groups significantly higher than control ($P = 0.0001$)	Current or post tobacco smokers were excluded	Unbalanced sample sizes; single time-point, 10 months post exposure; non-parametric analyses used Exposure assessment: it did not account for potentially confounding exposure in the intervening period between exposure of interest and measurement of effects; self-reported/ qualitative exposure among exposed groups used in analysis	Fireman et al. (2004)
FEV_1 (lung function) Leukocytes	Whole blood	WTC-exposed firefighters, pre/post	9434 for FEV trajectory analysis 2103 for secondary airflow limitation analysis	Higher blood eosinophil and neutrophil concentrations each associated with accelerated FEV_1 decline after adjustment for covariates (OR, 1.10 per 100 eosinophils/mL; 95% CI, 1.05–1.15; and OR, 1.10 per 1000 neutrophils/mL; 95% CI, 1.05–1.15, respectively)		Individuals experiencing accelerated FEV_1 decline were more likely to have incident airflow limitation	Zeig-Owens et al. (2018)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1 (lung function) MMP-3 MMP-12 MMP-1, -2, -7,-8, -9, and -13	Serum	WTC firefighting, nested case–control study	70 with WTC-L1 (lung injury); 123 controls from initial cohort of 1720	↓ MPP-3; ↓ MMP-12 ($P < 0.05$) Elevated MMP-3 and MMP-12 within 200 days of WTC exposure showed reduced odds of developing WTC-LI by 73% and 54% respectively Elevated MMP-1 and -8 but not predictive of lung injury No changes in MMP-2, MMP-7, MMP-9, and MMP-13 expressions			Kwon et al. (2013)
FEV_1 (lung function) MMP-2 TIMP-1	Serum	WTC firefighting, nested case–control study	Baseline cohort, 801 (never smokers) Resistant cases, 100; 77 with serum (recovered FEV_1 quicker) Cohort controls, 171; 137 with serum	Significant difference in lung function between cohort controls and those that were more resistant to persistent lung function decline ($P < 0.001$) From chest CT imaging: 14% of resistance cases had bronchial wall thickening, whereas 35% of the controls had evidence of airway inflammation ($P < 0.03$) MMP/TIMP balance reflects independent pathways to airway injury and repair Elevated TIMP-1 and MMP-2 predicts recovery of lung function Elevated MMP-1 reduces odds of recovery, years after WTC exposure	Pre-9/11 FEV_1, BMI, age		Nolan et al. (2014)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Chronic rhinosinusitis Sinus polyps IL-6 IL-8 TNFα Neutrophils FEV_1 (lung function) PMN	Serum	WTC firefighting Nested case–cohort study	179 study patients: 76 developed chronic rhinosinusitis; 62 were medically managed and 14 were refractory to medical management (≥ 3 months) and elected to have surgery	IL-8; TNFα and PMN count significant predictors ($P < 0.05$) of sinus disease severity Increasing IL-6, IL-8, GRO and neutrophil concentrations reduced risk of chronic rhinosinusitis progression; increased TNFα, increased risk of progression No significant differences in spirometric parameters including FEV_1 and FEV_1/FVC in cases vs controls Increase in IL-6 decreased the odds of abnormal FEV_1	Biomarkers used as continuous covariates in logistic regression models	6 months post exposure to 9/11; presence of sinus polyps indicative of chronic inflammation Exposure assessment: self-reported exposure, which will be accurate for the time of arrival; no individual data on tasks performed at WTC taken into account; possible unmeasured events before or after WTC exposure	Cho et al. (2014)
COPD Asthma Cytokines Eosinophils	Serum	WTC firefighting, repeated measurements	Subgroup of 215 from 2137 WTC-exposed	Eosinophil concentration ≥ 300 cells/μL was associated with increased risk of asthma/COPD overlap, but not with either in isolation IL-4 predicted asthma/COPD overlap; greater IL-21 concentration associated with isolated-asthma and isolated-COPD	Age, race, smoking, WTC exposure, first post-9/11 FEV_1/FVC ratio, and BMI	Reported results of regression models and 95% CI Exposure assessment: self-reported exposure, which will be accurate for the time of arrival; no individual data on tasks performed at WTC taken into account; possible unmeasured events before or after WTC exposure	Singh et al. (2018)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1 (lung function) GM-CSF IP-10 MDC	Serum	WTC firefighting, nested case–control cohort study	801 baseline cohort (never smokers) 70 cases of airflow obstruction 124 controls	Lung function ↓ in 12% of cases and ↑ in 3% of controls Elevated GM-CSF and MDC levels associated with increased risk of airflow obstruction in subsequent years	BMI, age, PMN	Cases of airflow obstruction defined as FEV_1 < the lower limit of normal (LLN)	Nolan et al. (2012)
FEV_1 (lung function) LPA Apo-A1 PMN	Serum	WTC firefighting, nested case–control study	801 baseline cohort: 62 cases and 111 controls	PMN count included in multivariable logistic model to predict decline in lung function and likelihood of developing WTC-lung injury		Exposure assessment: self-reported exposure, which will be accurate for the time of arrival; no individual data on tasks performed at WTC taken into account; possible unmeasured events before or after WTC exposure	Tsukiji et al. (2014)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
MCP-1 LPA Cytokines	Blood serum	WTC firefighting, first responders who had lung damage up to 16 yr after 11 September 2001, cross-sectional	15 cases with lung damage from WTC exposure, and 15 controls	↑ MCP-1 Positive correlations between LPA and membrane-bound soluble receptor for advanced glycation end-products; and positive correlations among various cytokines and chemokines; strong negative correlations between the cytokines and chemokines and several sphingolipids and omega fatty acids	Smoking	Statistically rigorous; only 1 analyte was at a higher concentration in exposed group; the other 8 analytes were at concentrations not significantly different between exposed and controls; correlation matrix of serum biomarkers in WTC-exposed first responders Exposure assessment: no information on exposures in the intervening period between exposure of interest and measurement of effects, but information used probably sufficient for research questions	Lam et al. (2020)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Sarcoidosis	Serum	WTC-exposed firefighters with sarcoid arthritis, repeated measurements	11 reported in study From 9/60 plus 2 of ongoing monitoring	Descriptive account 1 out of 9 elevated CRP Chronic inflammatory polyarthritis appears to be an important manifestation of sarcoidosis WTC exposure		Biopsy-proven sarcoidosis; 9 by transbronchial or mediastinal biopsy, 1 by both liver and bone biopsies, and 1 by Kveim testing Exposure assessment: self-reported exposure, which will be accurate for the time of arrival; no individual data on tasks performed at WTC taken into account; possible unmeasured events before or after WTC exposure	Loupasakis et al. (2015)
Sarcoidosis	Peripheral whole blood	WTC-exposed firefighters, nested case–control study	55:100	17 allele variants of HLA and non-HLA genes were found to be associated with sarcoidosis; similarities found between genetic variants with WTC-related sarcoidosis and those reported previously in sporadic sarcoidosis cases within the general population		Specifically reporting on genetic variants associated with WTC-related sarcoidosis Exposure assessment: genotype/genetic variants was the actual "exposure" of interest in this susceptibility study of sarcoidosis among WTC firefighters; no data on tasks of airborne exposures	Cleven et al. (2019)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Lung function process alteration and bronchial hyperreactivity							
FEV_1, FVC (lung function) Functional polymorphisms in TNFα; TGFβ1; IL-1β; IL-1RN; IL-13; and IL-8 genes	Blood or buccal cell samples for DNA analysis	Employment as a firefighter USA (Arizona), Phoenix Fire Department subset of active firefighters, cross-sectional study of subset from available medical data (1988–2003)	451 active firefighters	Interindividual variability in progressive decline in FEV_1 may be explained in part by genetic variations within genes involved in inflammatory responses	Age, race, ethnic group, smoking status, gender	Exposure assessment: "active firefighter" is a crude measure of exposure with potential for misclassification	Yucesoy et al. (2008)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1, FVC (lung function) CC16 SP-A BHR	Serum	Employment as a firefighter Netherlands, cross-sectional study from 23 brigades	402 firefighters 356 men, 46 women (combination of 305 volunteers, 60 professional [career], 37 both)	CC16 was negatively associated with the number of fires fought in last 12 months in current non-smokers ($P = 0.04$); this grew stronger when adjusted for FEV_1 ↑ CC16 in male firefighters ($P = 0.04$), positively associated with FEV_1 and FVC ($P = 0.03$) When the analysis was stratified for atopy, a weak association ($P = 0.07$) was found between CC16 and dose response slope (% decline in FEV_1/mg inhaled methacholine); which grew stronger when adjusted for smoking ($P = 0.04$) SP-A was positively associated with exposure to fire smoke within 2 days preceding testing for those that also had respiratory symptoms ($P = 0.003$), and this became stronger when adjusted for smoking ($P = 0.0007$); the strength of this relationship increased with reduction in time between exposure and testing. (i.e. < 24 h, $P = 0.0001$; vs < 3 days $P = 0.120$)	Sex, age, atopy, BMI, diurnal variation, smoking behaviour, lung function (FEV_1 and FVC), sampling time	Large cross-sectional study, with wide range of covariates controlled for Exposure assessment: self-reported exposure is prone to bias and misclassification, particularly with regard to frequency (number of fires fought)	Greven et al. (2011a)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1 (lung function) IL-10 genetic polymorphisms	Whole blood samples Buccal cells in mouthwash	Employment as a firefighter Arizona, USA, repeated measurements	1204 firefighters with ≥ 6 annual FEV_1 measures	↓ Lung function based on genotyping at the 1668 SNPs	Age, gender, race/ethnicity, smoking, baseline FEV_1	379 with SNP data	Burgess et al. (2004)
FEV_1, FVC (lung function) Airway responsiveness, HCT for provocation	NA	Training (smoke chamber) Singapore, recruits and professional [career] firefighters, pre/post	10 new recruits and 10 professional [career] firefighters	Airway responsiveness observed only among professional [career] firefighters after the challenge Changes in ventilatory function were seen in firefighters No changes in adjusted analyses	Age, height, length of service, time in smoke chamber, smoking pack-years, and pre-exposure level	All participants were smokers and male; results were only significant in unadjusted analyses Exposure assessment: high level, brief exposure was assured by design, but exposure intensity and composition not measured	Chia et al. (1990)
BHR FEV_1, FVC (lung function) Self-reported respiratory symptoms		Wildland (forest) firefighting Greece Forest firefighters from 2008, Repeated measures (follow-up within 1 wk of exposure and in the off-season ~3 months later)	60 with measures < 1 wk post-exposure and in the off-season	Post-exposure compared with off-season: pulmonary function effects ↑ Respiratory symptoms (wheezing, cough, expectoration, chest tightness) No differences in BHR	None	Cases serve as their own controls and may work as municipal firefighters in the off-season; all participants are male and high proportion smoke (87%) Exposure assessment: time away from firefighting adequately assessed	Gianniou et al. (2018)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1, FVC (lung function)	NA	Wildland Portugal, active wildland firefighters, cross-sectional	209 firefighters, no controls	11.8% had obstruction. 41% of obstructed individuals were non-smokers Progressive decline in FEV_1 and FEV_1/FEV_6 with increasing length of service	None	Descriptive study; reliant on self-reported data; 85.7% not using PPE; 42.9% smokers Exposure assessment: self-reported smoke intoxication may be misclassified; duration of service will however be relatively reliable	Almeida et al. (2007)
Bronchial reactivity FEV_1, FVC (lung function) Self-reported respiratory symptoms	NA	Employment as firefighter Greece, firefighters, cross-sectional	63 professional [career] firefighters, 29 trainees with < 1 yr experience; 18 healthy controls	↑ Atopy, allergic rhinitis, cough, dyspnoea, and BHR among professional [career] firefighters (BHR, 21% compared with 3% trainees)	Age, smoking, and pre-existing asthma in some comparisons	Source of controls unspecified; all men Exposure assessment: employment categories used for effects comparisons likely adequate; potential confounding of career length with age	Gianniou et al. (2016)
FEV_1, FVC (lung function) BHR Atopy	Blood	Employment as firefighter Netherlands, 54 municipal fire brigades, cross-sectional	402 firefighters, 305 volunteers, 60 professional [career], 37 both	↑ BHR associated with the number of fires fought in the last 12 months with ($P = 0.018$), and without ($P = 0.03$) adjustments for covariates); but not associated with working years This association was stronger among atopics	Smoking, sex, atopy, age, and exposure in main job held	Self-reported smoke exposure potentially problematic Exposure assessment: self-reported exposure prone to bias and misclassification, particularly with regard to the frequency (number of fires fought)	Greven et al. (2011b)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1, FVC (lung function) DL_{CO}	NA	Employment as firefighter USA (Washington), Seattle firefighters voluntary medical surveillance programme, repeated measures	812 firefighters with ≥ 2 yr DL_{CO}	Stable ventilatory capacity overtime was observed Overtime, DL_{CO} decline of –1.02 mL/min per mm Hg associated with year of measurement; decline of –0.006 mL/min per mm Hg associated with number of fires fought	Age, gender, race, height, prior smoke exposure	Annual measures over an 8-yr period, ≥ 2 yr DL_{CO} needed for inclusion Self-report questionnaires for exposure potentially problematic	Burgess et al. (1999)
FEV_1, FVC (lung function) Obstruction	NA	Employment as firefighter USA (Connecticut), cross-sectional	22 non-smoking firefighters; 31 smoking firefighters	35% of smokers and 13% of non-smokers had airway obstruction. In non-smoking group, obstruction only present in firefighters with > 25 yr-experience	Smoking, years of firefighting, age	Self-reported respiratory and occupational questionnaire	Loke et al. (1980)
Respiratory symptoms	NA	Employment as firefighter Netherlands, 54 municipal fire brigades, cross-sectional	1330 active firefighters Random sample of 2711 from Dutch population	Strong association found between self-reported inhalation incident and presence of respiratory symptoms (i.e. atopy, asthma, BHR-like symptoms)	Smoking, sex, atopy, age	Self-reported smoke exposure potentially problematic Exposure assessment: self-reported exposure prone to bias and misclassification, particularly with regard to the frequency (number of fires fought)	Greven et al. (2011c)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
FEV_1, FVC (lung function) Respiratory symptoms (upper and lower)	NA	WTC firefighting USA (New York), WTC Worker and Volunteer Medical Screening, pre/post (screened between 1 and 2.5 yr post-9/11)	9442 first responders	New or worsened upper and lower respiratory symptoms reported after 9/11 (compared with before), highest among workers that arrived on 9/11 and worked in the dust cloud At time of follow-up, 20.5% had low FVC compared with 4.4% expected in the general population	None; categorized participants by date of arrival and exposure to dust cloud	Eligible participants included any worker (firefighters but also others) in search/rescue/clean-up for ≥ 80 h or working with human remains examinations for ≥ 25 h	Herbert et al. (2006)
Bronchial reactivity (MCT) FEV_1, FVC (lung function)	NA	WTC firefighting USA (New York), WTC firefighters, pre/post (with follow-ups pre-9/11 and 2 post-9/11, 2 yr and > 10 yr after)	173 firefighters with pre-9/11 health data and 2 post-9/11 MCT measures	16% and 25% had BHR at the first and second follow-ups; BHR at follow-up associated with ↓ FEV_1 rate (15.39 mL/yr)	Age, abnormal lung function at baseline, smoking	MCT method differed at the first and second post-9/11 visits; the first may be overestimated; selection bias possible; all men, 95% White Exposure assessment: exposure not used in analysis reported	Aldrich et al. (2016)

Table 4.8 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)	Covariates controlled	Comments[b]	Reference
Lung injury based on abnormal spirometry	NA	WTC firefighting USA (New York), WTC firefighters, pre/post (followed up by 6 months post-9/11 with continued follow-up until 2017)	1475 firefighters with and 4264 without lung injury at 6 months post-9/11	BMI, dyslipidaemia, and smoking ↑ risk of WTC-associated lung injury	Age at 9/11, time to follow-up, smoking, race	Longitudinal follow-up and sophisticated statistical modelling are strengths; focus was on modifiers (metabolic syndrome) of the link between WTC and lung injury; no unexposed control group	Kwon et al. (2021)

9/11, WTC disaster on 11 September 2001, New York, USA; Apo-AI, -AII, apolipoprotein-AI, -AII; BALF, bronchoalveolar lavage fluid; BHR, bronchial hyperreactivity; BMI, body mass index; CC16, Club (Clara) cell protein 16; CFA, Country Fire Authority; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computerized tomography; cTnT, cardiac troponins; CVD, cardiovascular disease; DLCO, single breath diffusing capacity of carbon monoxide; EBC, exhaled breath condensate; ECP, eosinophil cationic protein; FEF25–75, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume (total amount air exhaled) in one second; FSTD, firefighting strategies and tactics drill; FVC, forced vital capacity, total amount air exhaled in 1 breath; GM-CSF, granulocyte/macrophage colony-stimulating factor; GRO, growth-regulated oncogene; HCT, histamine challenge test; HLA, human leukocyte antigen; HR, heart rate; hsCRP, high sensitivity CRP; ICAM-1, intercellular adhesion molecule-1; INF-γ, interferon gamma; IL, interleukin; IP-10, interferon inducible protein-10; LPA, lysophosphatidic acid; MCP-1, monocyte chemoattractant protein; MCT, methacholine challenge test; MDC, macrophage derived chemokine; maxMETs, maximal treadmill exercise testing; MMP, matrix metalloproteinases; MMP-1, interstitial collagenase; MMP-9, interstitial gelatinase; MPO, myeloperoxidase; NA, not applicable; 1-OHP, 1-hydroxypyrene; OR, odds ratio; O_2, oxygen; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; PMBC, peripheral blood mononuclear cells; PMN, polymorphonuclear neutrophils; PPE, personal protective equipment; ppm, parts per million; PVC, polyvinyl chloride; PTX3, pentraxin; RES, resveratrol; RH, relative humidity; sIL-2R, soluble interleukin-2 receptor; SAA, serum amyloid A; SAR, standardized admission ratio; SCBA, self-contained breathing apparatus; SD, standard deviation; SNP, single nucleotide polymorphisms; SP-A, serum surfactant-associated protein A; SSA, serum amyloid protein; TAC, total antioxidant capacity; TIMP, tissue inhibitors of metalloproteinases; TNFα, tumour necrosis factor alpha; TRF, time-restricted feeding; VCAM-1, vascular cellular adhesion molecule-1; sVCAM, soluble VCAM; VGEF, vascular endothelial growth factor; WTC, World Trade Center; WTC-LI, World Trade Center lung injury; vs, versus; yr, year.

[a] Type of fire may include wildland, wildland emissions, training, municipal, chemical fire, routine firefighting, etc.

[b] Factors to be considered for study quality included the methodology and design, reporting, and exposure assessment quality.

↑, increase; ↓, decrease.

Smith et al. (2019) also observed significant increases in P-selectin and matrix metalloproteinase-9 (MMP-9) in 24 male firefighters after exposure to live-fire structure firefighting drills. [The Working Group noted that this finding of PM-induced MMP-9 generation has been observed in airway epithelial cells where it lasted for 48 hours (Morales-Bárcenas et al., 2015).]

Watt et al. (2016) reported significantly higher baseline IL-6 and neutrophil concentrations in fire instructors, from the United Kingdom, than in healthy controls. After a 7-week no-heat exposure period, levels of IL-6, neutrophils, and lymphocytes were significantly reduced in the fire instructors. [The Working Group noted that this initial elevation in the baseline IL-6 concentration may be because of exposures before testing, and reflective of occupational exposure as a fire instructor.] After the 7-week no-heat exposure period, participants completed a 4-week training course during which there were 15 exposures to live training fires. After the first heat exposure of the training course, IL-6 was again significantly elevated in the fire instructors. Baseline IL-6 concentrations were still significantly elevated at week 4 compared with week 1 before the final heat exposure. Before exposure at week 4, IL-6 concentrations in fire instructors were also significantly higher than those of the control group, although they were still significantly lower than their original baseline measures. After fire exposure at the end of the training week, IL-6 levels were not significantly different from the initial baseline levels before the washout period. [The Working Group noted that although there was only a small sample group (n = 12), and a lack of control over the heat exposure and the specific tasks completed, the pre/post trial study design demonstrated the temporal relationship between the measurements and the firefighters' exposures.]

[The Working Group noted that, for the studies available throughout the present section (Section 4.1.4), repeated (and cumulative) exposures could be regarded as similar to chronic types of exposure. The Working Group also noted that fire instructors, who lead training exercises, are exposed in a similar manner to firefighters; however, they commonly oversee several live-fire exercises in a given day, and these are often repeated over several weeks, year after year (Fent et al., 2019). This suggests that fire instructors' cumulative exposures may be higher and more frequent. The Working Group considered that repeated inflammation may be expected among fire instructors and, over time, could be considered as chronic inflammation.]

Cordeiro et al. (2021) exposed 37 volunteer firefighters, from São Paulo, Brazil, to high temperatures and by-products of combustion in a structure fire simulator that exceeded 600 °C, for 20–30 minutes, and repeated two to three times per day, twice per week, for 4 weeks, as part of a structure training course. This exposure to high temperatures and PM was found to elicit an acute inflammatory process in the airways, with samples of nasal lavage and sputum showing significant acute increases in concentrations of pro-inflammatory and anti-inflammatory cytokines; IL-8; IL-10; IL-2; and the ratio of IL-12p40:IL-12p70. These markers of inflammation had returned to baseline by the end of the training course; however, CC16 concentrations were significantly higher at the end of the 4-week training course than at baseline, indicating possible lung injury. [The Working Group noted that the strengths of this study were the pre/post study design and the longitudinal sampling of nasal lavage and sputum samples to measure airway markers of inflammation.]

In two studies, conducted in Arizona, USA, the impact of smoke exposure during overhaul on markers of inflammation was investigated (Burgess et al., 2001, 2002). Changes in lung function, and in serum CC16 and surfactant-associated protein A (SP-A) were associated with concentrations of specific products of combustion (Burgess et al., 2001). [The Working Group

noted that the study by Burgess et al. (2001) was limited to the evaluation of overhaul exposure and to comparing effects in firefighters wearing air-purifying respirators and no respiratory protection.] In Burgess et al. (2002), there was a significant decline in sputum IL-10 concentration (70%) and mean lung function (forced vital capacity, FVC), after exposure to smoke during an overhaul. Significant increases in serum CC16 and SP-A concentrations were observed; however, these changes were not correlated with IL-10 measures. No significant changes occurred in concentrations of IL-8 and TNFα, despite the fact that IL-8 levels almost doubled. [The Working Group noted that changes in IL-10 concentrations after smoke exposure may result in changes in other inflammation mediators (including IL-8 or TNFα; Burgess et al., 2002) within the lung, which can lead to chronic respiratory effects. Additionally, the significant increases in CC16 and SP-A were indications of increased lung permeability after smoke exposure.]

Gaughan et al. (2014b) reported that increases in high-sensitivity C-reactive protein (CRP) were associated with a decrease in lung function in a cross-sectional study of 401 career firefighters from the midwestern region of the USA. [The Working Group noted that the finding of this study was relevant because CRP has been linked to the development of ischaemic heart disease and stroke, the two primary causes of death in individuals with chronic obstructive pulmonary disease (COPD). These are all chronic inflammatory conditions that have previously been reported in firefighters. However, in the absence of a control group, this finding should be interpreted with some caution.]

[The Working Group noted that all these studies reported significant changes in markers of acute inflammation after structure fire exposure. The strength of some of these papers lay in the study design, which included measures of inflammatory biomarkers collected both pre- and post-fire exposure. The elevations in markers of lung injury suggested tissue damage and chronic inflammation.]

(ii) Wildland fires

Gianniou et al. (2018) completed a thorough clinical assessment and compared markers of inflammation in induced sputum, serum, and bronchoalveolar lavage (BAL) fluid in 60 wildland (forest) firefighters who had completed several consecutive days of firefighting, during the 2008 fires in Greece, and again during the off-season, approximately 3 months after the exposure. The results indicated that eosinophilic and neutrophilic inflammation was evident in the bronchial airways after acute exposure to forest firefighting. Forest firefighting for > 10 hours induced a more intense systemic inflammation than did < 10 hours exposure. Inflammatory cytokine markers were significantly higher after occupational exposure than during the off-season, indicating an acute inflammatory response that did not appear to persist into the off-season (Gianniou et al., 2018). Regarding lung function, forced expiratory flow (FEF) at 25–75% of predicted FVC (FEF25–75), and forced expiratory volume in 1 second (FEV_1)/FVC were significantly reduced post-exposure, with an increased prevalence in respiratory symptoms compared with off-season. However, there was no significant difference in bronchial hyperreactivity off-season and post-exposure. [The Working Group noted that a strength of the study was the thorough clinical assessment of participants. The Working Group noted that these data were indicative of airway and systemic inflammation after a 7-day exposure period; however, the lack of a true baseline measure before deploying to the forest fires was a limitation. It was also hard to control for any additional exposure in the 3-month interim period before the follow-up sample was collected.]

Cherry et al. (2021) conducted a repeated measures study with 160 firefighters after the Fort McMurray fire disaster, a 3-month fire in

Alberta, Canada. Of a panel of 42 inflammatory markers, levels of 25 markers were significantly higher in samples collected in the first 19 days than in samples collected 16–20 weeks later. Clustered within fire service, cumulative exposure, dehydration, and time since last deployed to a fire were all related to late cluster scores of inflammatory markers, as assessed by principal component analysis (PCA). It was concluded that concentrations of inflammatory markers were related to estimates of exposure and decreased with time away from the exposure. [The Working Group noted some limitations with this study: samples were collected from two different locations, at different time-points, and no baseline samples were collected pre-exposure. The nature of the deployments also differed between stations, although estimates of exposure to PM were provided in the appendix to the manuscript.]

Significant increases in IL-8 concentrations pre- to post-shift were reported in three studies conducted in British Columbia, Canada; the Savannah River site, South Carolina, USA; and the Victoria region, Australia; respectively (Swiston et al., 2008; Hejl et al., 2013; Main et al., 2020). The increase in IL-8 was significantly higher in firefighters who spent > 75% of the work shift lighting the fires, as opposed to those who were completing other activities such as "holding" (i.e. maintaining the fire within pre-established boundaries) or "mop-up" (i.e. extinguishing actively smouldering areas) (Hejl et al., 2013). [The Working Group noted that the increase in IL-8 levels observed by Hejl et al. might be because of exposure to the lighter fluid (diesel: gasoline ratio, 3:1) used during the work shift.] Swiston et al. (2008) also showed evidence of inflammatory markers (i.e. granulocytes) in sputum samples collected from forest firefighters after a work shift. Serum concentrations of IL-6, IL-8, and monocyte chemoattractant protein (MCP-1) were also significantly increased after firefighting activity, indicating a systemic inflammatory response after occupational exposure to seasonal forest fires. Estimated exposure to PM was high (peak levels, > 2 mg/m^3), and 65% of the firefighters reported acute respiratory symptoms after the 8-hour shift. A significant increase in plasma IL-8 and IL-6 levels was also observed after a 12-hour shift of wildfire suppression activities associated with the 2009 "Black Saturday" natural disaster in Victoria, Australia. This effect was also accompanied by a significant decrease in IL-10 levels (Main et al., 2020).

Main et al. (2013) reported changes in plasma inflammatory markers across two consecutive days of live-fire suppression tasks (i.e. controlled forest burning) in Australia. It was found that several inflammatory markers changed significantly between pre- and post-shift measurements after a 12-hour shift (i.e. IL-1β, IL-5, IL-7, IL-10, and TNFα). Some inflammatory markers that presented an attenuated response on day 2 were IL-1β, IL-7, IL-4, IL-6, IL-8, and IL-13. [The Working Group noted that although a strength of this study was the repeated measures across two consecutive days, the lack of exposure data represented its limitation. In both instances, these data were indicative of an acute inflammatory response.]

Conversely, Wu et al. (2020b) reported no significant changes pre/post-shift for any of the inflammatory markers, when using EBC to measure cytokines. [The Working Group questioned the sensitivity of the EBC method to measure these biomarkers.]

[The Working Group noted that although most of these studies reported significant changes in markers of inflammation after wildland fire exposure, these effects were primarily acute with limited opportunities to follow up the assessment of chronicity.]

(iii) Employment as a firefighter

Evidence that acute exposure to fire smoke induces an acute neutrophilic airway and long-lasting systemic inflammation in otherwise healthy municipal firefighters was presented by

Greven et al. (2012). Nearly half (44%) of the participants (37 volunteer, 8 career, and 6 as both) reported elevated sputum neutrophil levels (> 60%) that were positively associated with serum IL-8, IL-10, and TNFα concentrations within 24 hours of exposure. A significant increase in serum IL-8 at 24 hours, and at 1 week post-exposure and 3 months post-exposure compared with pre-exposure was observed, as well as a significant increase in serum IL-6 concentrations at 3 months post-exposure. In addition, perceived exposure (i.e. the use of self-contained breathing apparatus, SCBA, and self-reported discomforting exposure to fire smoke) was positively associated with IL-8 concentrations, which were still significantly higher 1 week after exposure compared with baseline. A weak positive correlation was observed between post-exposure levels of neutrophils and particle counts in induced sputum. [The Working Group noted that the strength of this study was the longitudinal follow-up design measuring end-points that could be considered representative of chronic inflammation from both sputum and serum samples. Therefore, the Working Group considered that this study was particularly informative for this key characteristic. Although there was no information on exposure during the 3-month period between samples, airway neutrophilia is a common feature of many chronic inflammatory lung diseases and is associated with disease progression (Jasper et al., 2019).]

Evidence of the long-term effects of occupational exposure on airway and systemic inflammation in firefighters was reported by Gianniou et al. (2016). A thorough clinical assessment was conducted in three groups: career firefighters, trainee firefighters, and healthy controls. The results indicated that inflammatory markers (IL-8, eosinophil cationic protein (ECP), vascular endothelial growth factor (VEGF), and TNFα) in sputum supernatants from career firefighters were significantly higher than in samples from trainees. Serum IL-8 and TNFα concentrations were also significantly higher in the career firefighters than in the trainees. In addition, significantly higher levels of sputum and serum IL-8 and TNFα were reported for the trainees than for the healthy controls. [The Working Group noted that even with relatively short occupational exposure (≤ 1 year), there was a measurable increase in inflammatory markers.] In addition, longer duration of time in service was correlated with higher number of leukocytes in sputum and BAL fluid. From the bronchial biopsy samples provided, there was evidence of mild thickening of the basal membrane and focal increase of mucous production in all career firefighters, with trainees also exhibiting mild thickening of the basal membrane, and small increases in mucus production in almost all samples. The presence of eosinophils was greater in career firefighters than trainees from these tissue samples. Of note, the detection of allergic bronchial sensitization documented by the presence of atopy, and eosinophilia in induced sputum, BAL, and bronchial biopsies are all indicative of chronic inflammation. These results indicated that the effect on bronchial and systemic inflammation was augmented by factors reflective of extended exposure in career firefighters. [The Working Group noted that this study was particularly informative because of the extensive phenotyping and consistency of results (i.e. higher levels of eosinophils in both sputum and BAL), the parallel measurements of biomarkers in sputum and serum, and the use of employment categories used for effect comparisons. Recent evidence suggested that eosinophilia may be a cause, rather than a consequence, of lung cancers in some populations (Wang et al., 2022). However, the potential for self-selection bias was a limitation of the study because only career and trainee firefighters provided biopsies.]

[The Working Group noted that collectively the findings from Greven et al. (2012) and Gianniou et al. (2016) suggest the presence of

long-lasting bronchial and systemic inflammation in career firefighters.]

Watkins et al. (2021) was the only study on occupational exposure as a firefighter to investigate the number of fire heat exposures as the precipitating factor leading to an inflammatory response. Several inflammatory markers were analysed in samples from 110 fire service personnel (53 fire service instructors, and 57 career firefighters). Levels of neutrophils, IL-6, IL-1β, and CRP were significantly higher in fire service instructors than in firefighters. Multiple regression analysis revealed that inflammatory markers could be explained by the number of heat exposures per month. Instructors with > 9 heat exposures per month were 6–12 times as likely to be classified as "at risk" of cardiovascular disease or myocardial infarction and had biomarkers above healthy ranges. [The Working Group noted that this study was particularly informative because it apparently demonstrated a relationship between the inflammatory markers and number of exposures. However, the limitations of the study were self-reported exposures and the cross-sectional design.] Watkins et al. in a previous study (Watkins et al., 2019b) reported that fire service instructors had elevated baseline levels of inflammatory markers (i.e. IL-6 and IL-1β) compared with non-exposed controls. [The Working Group noted the matched healthy control group, and well-controlled study design as strengths of this study; however, the number of self-reported exposures might have been misclassified.]

Andersen et al. (2018a) reported a significant increase in vascular cellular adhesion molecule-1 (VCAM-1) and a decrease in lung function after participation in fire extinction activities. [The Working Group noted that IL-6 and IL-8 were below the levels of detection; however, this did not affect the results for VCAM-1 since it is usually expressed only after endothelial cells are stimulated by cytokines.] Andersen et al. (2018b) observed no changes in VCAM-1 levels or lung function after 3 days of live-fire training exercises, although CRP levels were statistically significantly increased after firefighting training when compared with the control samples collected 2 weeks after the firefighting training [The Working Group noted that these findings were suggestive of acute inflammation.]

A significant increase in interleukin-1 receptor antagonist (IL-1RA) and sputum macrophage count was associated with a slower rate of decline in lung function (Josyula et al., 2007). [The Working Group noted that systemic IL-1RA is natural inhibitor of IL-1β, thus the finding may be indicative of inflammation. However, sputum samples for the assessment of cytokine concentrations were collected at a single time-point only, and exposure history was not reported.]

A series of publications added to the extensive literature on the association between chronic inflammation and occupational exposure as a firefighter employee, although they had some flaws. Four studies reported clinical outcomes apparently associated with chronic inflammation in firefighters. Bergström et al. (1988) published a case report of a firefighter who developed chronic severe asthma that was fatal 25 months after onset. Bodienkova & Ivanskaia (2003) reported significant increases in IL-2, IL-6, IL-1β, and TNFα levels in firefighters with various forms of encephalopathy. Orris et al. (1986) presented case reports of two firefighters who developed chloracne after exposure to a silicon tetrachloride spill (see also Section 4.1.5). Kern et al. (1993) reported on a highly unique cluster of four cases of sarcoidosis (a disease characterized by the growth of collections of inflammatory cells –granulomas – in the body, most commonly in the lungs and lymph nodes) from a cohort study in Rhode Island, USA. [The Working Group noted that these studies, despite not clearly demonstrating mechanistic evidence of chronic inflammation from occupational exposure as a firefighter, presented examples of

diseases associated with chronic inflammation in firefighters.]

Several pre/post trial studies investigated therapeutic treatments to offset inflammation in firefighters, in acknowledgement of the emerging risk of inflammatory markers compromising firefighter health (i.e. precipitating cardiovascular disease and cardiovascular events, respiratory ill health, and acute and chronic lung function impairment) (Barceló-Coblijn et al., 2008; Macedo et al., 2015; Smith et al., 2019; Sotos-Prieto et al., 2019; Diaz-Castro et al., 2020a; McAllister et al., 2020, 2021). [The Working Group noted that these studies did not demonstrate clear mechanistic evidence of chronic inflammation from occupational exposure as a firefighter, rather they focused on the efficacy of these interventions to reduce the acute inflammatory response to firefighting.]

One paper reported a significant interaction effect between cognitive function (attention), inflammatory markers IL-6 and CRP, and alcohol consumption (Yun et al., 2021). [The Working Group noted that the alcohol consumption in this population may be indicative of a negative coping strategy. However, the cross-sectional study design did not allow for the assessment of alcohol consumption as a contributing factor for chronic inflammation.]

(iv) Exposure to heat, or mental and/or physical challenge

Several pre/post trials (n = 10) investigated the inflammatory responses of firefighters to different occupational stressors, such as heat, smoke, humidity, physical exertion or specific firefighting tasks, sleep restriction, and cognitive load, at multiple data time-points. [The Working Group noted that simulation or controlled pre/post trial designs have enabled the research community to specifically investigate the impact of different fireground stressors on inflammatory markers in firefighters.] There was evidence that the individual stressors such as PM (Ferguson et al., 2016), heat stress (Walker et al., 2015; Wolkow et al., 2017; Watkins et al., 2019b), humidity (Wright-Beatty et al., 2014), strenuous physical activity (Webb et al., 2011; Wolkow et al., 2015a), restricted sleep (Wolkow et al., 2015a), decision-making (Huang et al., 2010a), and a combination of different factors or stressors (Smith et al., 2019) induce significant acute inflammatory responses (see Table 4.8).

Walker et al. (2015) reported significant increases in levels of leukocytes and neutrophils pre- to post-exposure to a repeated work protocol task in a heat chamber (100 °C ± 5 °C). Number of cells returned towards baseline within 24 hours of exposure. From the same cohort of municipal firefighters, higher lean body mass was associated with significantly lower values of TNFα at all time-points (Walker et al., 2017). [The Working Group noted that sustained increases in levels of leukocytes and platelets may also increase the risk of cardiac events in firefighters when performing repeat work tasks in the heat, which is particularly relevant during multi-day deployments after natural disasters.]

Wolkow et al. (2015a, b, 2017) examined the impact of repeated days of simulated wildfire suppression tasks on markers of inflammation in volunteer firefighters, with and without the additional stressors of restricted sleep (Wolkow et al., 2015a) and heat exposure (Wolkow et al., 2017). Collectively, these papers indicated that diurnal levels of IL-6 were above normal ranges in these volunteer firefighters, and IL-6 significantly increased across the 3-day study period (Wolkow et al., 2015a). Increases in morning IL-6 levels were associated with a significant increase in evening cortisol in sleep-restricted firefighters, and a daily increase in cortisol levels across the 3-day study period (Wolkow et al., 2015b) (see Section 4.1.6). IL-8 levels were also significantly higher in the groups of firefighters who had 8 hours of sleep compared with those who had 4 hours (Wolkow et al., 2015a), whereas IL-4 was significantly higher under hot

conditions (ambient temperature controlled at 33 °C) (Wolkow et al., 2017).

[The Working Group noted that the occupational exposure studies, presented earlier, focused on the inflammatory consequences of smoke, PM exposure, and the implications or evidence for the development of associated respiratory complaints. In contrast, the simulation training and pre/post trial studies focused mainly on elucidating the inflammatory mechanisms underpinning the risk of cardiovascular disease or sudden cardiac events. The health effects of repeated occupational exposure to heat are yet to be understood. The work on fire service instructors suggested that these individuals develop maladaptation to repeated fire exposures, showing elevated resting cytokine levels and an increased prevalence of symptoms of ill health (Watkins et al., 2019b).] Also, Huang et al. (2010a) observed changes in pro-inflammatory cytokine IL-2 levels, but not IL-6 levels, in firefighters exposed to a decision-making challenge (firefighting strategies and tactics drill) while participating in moderate intensity exercise (see also in Section 4.1.5).

(v) Catastrophic events

Firefighters from the WTC cohort, with elevated levels of CRP within 6 months of the event, had a significantly increased risk of developing decreased lung function (FEV_1) as assessed by subsequent pulmonary testing (Weiden et al., 2013). Induced sputum from firefighters who were highly exposed to the WTC dust revealed significantly higher cell counts (i.e. macrophages, neutrophils, lymphocytes, and eosinophils) 10 months after the event than those for a control group of health-care workers from Tel Aviv who were not exposed to WTC dust (Fireman et al., 2004). There was no significant difference in cell counts between the two firefighter cohorts, although the cell counts for firefighters in both cohorts were significantly higher than those for the respective health-care workers. [The Working Group noted that even without the exposure to WTC dust, all firefighters presented with significantly higher cell counts than did the control group. This was in spite of significant differences in the particle analysis and percentage of samples with different particle sizes between induced sputum from both populations.]

Several studies reported on the WTC-exposed cohort. Clinical investigations and nested case–cohort studies focused on the relationship between dust and PM exposure from the WTC disaster and subsequent acute and chronic inflammation-derived respiratory effects experienced in the WTC-exposed population (e.g. Kwon et al., 2013; Nolan et al., 2014; Zeig-Owens et al., 2018), from bronchial hyperreactivity (Aldrich et al., 2016), chronic rhinosinusitis and sinus polyps (Cho et al., 2014), and COPD (Singh et al., 2018) to chronic inflammatory polyarthritis (Loupasakis et al., 2015) and sarcoidosis (Loupasakis et al., 2015; Hena et al., 2018; Cleven et al., 2019). [As mentioned in Section 4.1, the findings from the WTC-exposed cohort may not be generalizable to other firefighting populations because of the massive acute exposure to WTC dust, which differed from dust from other live fires in terms of its PM composition. The Working Group noted that possible unmeasured events before or after WTC exposure could have also affected the results.]

Levels of IL-8 and TNFα and polymorphonuclear neutrophils (PMN) count were all significant predictors of sinus disease severity in firefighters exposed to WTC dust (Cho et al., 2014). Singh et al. (2018) further identified several inflammatory markers that represented risk factors for the subsequent development of irritant-associated asthma/COPD overlap (i.e. the firefighter developed both asthma and COPD). Specifically, elevated serum eosinophil and IL-4 levels were associated with subsequent asthma/COPD overlap. Greater serum IL-21 concentration was also associated with the development of isolated

asthma and isolated COPD in WTC-exposed firefighters (Singh et al., 2018).

Nolan et al. (2012) indicated that mediators of metabolic syndrome, inflammation, and vascular injury in early serum samples were predictive of lung function in the WTC-exposed cohort. Tsukiji et al. (2014) drew on this same population to investigate risk of developing WTC lung injury. It was found that increased levels of lysophosphatidic acid (LPA) and apolipoprotein-AI (ApoA1) in serum were significant predictors of WTC lung injury-associated loss of FEV_1 when sampled within 6 months after the WTC event and when adjusting for several factors, including PMN count (Tsukiji et al., 2014).

Lam et al. (2020) compared data for nine analytes in serum collected within 200 days of exposure from 15 WTC-exposed first responders who, up to 16 years later, had a defined lung injury; the authors also included 15 controls. The firefighters were non-smokers who had normal lung function before the WTC event and who, during the 16-year follow-up, were identified as having a lung injury if their percentage of predicted forced expiratory volume ($FEV_{1,\%Predicted}$) was less than the lower limit of normal, as defined by the National Health and Nutrition Examination Survey III. Control firefighters had an $FEV_{1,\%Predicted}$ that was greater than or equal to the lower limit of normal. There was a significant difference in the concentration of one analyte only, chemokine MCP-1, which was found at higher concentrations among the exposed group (Table 4.8).

Using these data, Lam et al. (2020) performed a correlation matrix and found strong correlations between LPA and soluble receptor for advanced glycation end-products (RAGE); strong correlations among various cytokines/chemokines, including interleukins IL-1α, IL-8, and IL-10, macrophage inflammatory protein (MIP-1α), granulocyte/macrophage colony-stimulating factor (GM-CSF), and TNFα; and negative correlations between many of these cytokines/chemokines and several sphingolipids and omega fatty acids (Table 4.8). [The Working Group noted that LPA and RAGE have key roles in the development of lung injury related to WTC exposure. In addition, the inflammatory response could be partly a result of dyslipidaemia-driven inflammation.]

In the same study, Lam et al. (2020) exposed the human THP-1-derived macrophages to WTC-PM_{53} (≤ 53 μm) at 100 μg/mL for an acute exposure of 24 hours and found increased levels of GM-CSF, IL-8, IL-10, and MCP-1. These results showed that WTC-PM_{53} induced inflammation biomarkers in human cells in vitro. Co-exposure to WTC-PM_{53} plus LPA resulted in a synergistic decrease in expression of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), protein kinase B (*p*-Akt), and STAT3/5 signalling. In addition, in vitro acute exposure of the cell line RAW264.7 mouse-derived macrophages for 24 hours to WTC-PM_{53} increased levels of various cytokines, such as IL-1α, TNFα, NF-κB, and IL-10 (Lam et al., 2020). In vitro acute exposure of these cells to WTC-PM_{53} plus LPA resulted in a synergistic decrease in expression of NF-κB, *p*-Akt, and STAT3,5b). [This in vitro study was not designed to address the issue of chronic inflammation and does not provide useful information relative to chronic inflammation.]

In addition, three studies reported on cases of sarcoidosis among firefighters exposed to WTC dust (Loupasakis et al., 2015; Hena et al., 2018; Cleven et al., 2019). Hena et al. (2018) described the clinical course of sarcoidosis in firefighters followed up 8 years after diagnosis. Loupasakis et al. (2015) reported on 11 case examples of sarcoidosis with polyarticular arthritis. Diagnoses of sarcoidosis were based on clinical, radiographic, and pathological criteria. Nine of the 60 firefighters who developed sarcoidosis after 11 September 2001 (9/11) presented with polyarticular arthritis, there were a further two cases diagnosed before 9/11 in firefighters who

developed sarcoid arthritis after WTC exposure, and all had biopsy-proven pulmonary sarcoidosis (Loupasakis et al., 2015). [The Working Group noted that from the emergent data on the 11 case examples presented with biopsy-proven sarcoid arthritis, it was concluded that chronic inflammatory polyarthritis appears to be an important manifestation of sarcoidosis in firefighters with WTC exposure and sarcoidosis.]

Genetic susceptibility is also an important molecular factor to consider in the associations between exposures and ultimate risk of cancer. Cleven et al. (2019) examined genetic susceptibility to sarcoidosis among cases that developed because of WTC-related exposures. All cases (n = 55) and non-sarcoidosis controls (n = 100) were selected who were followed up for 14 years after the WTC disaster. A custom panel was used to fully sequence 51 genes involved in immune response, inflammation, granuloma formation, and general risk of sarcoidosis. Among 3619 common variants detected among all participants, 17 were significantly more common among sarcoidosis cases and 764 specifically among extrathoracic sarcoidosis cases. [The Working Group noted that this study demonstrated the potential for gene–environment interactions in occupational disease. This may in part explain the highly unique cluster of four sarcoidosis cases from the Rhode Island cohort observed in Kern et al. (1993).]

[The following studies reviewed by the Working Group were considered less informative for the key characteristic "induces chronic inflammation" since the protocol did not allow specific conclusions to be made regarding changes in biomarkers of chronic inflammation and exposure to structure fires or employment as a firefighter: Kudaeva & Budarina (2005, 2007); Barceló-Coblijn et al. (2008); Wolkow et al. (2016a, b); Adetona et al. (2017); Sotos-Prieto et al. (2019); McAllister et al., 2020). For this reason, they were not reviewed in Section 4.1.4.]

(b) Alteration in lung function processes and bronchial hyperreactivity

Among the available studies providing information on chronic inflammation, several reported altered lung function after occupational exposure to smoke or PM. This was often used as a proxy for lung injury, which may be indicative of an inflammatory state. From the papers reviewed, it is suggested that these exposures lead to a significant decline in lung function associated with alterations in inflammatory markers (Burgess et al., 2004; Gaughan et al., 2014b; Andersen et al., 2018b; Gianniou et al., 2018; Zeig-Owens et al., 2018), pneumoproteins (Burgess et al., 2001, 2002; Greven et al., 2011a), or respiratory symptoms (Greven et al., 2011b, c).

[The Working Group noted that impairment of lung function could be partly explained by changes observed, through clinical investigations, in the lower airway tract, although it is not clear to what extent the observed inflammatory response and pathological changes represent permanent damage or are part of a natural temporary defence mechanism. The transition to a permanent condition may depend on the duration or extent of the exposure, as reported in the studies from Gianniou et al. (2016) and Watkins et al. (2021), and the subsequent damage. In addition, it has been suggested that the degree of lung function decline can be also explained by variations in genes involved in inflammatory responses, which would account for observed interindividual variability (Burgess et al., 2004; Josyula et al., 2007; Yucesoy et al., 2008).]

There were several papers that reported changes in lung function in the absence of specific markers of chronic inflammation. Greven et al. (2011c) reported an association between respiratory symptoms and fire exposure or smoke inhalation. There was a significant relationship between bronchial hyperreactivity and the number of fires fought in the last 12 months (Greven et al., 2011b). CC16 protein

was inversely associated with the number of fires fought in the last 12 months, and this association grew stronger when adjusting for lung function (Greven et al., 2011a). [The Working Group noted that a decrease in CC16 levels is often observed in individuals with asthma, and although there was a trend for an association with firefighters diagnosed with asthma in the current study, it was not significant.] Four studies assessed lung function (by spirometry) without additional measures (Loke et al., 1980; Burgess et al., 1999; Almeida et al., 2007; Kwon et al., 2021).

In a non-smoking group of 22 firefighters, 4 had evidence of obstruction of the airways. This disease of the small airways was only present in firefighters with > 25 years of experience. Irreversible lung injury was present in one firefighter who had been trapped in a basement fire (Loke et al., 1980). [The Working Group noted that, although the self-reported exposure is a limitation of the studies, these results are indicative of persisting respiratory symptoms and lung injury or damage after smoke inhalation and are therefore suggestive of chronic inflammation.]

The Working Group reviewed studies of firefighters that included outcomes relevant to allergic airway sensitization (i.e. presence of atopy and bronchial hyperreactivity) and/or increased respiratory symptoms (wheezing, cough, chest tightness, sneezing, and expectoration), since these outcomes can be relevant in the development of cancers of the respiratory tract (see Section 2.1). Occupational exposures as a firefighter included various airborne chemical agents, some of which are carcinogens or potential carcinogens (e.g. PM, VOCs, sVOCs, PAHs, asbestos, PFAS, etc.), with inhalation being the predominant route of exposure (see Section 4.1 and Sections 1.4.1, 1.4.4, and 1.5.1). Seven studies in humans were identified that assessed bronchial hyperreactivity, atopy, allergic rhinitis, and/or respiratory symptoms (Chia et al., 1990; Herbert et al., 2006; Greven et al., 2011b, c; Aldrich et al., 2016; Gianniou et al., 2016, 2018). Many of these studies also measured immune–inflammatory markers; these markers are also discussed above.

Several studies assessing bronchial hyperreactivity are briefly discussed here, as the Working Group deemed this an important outcome relevant to chronic airway inflammation. Bronchial hyperreactivity was assessed in relation to employment as a firefighter (Greven et al., 2011b, c; Gianniou et al., 2016), wildland firefighting (Gianniou et al., 2018), and among firefighters and other first responders to the WTC event (Aldrich et al., 2016). Comprehensive tests for bronchial inflammation and hyperreactivity among groups of professional and trainee municipal firefighters and non-firefighter controls were compared (Gianniou et al., 2016). Professional firefighters had a higher prevalence of atopy, allergic rhinitis, and bronchial hyperreactivity than did trainees and healthy controls. Among a large sample of firefighters from brigades throughout Denmark, the number of fires fought in the past 12 months was positively associated with bronchial hyperreactivity. This association was stronger among individuals with atopy (Greven et al., 2011b). Greven et al. (2011c) noted a positive association between an inhalation incident and respiratory symptoms related to bronchial hyperreactivity among 1330 firefighters in Denmark. [The Working Group noted that both exposure and symptoms were self-reported; bronchial hyperreactivity was not measured directly.] Bronchial hyperreactivity was assessed in wildland firefighters within 1 week of exposure and compared with samples collected 3 months later in the off-season (Gianniou et al., 2018); no differences in bronchial hyperreactivity or provocation over time were noted.

Aldrich et al. (2016) provided long-term follow-up of WTC responders. New York firefighters with no documented asthma and normal spirometry before the event who also participated in subsequent follow-ups (2 years and > 10 years after the event) were included (n = 173). Bronchial hyperactivity was seen in

16% of firefighters at 2 years after the WTC event and in 25% of firefighters at the second follow-up. Participants with bronchial hyperreactivity at the first follow-up had more respiratory symptoms, abnormal FEV_1, and provocability. [The Working Group noted that although the authors suggested that a selection bias may have occurred and the protocol to measure bronchial hyperreactivity changed between the two follow-ups, the results indicated potential long-lasting changes to airway hyperreactivity among WTC-exposed firefighters.]

[The Working Group noted that collectively these studies suggest that bronchial hyperreactivity is an outcome associated with firefighting. These data were considered alongside findings described previously, since this outcome is relevant to chronic inflammation of the airways.]

4.1.5 *Is immunosuppressive*

(a) Exposed humans

See Table 4.9.

Lymphocyte counts, lymphocyte subsets, and immunoglobulin levels were the end-points considered relevant to the key characteristic "is immunosuppressive" and reported in this section. An increase in lymphocyte count is indicative of leukocytosis (noted in Section 4.1.4), whereas a decrease suggests immunosuppression. Reduced immunoglobulin levels may also indicate immunosuppression, increasing the risk of infection; whereas an increase in immunoglobulin levels suggests upregulation of humoral immunity, current infection, or increased allergy sensitivity.

Twenty studies available to the Working Group evaluated mechanistic end-points relevant to immunosuppression after occupational exposure as a firefighter. Studies assessed a variety of exposure types, including structure fires (mainly training; five studies), wildland (forest) fires (one study), employment as a firefighter (four studies), exposures with a heat, mental, or physical challenge (six studies), and catastrophic events (four studies). Two additional studies investigated the prevalence of infection with the SARS-CoV-2 virus (the cause of COVID-19 disease) among firefighters.

(i) Structure fires

A controlled training fire exercise resulted in increased lymphocyte counts immediately after exposure followed by reduction 90 minutes after exposure. T-lymphocyte proliferation also increased after exposure, although this correlated with increased lymphocyte numbers (Smith et al., 2005). [The Working Group proposed that it was probably altered lymphocyte numbers that caused the proliferation response rather than cell responsiveness.] Watkins et al. (2019a) also reported increased lymphocyte counts immediately after training fire scenarios conducted by instructors, with a positive correlation between change in core temperature and post-exposure lymphocyte values. [The Working Group noted that Smith et al. (2005) replicated firefighting tasks and rest periods across participants, whereas Watkins et al. (2019a) did not control for tasks because collection was performed during training courses. Neither study gave results suggestive of immunosuppression; both studies used small sample sizes and did not include flow cytometric analysis of cell subsets.]

Two studies (Smith et al., 2004; Watt et al., 2016) provided a chronic assessment of structure-fire training exposures. Four days of training fire exposures resulted in increased lymphocyte counts on days 3 and 4 (Smith et al., 2004). Blood samples from instructors revealed reduced lymphocyte counts after a 7-week break from fire exposures, but no further changes were detected immediately after fire exposure or 4 weeks after instructing a course (Watt et al., 2016). Immunoglobulin G (IgG) levels immediately after exposure decreased after a 4-week instructing course compared with pre-course levels. However, comparison of blood samples from instructors with those from an age-matched

Table 4.9 End-points relevant to immunosuppression in exposed firefighters

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Structure fires							
Lymphocyte count, lymphocyte proliferative response	Blood	Structural [municipal] firefighting (training) USA, male firefighters, pre/post trial	11, 0	↑ No. of lymphocytes post ($P < 0.001$) ↓ Lymphocytes after 90 min ($P < 0.05$) ↑ Proliferation post ($P < 0.007$)	Diet, firefighting tasks, PPE, rest periods	Small sample size (3 trials consecutively completed, average time to completion 5 min 29 s to 6 min 17 s, 10 min rest between trials 2 and 3) Exposure assessment: appropriate in terms of assessing the effect of firefighting; no specific firefighting hazard assessed	Smith et al. (2005)
Lymphocyte count	Blood	Structural [municipal] firefighting (training) United Kingdom, fire service instructors (14 men, 2 women), pre/post trial comparing training days	16, 0	↑ Lymphocyte count ($P < 0.01$) No changes in lymphocyte count between exposure combinations Positive correlation between change in core temperature and post-exposure lymphocytes ($P = 0.002$)	Menstrual cycle phase for female participants	No non-exposed control group; small sample size; roles and duration of exposure varied between participants (day of exposures, 3-day options, 1 – demo and attack, 2 – multi compartment × 2, 3 – demo, attack and multi compartment) Exposure assessment: exposure to different fire exercises appropriately tested as exposure for the effects assessments that were done in the experiment	Watkins et al. (2019a)
Lymphocyte count	Blood	Structural [municipal] firefighting (training) USA, male firefighters, pre/post-exposure across 4 days, comparison made across exposure and day 1 to days 2, 3 and 4)	16, 0	↑ Lymphocytes after exposure ($P < 0.001$) ↑ Lymphocytes on days 3 and 4 ($P = 0.046$)	Medically cleared for duty	Limited detail on exposure tasks and durations; no non-exposed control group to compare daily fluctuations Exposure assessment: specific firefighting exposure was not evaluated but effect of involvement in firefighting appropriately tested with the study design; possibly prior exposure during the earlier days of training might have confounded results but not enough information to determine if this occurred	Smith et al. (2004)

Table 4.9 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Lymphocyte count, Ig concentrations	Blood	Structural [municipal] firefighting (training) United Kingdom, male firefighters (instructors) and non-exposed controls (university lecturers), pre/post trial	6, 6	↓ Lymphocytes pre to post break ($P < 0.05$) IgG, no difference between instructor and control samples at any time-point	Time since recent exposure, no additional operational exposures; control group no exposure to > 25 °C in previous 4 months	Variation in exposure duration and roles conducted; small sample size Exposure assessment: inadequate since potential simultaneous exposure to smoke was not considered; the quantitative heat exposure measure that was collected was not used in exposure–response analysis	Watt et al. (2016)
Ig concentrations	Blood	Structural [municipal] firefighting (plastic) Sweden, case report (1 male firefighter	1, 0	No change in immunoglobulin		Single time-point post exposure assessed: study focused on development of severe asthma, which led to death Exposure assessment: qualitative description of the exposure due to burning plastic; PPE was not used	Bergström et al. (1988)
Wildland fires							
Lymphocyte proportion	Sputum, BALF	Wildland Greece, firefighters, repeated measures design	60, 0	No changes in lymphocyte proportion several days post-exposure vs 3 months off-season		Visit 1 24–48 h after fire exposure; unclear if PPE was worn; 87% current smokers with history of 9 ± 5 packs/year; participant's sex not detailed; samples stained and manually counted – presented as percentage of non-squamous cells Exposure assessment: time away from firefighting adequate for effects that were tested; potential exposure misclassification for length of firefighting	Gianniou et al. (2018)

Table 4.9 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Employment as a firefighter							
Lymphocyte count	Blood	Employment as a firefighter Canada, male firefighters (≤ 10 yr experience vs ≥ 20 yr experience) and non-exposed controls, cross-sectional	30 (15, 15), 15	Firefighters vs control No changes in Th1 and Th2 ↑ Th17; ↑ Th22; ↑ Tregs ($P < 0.001$) No changes in subsets between firefighter experience groups No correlation between Th17 and Treg in high experience group; correlation was present in lower experience group ($P = 0.0013$)	Non-smokers only	Controls age-matched to firefighters; no information regarding timing of sample to previous exposure Exposure assessment: cross-sectional design with qualitative measures of exposure and potential for confounding by non-firefighting related exposures	Ricaud et al. (2021)
Lymphocyte counts, IgG concentrations	Blood	Employment as a firefighter United Kingdom, firefighters (55 men, 2 women) vs fire service instructors (47 men, 6 women), cross-sectional	57 firefighters, 53 instructors	No changes in lymphocyte counts ↑ IgG in instructors ($P < 0.001$) Regression analysis revealed no association between IgG and age, time in service or weekly exposure number Positive association between IgG and monthly exposure number ($P < 0.05$)	Exercise and fire exposure avoided 12 h before sample collection	Fire exposures and health complaints self-reported; groups matched on age, body mass, and time in service Exposure assessment: self-reported frequency prone to misclassification	Watkins et al. (2021)

Table 4.9 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Lymphocyte proportion, IgE concentration	Blood, BALF	Employment as a firefighter Sweden, male firefighters (≥ 3 yr of experience) and healthy control, cross-sectional	13, 112	↑ Proportion of lymphocytes ($P < 0.05$) No changes in IgE		Unbalanced sample sizes; non-smoking control, but 5 ex-smokers in firefighter group; unclear regarding control occupation and heat/smoke exposure; 9/13 firefighters had performed firefighting in the last 3 months, of these, 4/9 had used PPE; exposures were self-reported; samples stained and counted – presented as percentage of non-squamous cells Exposure assessment: heterogeneous group, some without recent exposures; self-reported number of fires fought may be misclassified	Bergström et al. (1997)
Lymphocyte proportion	Sputum, BALF	Employment as a firefighter Greece, male firefighters, (professional [career] vs part-time 1 yr trainees vs control), cross-sectional	63, 29, 18	No changes in lymphocytes between groups Positive correlation between years of experience and lymphocytes ($P = 0.016$)	Use of respiratory protection reported to be similar between firefighter groups	No information regarding exposure types, frequency, or time since last exposure; smokers included; years of service for professionals [career] was short (9 ± 1 yr); samples stained and counted – presented as percentage of non-squamous cells Exposure assessment: employment categories used for effects comparisons likely adequate; potential confounding of career length with age	Gianniou et al. (2016)

Table 4.9 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Exposure to heat, mental, or physical challenges							
Lymphocyte count	Blood	Mental and physical challenge USA, male firefighters, pre/post trial (laboratory cycling exercise)	9, 9 (Huang et al., 2010a) 10, 10 (Huang et al., 2010b)	No change CD8+ ↑ After exercise CD56+ ($P < 0.001$) ↑ After exercise CD56+ and CD3− NK cells ($P < 0.001$) ↓ After exercise CD3+ T-cells, CD3+ and CD4+ helper T-cells, CD4:CD8 ratio, CD19+ B-cells, and total lymphocytes ($P < 0.001$)	Exercise intensity and duration, cardiovascular disease, smoking status, no fire exposure in previous 72 h	Exercise modality (cycling) not similar to firefighting; small sample size Exposure assessment: engagement in experimental drill exercise appropriately tested as exposure for the effects assessments that were done in the experiment	Huang et al. (2010a, b)
IgG, IgA, IgM concentrations	Blood	Physical challenge Portugal, male firefighter recruits, repeated measures design	24 (12 with and 12 without supplement), 0	No change in IgG, IgA, IgM	Diet, training activities, injury/illnesses	No non-training control group; sample were recruits, baseline levels may not be representative of firefighters; statistical follow-up tests unclear Exposure assessment: engagement in experimental fitness test appropriately tested as exposure for the effects assessments that were done in the experiment in relation to supplement intervention	Santos et al. (2020)
Lymphocyte count, IgG concentrations	Blood	Heat United Kingdom, fire service instructors (9 men, 2 women) vs controls (university lecturers), pre/post trial	11, 11	↑ Lymphocytes in both groups post-exposure ($P < 0.05$) ↑ IgG at rest in instructors vs control ($P = 0.001$)	Control group no exposure to > 25 °C in previous month	Control group matched on age, sex, body fat percentage; small sample size; same response noted same trial conducted 2 months later Exposure assessment: number of self-reported fires may be misclassified; heat exposure was under controlled conditions	Watkins et al. (2019b)

Table 4.9 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Lymphocyte count	Blood	Heat Australia, male firefighters, pre/post trial (pre vs post, 1 h post, 24 h post)	42, 0	↑ Lymphocytes 1 h post-exposure ($P < 0.01$) All markers returned to baseline in 24 h	Exposure temperature, physical tasks and durations, rest periods	Well-controlled design with repeated time-points Exposure assessment: exposure to heat appropriately tested as exposure for the effects assessments that were done in the experiment	Walker et al. (2015, 2017)

BALF, bronchoalveolar lavage fluid; Ig, immunoglobulin; NK, natural killer; PPE, personal protective equipment; vs, versus; yr, year.

[a] ↑, increase in biomarkers, ↓, decrease in biomarkers

[b] Factors to be considered for study quality included the methodology and design, reporting, and exposure assessment quality.

control group revealed no differences in lymphocyte count or IgG levels at any time-point (Watt et al., 2016). [The Working Group noted that the training fire exposures varied in duration and task, and only a small sample size (six instructors) was studied.]

In a case study of an acute exposure to a structure fire (see also in Section 4.1.4) experienced by a firefighter without breathing protection, no change in immunoglobulin levels was reported, although the firefighter developed severe chronic asthma, which ultimately resulted in the incident being fatal (Bergström et al., 1988). [The Working Group noted that because of the case-study nature and lack of breathing protection, it was unlikely that this study provided an accurate representation of typical fire-exposure responses. No samples were available for comparison with pre-exposure levels.]

(ii) Wildland fire

One study assessed the consequences of wildland (forest) fire exposure, revealing no difference in lymphocyte counts in samples collected after several continuous days of firefighting compared with samples collected 3 months into the off-season (Gianniou et al., 2018). [The Working Group noted that limited time-points were assessed, and there was no baseline measurement or cell subset analysis.]

(iii) Employment as a firefighter

Four studies made use of cross-sectional designs to compare firefighters with non-exposed controls. Analysis of immune cell subsets from operational firefighters with varying experience levels (Ricaud et al., 2021) revealed no difference between firefighters and controls in CD4+ T-helper Th1 and Th2 cells. Instead, CD4+ Th22, Th17, and T-regulatory (Treg) cells were significantly increased in firefighters. There was no difference in any subset when firefighters with ≤ 10 years of experience were compared with those with ≥ 20 years of experience. However, correlation between Th17 and Tregs was not present in the group of more experienced firefighters. [The Working Group noted that this absence of correlation may indicate an imbalance in immune homeostasis. Furthermore, it has been reported that in some instances of cancer, tumour cells promote the expansion of Tregs, which leads to a decrease in the anti-tumour immune response (Nishikawa & Sakaguchi, 2014). The Working Group noted that firefighters and controls were age-matched, and all participants were non-smokers.] Comparison between firefighter subpopulations (firefighters versus instructors) demonstrated no difference in lymphocyte counts between groups, but IgG levels were increased in instructors (Watkins et al., 2021). The authors reported that there was no association between IgG and years of experience, as assessed by multiple regression analysis; however, the number of fire exposures per month was associated with IgG. The study also noted increased symptoms of ill health among instructors, including severe fatigue, coughs, and colds; instructors exhibiting values above the reference ranges for IgG were 6.45 times as likely to experience ill health symptoms as those with values below the reference ranges. [The Working Group noted that the increased IgG levels may be representative of increased humoral immunity but highlighted that additional biomarker analysis is needed to investigate the balance between humoral and cellular immunity. In addition, the Working Group noted that the sample size was large, but only a single time-point was measured, and exposures and health were self-reported. The Working Group also noted that respiratory symptoms (such as coughing, wheezing, phlegm, and reduced lung function) have been reported in numerous studies, although study design and measurements have not established a clear link with infection and immunosuppression, instead implicating inflammation as the key pathway (see Section 4.1.4).]

Serum immunoglobulin E (IgE) levels did not differ between male firefighters and healthy controls, but an increase in the proportion of lymphocytes in BAL in firefighters was detected, although values remained within reference ranges (Bergström et al., 1997). Gianniou et al. (2016) reported no difference in lymphocyte counts between active firefighters, trainees of 1 year, and controls, although correlation analysis did reveal an association between time in service and lymphocyte count. [The Working Group noted that detail on exposures was limited and that increase in lymphocyte count could be indicative of inflammation (see Section 4.1.4), not immunosuppression.]

A recent assessment of the prevalence of coronavirus SARS-CoV-2 infection in military firefighters reported that 14–46% of test responses were positive based on immunoglobulin M (IgM) and IgM antibody lateral flow tests or real-time polymerase chain reaction tests (Borges et al., 2021). [The Working Group commented that this prevalence highlighted the importance of immunization for workers who engage with the general population, work within restrictive spaces, and often complete tasks involving physical contact. However, no statistical comparison with a non-fire exposed control group was provided, and there was no information on the fire exposure history of the firefighters included in the study.] Further investigation of SARS-CoV-2 in emergency first responders by Montague et al. (2022) identified no difference in infection prevalence between firefighters and other similar occupations (such as the police and medical staff).

(iv) Exposure to heat, or mental and/or physical challenge

Two studies conducted crossover-controlled laboratory trials (Huang et al., 2010a, b) involving active firefighters who performed a 37-minute cycling exercise with and without a firefighter strategy and tactics drill. Mental challenge did not exacerbate any immune marker responses: exercise both with and without mental tasks resulted in no change in CD3+ and CD8+ cytotoxic T-cells, increased CD56+ (Huang et al., 2010b) and CD3− natural killer (NK) cells immediately after stress, and decreased CD3+ T-cells, CD3+ CD4+ T-helper cells, the CD4:CD8 ratio, CD19+ B-cells, and total lymphocytes (Huang et al., 2010a). All levels recovered to baseline 1 hour after exercise (Huang et al., 2010a). [The Working Group noted that these responses may indicate an increase in the innate immune response but suppression of adaptive immunity in relation to exercise, although the trial did not simulate firefighter tasks in terms of exercise modality, temperature, clothing encapsulation, or smoke exposure. Generalizability to fire scenarios was therefore limited. The Working Group also noted that both studies had small sample sizes, and there was uncertainty regarding the crossover of participants between studies.]

One randomized control trial study assessed recruit firefighters before and after a 5-week training programme. No differences in IgG, IgA, or IgM were detected, and values were within normal ranges (Santos et al., 2020). [The Working Group noted that the training programme did not include any fire suppression activities or a non-training control group. The lack of differences noted in this study did not therefore necessarily represent the consequences of fire-exposure training courses.]

Firefighters' occupational exposure promotes physical exertion and heat stress, which contributes to increased body and skin temperatures (see Section 1.5.1(f)). Watkins et al. (2019b) reported increased lymphocyte counts in fire service instructors and in a control group of university staff after exposure to heat (50 ± 1.0 °C) while wearing protective clothing and exercising for 40 minutes (Watkins et al., 2019b). Lymphocyte counts were not different between groups; however, instructors exhibited elevated IgG levels compared with controls before exercise (Watkins et al., 2019b). [The Working Group noted that the

lack of difference in acute responses between the instructors and the control group may suggest that the magnitude of the lymphocyte response is not altered by a history of repeated exposures. However, the study did not control for other exposures in the control group, besides heat exposure in the previous month.] Assessment of responses to simulated search tasks in a heat chamber (~100 °C) also noted leukocytosis, which included elevated lymphocyte counts from the end of the exposure to 1 hour after exposure (Walker et al., 2015, 2017). Subsequent measurement at 24 hours after exposure revealed that lymphocyte counts had returned to resting levels (Walker et al., 2015, 2017). [The Working Group noted that the studies by Walker et al. used a large sample (n = 42), and by using the simulated scenario were able to control for numerous confounding factors, such as environmental temperature, task type and duration, and rest periods. The inclusion of additional measurement points beyond immediate cessation of exercise provided detail on the time course of responses. The lack of cell subset analysis in these three studies limited the conclusions that could be drawn regarding immunosuppression. The responses reported in these studies were the consequence of physiological strain and heat, not smoke exposure.]

(v) Catastrophic events

Firefighters may experience exposure to chemicals and physical factors during building collapse and other catastrophic events; detailed exposures are presented in Section 1.5.1(g) (Table 1.5.2). Four cross-sectional investigations focused on exposure to specific incidents (Bodienkova & Ivanskaia, 2003; Fireman et al., 2004; Kudaeva & Budarina, 2005, 2007). [The Working Group reviewed the studies by Kudaeva & Budarina, (2005, 2007) but considered them not informative since they did not provide detail regarding the toxic substance exposure and included limited information regarding sample timing and group sizes.] Bodienkova & Ivanskaia (2003) conducted a cross-sectional analysis 7 years after exposure at the 1992 "Irkutskcable" factory fire in Shelekhov, Russian Federation [the Working Group noted that the study did not provide details about the event]. Reduced lymphocyte count, including decreased CD3+ and CD4+ T-helper cells, CD8+ T-cytotoxic cells, and increased IgA in firefighters with encephalopathy compared with non-exposed controls were reported. [The Working Group highlighted that limited detail was available regarding the interim 7-year period, and only exposed firefighters diagnosed with encephalopathy were included in the study (other exposed firefighters were not considered).] Fireman et al. (2004) identified increased lymphocytes in firefighters who attended the WTC event compared with control health-care workers in Israel; however, this elevation was also noted in Israeli firefighters. [The Working Group noted that only a single sample was analysed 10 months after the WTC event, with no details on exposure in the interim period.]

[The Working Group concluded that the complexities of immune regulation are time dependent, and limited subset assessment was available to develop understanding of the balance of upregulation and suppression between innate, humoral, and cellular immunity. The overall evidence did not rule out an association between firefighting and immunosuppression. From the limited studies available, there was some indication that firefighting may be immunomodulatory (as noted in the review of Ricaud et al. (2021) and Watkins et al. (2021)). However, because of a paucity of evidence, the available literature was not sufficient to indicate an immunosuppressive response to firefighting.]

(b) Human cells in vitro

No data were available to the Working Group.

(c) Experimental systems

(i) Non-human mammals in vivo

One experimental transcriptomic model study in mice suggested an immunomodulatory impact of firefighting overhaul exposures when respiratory protection was not used (Gainey et al., 2018) (see Section 4.1.6). In vivo exposure of mice to either flaming or soldering emissions from peat, oak, or eucalyptus suppressed cytokine levels in allergic or non-allergic animals (Hargrove et al., 2019). [The Working Group noted that this was most likely because of smoke-induced suppression of allergic inflammatory responses by carbon monoxide.]

(ii) Non-human mammalian cells in vitro

No data were available to the Working Group.

4.1.6 Modulates receptor-mediated effects

(a) Exposed humans

See Table 4.10.

The modulation of receptor-mediated effects described in this section was assessed through the activation of binding to AhR and changes in circulating hormone levels associated with firefighters' exposures. Most of the studies investigated levels of hormones (namely cortisol, adrenocorticotropic hormone, catecholamines, and melatonin) related to acute exposures, and some studies investigated long-term exposures by employment as a firefighter (via levels of testosterone, thyroid function hormones, and anti-müllerian hormone). Considering the availability of the data, the studies reported below are grouped by end-point.

(i) Aryl hydrocarbon receptor

Four studies investigated AhR mediation in firefighters: one study involved a structure fire exposure (Beitel et al., 2020), and three studies considered exposures of employment as firefighter (Orris et al., 1986; Chernyak & Grassman, 2020; Ricaud et al., 2021).

Beitel et al. (2020) used a potency toxicity bioassay to evaluate AhR activation in extracts of urine and skin-wipe samples collected from firefighters before and after a fire drill, in Arizona, USA. The study included 11 firefighters; 10 firefighters participated in the training fire drill and there was one control, a by-stander in full gear, who did not enter the training building. The assay in a rat hepatoma reporter cell line transfected with a luciferase gene (polycyclic aromatic hydrocarbon-chemical activated luciferase gene expression, PAH-CALUX) measured increased agonistic response activity in samples of urine from 3 out of the 10 firefighters who participated in the fire drill. The assay response was significantly correlated with hydroxylated PAH concentrations in the urine samples, with < 1% of the bioassay response predicted by the quantified compounds excreted in the urine. The skin-wipe sample extracts showed a significant increase in AhR active compounds after firefighting compared with before firefighting, and for skin samples collected both from the neck and the calf (Beitel et al., 2020). [The Working Group noted that the observation that the urinary response exceeded the prediction for hydroxylated PAHs could be related to the urinary excretion of other compounds with AhR activity (Beitel et al., 2020), with the use of the bioassay being a strength for the analysis of complex mixtures. The Working Group further noted the small sample size of the study, particularly with high variability of the urinary excretion patterns and baseline levels, but also noted the appropriate pre-/post-exposure design. The Working Group noted that the assay response indicated that the firefighters were exposed to AhR agonists.]

Ricaud et al. (2021) investigated the potency of the AhR agonistic response in serum collected from firefighters in Montreal, Canada, and using a human liver carcinoma cell line transfected with a xenobiotic response element (XRE)–luciferase reporter gene. The firefighters were stratified by employment length (with < 10 or

Table 4.10 End-points relevant to modulation of receptor-mediated effects in exposed firefighters

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
AhR bioassay, potency toxicity assay (PAH CALUX)	Skin wipes (neck and calf) and urine	Live-fire training (burning wood pallet, furniture, carpet, and miscellaneous objects) (14 min) USA (Arizona), pre/post trial study on male firefighters before and after firefighting training activities with use of full PPE	10, 1	↑ AhR bioassay activity in skin sample extracts from post-firefighting ($P = 0.025$ for calf wipes); +, Positive correlation between bioassay response and OH-PAHs concentrations found in urine ($P = 0.008$), with < 1% of the response predicted by the quantified urinary OH-PAHs	Only non-smokers included; participants were asked to refrain from grilled food 12 h before the drill and until last urine was sampled	Small sample size with high inter-variability; the control (n =1) had unclear tasks and location Exposure assessment: biomarkers are appropriate with regards to their half-lives; potential for residual confounding by other environmental exposure, especially diet	Beitel et al. (2020)
AhR bioassay activity, potency toxicity assay (HepG2-XRE luciferase assay)	Serum	Employment as firefighter Canada, cross-sectional study on 30 male firefighters (15 with ≤ 10 yr and 15 with ≥ 20 yr of experience) and 15 healthy controls	30, 15	↑ AhR bioassay activity in firefighters compared with controls ($P < 0.05$ for firefighters ≤ 10 yr and $P < 0.01$ for firefighters ≥ 20 yr) ↑ AhR bioassay activity in firefighters hydrophobic purified fraction of sera for both groups ($P < 0.001$) and ↓ activity for all groups when added antagonist ($P < 0.05$)	Only non-smokers included; groups matched on age and sex	Exposure assessment: limited to length of employment; roles or recent exposures not described Exposure assessment: cross-sectional design with qualitative measures of exposure and potential for confounding by non-firefighting-related exposures	Ricaud et al. (2021)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
CYP1A2 activity (antipyrine metabolite excretion) and *AHRR* expression	Blood and 24-h void urine (collected in 2009–2010)	Mix (historical industrial fire and employment as firefighter in region with wildland fire events) Russian Federation, cross-sectional study in a cohort of 28 male firefighters (11 current and 17 former firefighters) and 10 controls using antipyrine as a metabolic probe; 20 out of the initial 30 firefighters were involved in a fire incident in a cable factory (in 1992), without use of respiratory protection	28, 10	CYP1A2 activity was positively associated with dioxin body burden among carriers of the *AHRR* G allele ($P = 0.04$) and associated with higher levels of *AHRR* transcript expression	Groups, matched on age and BMI, models adjusted for smoking (urinary cotinine), dioxin body burden, *AHRR* (565 > G) genotype, *AHRR* gene expression	Small sample size; included smokers Exposure assessment: appropriately used biomarker of cumulative exposure in analysis of chronic effect, especially for current firefighters	Chernyak & Grassman (2020) Complementary study, Chernyak et al. (2012)
Chloracne diagnosis	Physical examination, biopsy, and blood sample	Historical fire events and employment as firefighter USA (Illinois), case report of 2 firefighters reportedly involved in historical incidents and fires who were diagnosed with chloracne	2	The 2 cases of chloracne had historical exposures potentially consistent with the diagnosis Blood PCB levels < 10 µg/L for both cases	None	Small sample size; no controls; long lag time between possible exposure and assessment; risk of recall bias Exposure assessment: description of exposure based on self-reported participation in historical fire incidents	Orris et al. (1986)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Testosterone and cortisol (ELISA immunoassay)	Plasma (morning, 4 samples on days 1, 4, 8, and 11)	Real-fire training and physical exertion (11 days of training, including 7 in prescribed burns) USA (Montana), pre/post trial study on 16 wildland firefighters (14 men and 2 women) during critical training	16	No changes in testosterone ↑ Cortisol ($P = 0.03$) ↓ T:C ratio ($P = 0.01$)	Intra-individual	Small sample size; sequence design without control group; not possible to retrieve hormone levels segregated by sex, although time analysis was available for men Exposure assessment: engagement in the training appropriately tested as exposure in the pre/post design; exposure misclassification due to self-report of muscle soreness unlikely to affect result	Christison et al. (2021)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Testosterone (IRMA immunoassay) and cortisol (biotin-streptavidin immunoassay)	Plasma (testosterone) and saliva (cortisol) (between 9 h and 10 h, 5 blood and 30 saliva samples)	Employment as firefighter United Kingdom repeated measures in a cohort of 72 male probationary firefighters, recruited during education and followed for 1 yr, measured in 5 sessions with 3-month intervals (on the first day shift of an 8-day shift cycle)	72	↓ Testosterone from 3 to 12 months ($P < 0.001$) ↑ Cortisol from 3 to 12 months ($P < 0.03$) Session with higher daily stress were associated with lower cortisol ($P < 0.01$) and higher testosterone levels ($P < 0.025$)	Intra-individual; daily stress, anxiety, and depression inventories; control for shift work	The study included smokers, but the authors reported elsewhere a stable pattern of smoking habits and accounted for intra-individual changes; possible overlapping sample with (Roy et al., 1998; Roy, 2004) Exposure assessment: tool used to quantify job described in Roy (2004) publication attempted to account for subjectivity in reporting exposure by testing the effect of intraindividual variation in exposure measures on outcomes	Roy et al. (2003)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Testosterone (ECLIA immunoassay)	Serum (morning)	Employment as firefighter (metropolitan fire department) USA (Florida), cross-sectional study among 326 male career firefighters stratified by testosterone levels (126 borderline or low and 200 within reference levels)	126, 200	Prevalence of low and borderline testosterone levels, 37% Borderline-low testosterone associated with decreased LVWT ($P < 0.01$)	Age, BMI, SBP, and HbA1c; group with high levels ($n = 15$) eliminated from further analysis (possible supplementation)	Cross-sectional nature; population sample with large ranges for age (19–69 yr) and BMI; potential for interference of night work Exposure assessment: employment as firefighter, without further information on duration of employment, specific tasks or exposures; firefighting exposure was not quantified	Lofrano-Porto et al. (2020)
Testosterone (Access 2 immunoassay)	Whole blood (morning sample at 8 h at the start of 24-h shift, after 2 days off)	Employment as firefighter (military) Kazakhstan, cross-sectional study on 100 male military firefighters from 3 occupational subgroups: firefighters (49), fire-truck drivers (22) and management and engineers (29) and their burnout risk measured with the MBI-GS tool	100	No changes in testosterone levels per occupational group ↑ Testosterone was associated with professional efficacy burnout	Age, smoking, exercise, and health-related quality of life; by design, controlled for night shift [colinearity between age and years in service, with the latter excluded from analysis]	Cross-sectional nature; no control group; no BMI data; groups not matched on age, years in service, marital status, education, and smoking status Exposure assessment: potential for overlap in current and past overlap exposure categories (occupation)	Vinnikov et al. (2021)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Testosterone and estradiol (RIA immunoassay)	[Serum]	Employment as firefighter USA (Ohio), cross-sectional study with 12 active male firefighters (mean age, 46.2 ± 6.3 yr), used as control group, and 38 male coronary patients (admitted to hospital with acute myocardial infarction or undergoing evaluation of chest pain with or without CAD)	12, 38	↓ Estradiol for firefighters vs acute patients ($P < 0.01$) No changes in testosterone ↑ BMI in firefighters compared with patients without CAD ($P < 0.025$)	Age and BMI	Small sample size; cross-sectional nature; sample timing not reported; no comparison with healthy participants; firefighting exposure not assessed; incongruence in biosample definition in methods and table heading Exposure assessment: employment as firefighter, without further information on duration of employment, specific tasks or exposures; firefighting exposure was not quantified	Luria et al. (1982)
Testosterone and cortisol (RIA immunoassay)	Saliva (2 samples)	Stress from examination (dog handlers) and employment as firefighter USA (California), pre/post study in a disaster dog handler certification test, using 16 handlers (7 firefighters among them) and 6 evaluators	7, 9	No changes in testosterone ↓ Cortisol levels for firefighters ($P < 0.05$)	Dichotomized timing of post sample	Small sample size; controls not matched; food and caffeine intake not controlled; post-sample time span from 09:30 to 15:00; occupation not described for non-firefighters Exposure assessment: firefighting exposure was not quantified	Lit et al. (2010)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol and ACTH (RIA immunoassay)	Plasma (3 samples, [morning])	Live-fire training (17 min) USA (Illinois), pre/post trial study in male professional [career] firefighters with use of full PPE (before, immediately after and 90-min recovery of fire drill)	11	↑ACTH ($P = 0.002$) ↑ Cortisol ($P < 0.001$) and was still elevated after 90 min	Intra-individual; by design, control of food intake, and physical and thermal strain	Small sample size; sequence design without control group; reported cortisol units may be wrong Exposure assessment: appropriate in terms of assessing the effect of firefighting; no specific firefighting hazard assessed	Smith et al. (2005)
Cortisol and ACTH (CLIA immunoassay)	Serum (4 samples, before, immediately, 4 h and 24 h after exposure)	Live-fire training (40 min) Republic of Korea, pre/post trial study on firefighting instructors performing live fire suppression in training facility and firefighting instructors performing physical exercise with full PPE without ambient heat	7, 7	↑ ACTH immediately after live-fire simulation ($P < 0.05$) No changes in cortisol level among the groups, with level elevated after the live-fire simulation	None	Small sample size; physical exertion not controlled; repeated measurements (intra-individual) dependence not considered in analysis; sex and sampling timing not reported; cortisol detection method not reported Exposure assessment: involvement in controlled hot working and smoke exposure conditions appropriately tested as exposure for the effects assessments	Kim et al. (2018)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (ELISA immunoassay)	Saliva (4 samples: morning baseline day, morning exposure day, immediately after exercise and 30 min after exercise)	Search and rescue exercise while using full PPE [live-fire training] (60 min) United Kingdom, RCT on the combined glucose and caffeine administration to participants attending a 3-day basic fire-training course; 3 groups: placebo drink, high glucose and low caffeine drink and low glucose and high caffeine drink	27, 26, 27	↑ Cortisol after exposure to fire-fighting exercise ($P = 0.019$) No changes (or difference) among groups	Control by design (matched) on age, gender, BMI, years of education and time of awakening	Exposure assessment: engagement in live-fire drill appropriately tested as exposure for the effects assessments	Sünram-Lea et al. (2012)
Cortisol (ELISA immunoassay)	Saliva (6 samples over 3 days, collected between 13:30 and 16:00	3 training days with live-fire on third day (60 min) United Kingdom, pre/post trial study on novice firefighters (men and women) over a 3-day firefighting course with morning classroom and afternoon exercises of 2 h, with increased intensity over the 3 days (live-fire only on the third day) and 11 non-firefighter control participants	21, 11	↑ Anticipatory cortisol in firefighters group ↑ Cortisol levels after live-fire firefighting for both firefighter groups (assessed immediately or after 20 min) ($P = 0.03$) No changes in cortisol levels in training sessions without live fire	By design control of awakening patterns [Mixed ANOVA accounted for intra-day variation, no intra-individual]	No information on smoking status Exposure assessment: appropriate in terms of assessing the effects of live-fire suppression	Robinson et al. (2013)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (ELISA immunoassay)	Saliva (5 or 6 samples depending on group: 2 at baseline, 2 or 3 after evolutions, 1 at recovery and 1 at completion of protocol)	Live-fire training (wood fire) (30 or 45 min) USA (Pennsylvania), pre/post trial study to examine the influence of workload duration of experienced firefighters (mean age, 30.3 ± 8.3 yr) engaged in fire suppression; randomized groups: 2 or 3 bouts of fire suppression activity	42	No difference in cortisol output was found between the groups ↓ Cortisol over the course of the live-fire evolution in both groups ($P < 0.05$)	Intra-individual	Men and women included; difficulties in controlling length of exercises; loss of samples due to reduced saliva at later time-points; staggered experiment start times and cortisol samples; high anticipatory (baseline) levels Exposure assessment: appropriate in terms of assessing the effects workload suppression training	Rosalky et al. (2017)
Cortisol (CLIA immunoassay for serum samples and LC-MS/MS for saliva samples)	Serum and saliva simultaneously sampled 3 times (1 h before, immediately after and 10 h after the simulation training)	Simulated terrorist attack (shooting, hostage and live-fire in parked cars) (2 h) Netherlands, pre/post trial on first responders before and after a simulated emergency exercise; participants included 5 different groups of first responders including firefighters	10 firefighters, 26 other first responders (ambulance crew, emergency department, police officers, rapid response team) and 34 observers used as control group	↑ Cortisol levels among first responders 1 h after the training ($P < 0.05$) No changes between the first responder groups	None	Repeated measurements (intra-individual) dependence not considered in time-dependence analysis; age and gender not matched between groups; groups with small sample sizes	Smeets et al. (2021)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (ELISA immunoassay)	Saliva (5 samples: 2 samples on resting day at 7:00 and between 17:00 and 18:30, and 3 samples in intervention session, before, 30 min and 90 min after intervention)	Physical exertion while using full PPE (total weight of ensemble was 23 kg, no fire involved) (12 min) Italy, pre/post trial study on male firefighters (mean age, 32 ± 1 yr) to investigate the effect of firefighting simulation exercise (climb ladder and descend carrying dummy, run, complete a maze in the dark and run again)	20	↑ Cortisol levels 30 min after intervention ($P < 0.001$), with return to baseline after 90 min	Intra-individual	Sequence design Exposure assessment: physical exertion was assessed using a simulated rescue intervention	Perroni et al. (2009)
Cortisol (ELISA immunoassay)	Saliva (morning, 3 samples per session)	Simulated fire-grounds test (9 firefighter-specific tasks, no fire) while wearing full PPE and SCBA (7–10 min) USA (Texas), pre/post trial on 13 professional [career] male firefighters challenged in a firegrounds test after an 8-wk time period under a TRF protocol (14 h fasting:10 h feeding); saliva sampling before, immediately and 30 min after the test	13	↑ Cortisol concentrations pre and 30 min post firefighting simulation test following TRF ($P < 0.05$) ↓ Cortisol concentrations immediately after firefighting simulation test following TRF ($P < 0.05$)	Intra-individual	Small sample size; sequence design; no report or control of firefighting duties before sessions Exposure assessment: engagement in experimental fitness test appropriately tested as exposure for the effects assessments that were done in the experiment	McAllister et al. (2021)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (ELISA immunoassay)	Saliva (total of 10 samples per subject, with 5 samples per boot-type-session: baseline, immediately after 2 trials and 30 min after second trial)	Simulated stair climb (2 trials of 3 min per boot-type-session, no fire) USA (Mississippi), pre/post trial to examine the physiological difference between 2 boot types (rubber boots and leather boots) used while performing a simulated stair climb wearing full firefighting equipment	12	↑ Cortisol levels when using leather boots ($P < 0.05$) No correlation between cortisol and variables of leg strength	Intra-individual; counterbalanced order of testing	Small sample size Exposure assessment: engagement in experimental stair climb exercise appropriately tested as exposure	Huang et al. (2009)
PGC-1α, NE and EPI (ELISA immunoassay) ACTH, PTH and insulin (Luminex multiplex immunoassay)	Plasma (5 samples)	Physical exertion (and employment as firefighter, no fire) Spain, RCT on 2 weeks ubiquinol supplementation on 100 male firefighters	50, 50 [some lost in follow-up, being 34–34 for the last assessment]	↑ PGC-1α with exercise and higher in ubiquinol group ↑ ACTH with exercise, no effect on ubiquinol ↑ EPI and NE with exercise ($P < 0.05$) ↑ NE with ubiquinol ($P < 0.05$) ↓ Insulin with exercise ↑ PTH in ubiquinol group	Smoking, self-reported information on diet and physical activity	Blood sampling day-timings not reported; firefighters used as a convenience group without control for occupational activity Exposure assessment: engagement in experimental physical exercise appropriately tested as exposure in the RCT design to test an intervention	Diaz-Castro et al. (2020b)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
NE and EPI (HPLC-ECD)	Plasma (11 samples)	Physical exercise and mental challenge (no fire) USA (Mississippi), pre/post trial on experienced male firefighters performing simulated exercise with or without simultaneously being challenged with a computerized firefighting strategy and tactics drill	9	↑ NE and EPI after challenge, with greater increase after dual challenge (physical and mental) +, NE was correlated with IL-2 in dual challenge	Intra-individual	Small sample size; possible overlapping sample with Webb et al. (2011) Exposure assessment: engagement in experimental drill exercise appropriately tested as exposure for the effects assessments that were done in the experiment	Huang et al. (2010a)
Cortisol (RIA immunoassay), ACTH (IRMA immunoassay), NE and EPI (HPLC-ECD)	Plasma (11 samples)	Physical exercise and mental challenge (no fire) USA (Mississippi), pre/post trial on experienced male firefighters performing simulated exercise with or without simultaneously being challenged with a computerized firefighting strategy and tactics drill	12	↑ Cortisol after dual challenge ↑ NE and EPI after challenge, with greater increase after dual challenge No change in ACTH for condition or time	Intra-individual	Small sample size; reported catecholamine units may be wrong; possible overlapping sample with Huang et al. (2010a) Exposure assessment: engagement in experimental drill exercise or mental challenge appropriately tested as exposure for the effects assessments	Webb et al. (2011)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (ELISA immunoassay) and relationship with cytokines (Milliplex MAP human cytokine immunoassay)	Saliva (cortisol, 9 samples) and plasma (cytokines, 4 samples)	Simulated physical demands involved in wildfire suppression and sleep restriction (no ambient heat or smoke) Australia, pre/post trial study in deployed firefighters (30 men and 5 women) during 3 days performing simulated occupational physical demands with or without sleep restriction	17, 18	↑ Morning IL-6 related to ↑ evening cortisol in sleep restriction group, while in control group a ↑ IL-6 was associated with a ↓ in evening cortisol	Intra-individual (additionally sex, age, and BMI); control for fluid consumption; matched groups	Small sample size; no crossover condition Exposure assessment: longer sleep opportunity does not automatically result in more sleep; authors did present the actual hours slept, which was significantly different between groups	Wolkow et al. (2015b)
Cortisol (ELISA immunoassay) and relationship with cytokines (Milliplex MAP human cytokine immunoassay)	Saliva (cortisol, 8 samples) and plasma (cytokines, 4 samples)	Simulated physical demands and ambient temperature Australia, pre/post trial study in deployed firefighters during 3 days performing simulated occupational physical demands involved in wildfire suppression in mild or hot ambient temperature condition	19, 18	↑ Cortisol across time-points, independent of condition ($P < 0.001$) ↑ Morning IL-6 related to elevated cortisol independent of condition ($P < 0.024$)	Intra-individual; matched groups	Small sample size; no crossover conditions Exposure assessment: exposure to 2 different temperatures appropriately tested as exposure for the effects assessments that were done in the experiment	Wolkow et al. (2017)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (biotin-streptavidin immunoassay with TR-FIA)	Saliva (8 samples from 10 h to 12 h)	Mental challenge (arithmetic task and speech task, no fire) United Kingdom, pre/post trial study on probationary male firefighters before and after mental challenge tasks by smoking status	86 (52 non-smokers and 34 smokers, with 19 moderate and 15 heavy smokers)	↑ Cortisol after mental challenge among non-smokers	Intra-individual; stable pattern of smoking habits; groups were comparable in terms of alcohol consumption, exercise levels, life events, daily stress and social support, psychological characteristic, but not for body weight (lower in smokers)	Overlapping sample with Roy (2004)	Roy et al. (1994)
Cortisol (biotin-streptavidin immunoassay with TR-FIA)	Saliva (7 samples between 10 h and 12 h)	Mental challenge (arithmetic task and speech task, no fire) United Kingdom, pre/post trial study on probationary male firefighters before and after mental challenge, and association with prior life events and social support	90	↑ Cortisol levels after mental challenge tasks No difference between high or low social-support groups	Intra-individual; no significant differences in smoking status among groups	No control for smoking habits; possible overlapping sample with Roy et al. (2003); Roy (2004)	Roy et al. (1998)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (biotin-streptavidin immunoassay with TR-FIA)	Saliva (8 samples beginning between 9 h and 10 h)	Mental challenge (arithmetic task and speech task, no fire) United Kingdom, pre/post trial study on probationary male firefighters before and after mental challenge tasks, within 1 month of participants joining their fire station; sessions were arranged for the first day of the 8-day shift cycle (2 days, 2 nights and 4 days off)	82	↑ Cortisol levels after mental challenge tasks	Intra-individual	No control for smoking habits; possible overlapping sample with Roy et al. (1998, 2003) Exposure assessment: tool used to quantify job attempted to account for subjectivity in reporting exposure by testing the effect of intraindividual variation in exposure measures on outcomes	Roy (2004)
Cortisol (RIA immunoassay)	Saliva (4 samples for cortisol awakening response and 5 samples in the afternoon after exposure assessment)	Use of protective mask, no fire Switzerland, pre/post trial study on male recruits from the ERS of the Swiss Army, used as controls to male army recruits having a fear of wearing protective mask, assessed before and after cognitive-behavioural treatment	39, 46	↓ Cortisol for ERS recruits (morning levels as well as initial and final levels after mask use sessions) ($P < 0.05$)	Control of age by design	The ERS recruits were compared with a group suffering use of mask phobia Exposure assessment: appropriate design comparing pre and post levels among participants with condition of interest to the general control; condition of interest was self-reported	Brand et al. (2011)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (biotin-streptavidin immunoassay with TR-FIA)	Saliva (morning sample)	Employment as firefighter [municipal] United Kingdom, cross-sectional study on the associations of morning cortisol and social desirability scores among firefighters (mean experience, 15.2 yr), stratified by age group	85	+, Morning cortisol was correlated with social desirability scores for firefighters under age 45 yr ($n = 60$, $P = 0.03$) but not for all samples ($n = 85$) or for age > 45 yr ($n = 25$)	None	Cross-sectional nature; 1 single sampling; no control group	Brody et al. (2000)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (RIA immunoassay)	Saliva (sampled between 2000–2002)	Occupational participation in a major historical air disaster Netherlands, cross-sectional study on cortisol associations with PTSD and NLE established after a major air disaster in 1992	1082, 798	Exposure to the air disaster was not associated with cortisol +, Exposed participants who self-reported more intrusion symptoms had lower cortisol levels ($P < 0.05$)	Salivary sampling time, age, gender, and smoking status	Cross-sectional nature; no control for food and coffee intake, and cigarette use; large salivary sampling time span (09:00 to 16:30); not possible to retrieve results from firefighters among the study population; incongruences in numbers of excluded participants described in text and tables Exposure assessment: sample population included firefighters and police but relationships between exposure of interest and outcome were not analysed according to the occupation, which is a potentially relevant exposure metric; the 8-yr criterion for dichotomization of NLE was not justified	Witteveen et al. (2010)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Cortisol (RIA immunoassay)	Saliva (4 samples during 1 working day at 7:00, 11:00, 15:00, and 22:00)	Employment as firefighter (day without emergency situation) Czechia, repeated measurements on 136 male firefighters and 40 male and 102 female primary school teachers; firefighters were asked to perform sample collection on a day without emergency situations and teachers during their busiest workday	136, 142	↓ Cortisol (diurnal slope, morning, evening, and hormonal output) for male firefighters ($P = 0.042$)	Gender, age, physical activity, and smoking status	Cross-sectional nature; no control day measurements; age, work experience, marital status and education level not matched between groups	Susoliakova et al. (2014)
Cortisol (CLIA immunoassay)	Serum and urine (blood at 09:00, urine from 22:00 to 07:00, multiple samples)	Work shift organization (routine work) Republic of Korea, pre/post trial; repeated measurements on 325 firefighters (303 men and 22 women), including routine jobs of fire suppression, emergency medical service, rescue and fire investigation, with different work shift cycle schedules (3-, 6-, 9- or 21-day cycles)	325	↑ Serum cortisol levels after night or 24-h shift and different for different schedules; recovery of urine cortisol was delayed for those working on 6- and 21-day cycles	Sex, age, chronotype, depression, job, PTSD, sleep disorder, fatigue, caffeine, subjective health condition and sleep quality	Workload not controlled Exposure assessment: adequate exposure assessment using apparent work-shift categories for the effect that is being assessed	Lim et al. (2020)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
TSH and total T4 (ELISA immunoassay)	Plasma (collected in 2014–2015)	Employment as firefighter (years of work, on duty shift, firefighting in the last 24 h or 7 days, use of SCBA, job function) USA (California), cross-sectional study on associations between urinary excretion of metabolites of flame retardants and thyroid function among women firefighters compared with office workers	84, 81	↑ BDCPP in firefighters and associated with a T4 decrease ($P < 0.05$)	Age and creatinine; by design control of medication; food consumption not associated with metabolite excretion for either group	Cross-sectional nature; exposure markers analysed in spot urine samples Exposure assessment: although creatinine-corrected, spot urine was used for this cross-sectional study; levels may be impacted by non-work sources	Trowbridge et al. (2022)
TSH, unbound T4 and T3	Blood (2 samples, baseline and week 52) (2019–2021)	Employment as firefighter Australia, randomized clinical trial examining the effect of plasma and whole blood regular donation on PFAS blood levels and thyroid function on firefighters with baseline PFOS level ≥ 5 ng/mL	285	Plasma and blood donation decreased significantly PFAS levels, and plasma donation had a larger treatment effect than blood donation; unchanged levels of thyroid function hormones; group-screening level interactions for low and high levels of TSH (with plasma donation associated with larger increase of TSH for higher baseline TSH)	Intra-individual (mean change)	Thyroid function hormone detection method not reported Exposure assessment: exposure (whole blood vs plasma donations vs no donations) was controlled for in the design of the clinical trial	Gasiorowski et al. (2022)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
AMH (picoAMH ELISA)	Dried blood spots	Employment as firefighter USA (Arizona) and Canada, cross-sectional study on association of AMH and firefighting occupation among 106 female firefighters and 58 non-firefighter female controls.	106, 58	↓ 33.4% (95% CI, −55.0 to −0.14) AMF in firefighters Among firefighters, no change in AMH for number of live fires responded to in a typical month or years worked in the fire service	Age and BMI; only non-smokers included	No information on non-firefighters' occupation Exposure assessment: it was qualitative as history of firefighting; use of PPE was accounted for	Davidson et al. (2022)

Table 4.10 (continued)

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Melatonin (ELISA immunoassay)	Saliva (every 4 h during night shift, 4 samples)	Night work shift organization (routine work at petrochemical plant) Islamic Republic of Iran; repeated measurements on firefighters at a petrochemical plant following 2 different night shift work plans (7 or 4 consecutive night shifts)	64	Melatonin night rhythm was different among the 2 work shift cycles ($P < 0.001$)	Participants were asked to keep regular sleep schedules and avoid eating 1 h before sampling; models adjusted for light exposure and caffeine consumption	Melatonin rhythm only assessed in the last night of both shift cycles (with different cycle lengths), not assessed during the day or day shifts; cross-sectional nature; incongruent reporting of group demographic differences; caffeine assessment method not described; inconsistent description of how many participants lived far from their families Exposure assessment: it was accurate; participants were selected on the basis of apparent work shift categories	Kazemi et al. (2018)

ACTH, adrenocorticotropic hormone; AMH, anti-müllerian hormone; BDCPP, bis(1,3-dichloro-2-propyl)phosphate; BMI, body mass index; CAD, coronary artery disease; CALUX, chemical activated luciferase gene expression; CLIA, chemiluminescence immunoassay; CYP1A2, cytochrome P450 1A2; ECLIA, electrochemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EPI, epinephrine; ERS, emergency rescue service; HbA1c, glycosylated haemoglobin; HPLC-ECD, high performance liquid chromatography-electrochemical detection; IL-2, interleukin 2; IQR, inter-quartile range; IRMA, immunoradiometric assay; LVWT, left ventricular wall thickness; MBI-GS, Maslach Burnout Inventory-General Survey; NE, norepinephrine; NLE, negative life events; OH-PAHs, hydroxylated PAHs; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; PFAS, perfluoroalkyl and polyfluoroalkyl substances; PFOS, perfluorooctanesulfonic acid; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1 α; PPE, personal protective equipment; PTH, parathyroid hormone; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; RIA, radioimmunoassay; SBP, systolic blood pressure; SCBA, self-contained breathing apparatus; T4, thyroxine; T:C, testosterone:cortisol ratio; TRF, time-restricted feeding; TR-FIA, time-resolved fluorometric end-point determination; TSH, thyroid-stimulating hormone; XRE, xenobiotic response element; vs, versus; yr, year.

[a] +, positive; –, negative; +/–, equivocal; (+) or (–), positive or negative result in a study of limited quality; ↑, increase; ↓, decrease.

[b] Factors to be considered for study quality included the methodology and design, reporting, and exposure assessment quality.

> 20 years of experience) and compared with an age- and sex-matched control group of healthy non-firefighters. The bioassay activity increased significantly when the transfected cells were treated with heat-inactivated serum from either firefighter group compared with the control group but was not different between the two groups of firefighters. [The Working Group noted that recent exposures or the different roles that firefighters assume may have the potential to affect the ability to distinguish between firefighter employment length.] Significant AhR activity was also reported when the bioassay was treated with purified hydrophobic fraction of firefighters' sera. A ligand–receptor interaction was confirmed by a significant decrease in the bioassay activity, for all groups, when an AhR antagonist (GNF351) was added to the purified serum fraction. [The Working Group deemed this an informative study because of the investigation of heat-inactivated serum, purified fraction of serum, and confirmation of an antagonistic effect, and the inclusion of solely non-smoking, male, and age-matched participants, who were compared with a control group of non-firefighters.]

Chernyak & Grassman (2020) investigated the effect of the AhR repressor (*AHRR*) polymorphism (565C > G or Pro185Ala, rs2292596) on the activity of hepatic enzyme cytochrome P450 1A2 (CYP1A2), a downstream target of AhR, in blood samples from 28 male firefighters (former and current) and 10 matched male non-firefighter controls. The firefighters were recruited from a cohort established after an historical industrial fire in a cable factory in Shelekhov, Russian Federation, which they had attended without use of respiratory protection; samples were collected 17 years after the incident. CYP1A2 activity, assessed in urine using antipyrine as a metabolite probe, was positively associated with dioxin body burden among carriers of the *AHRR* G allele (Chernyak & Grassman, 2020). The study indicated that the variant alanine (GG and GC) exhibited stronger AhR repression than did the CC genotype, determined as higher gene expression of *AHRR* and lower activity of CYP1A2. The models using current firefighters showed the best fit, with dioxin body burden being significantly associated with CYP1A2 activity when adjusting for *AHRR* genotype. In a previous study from the same group using the same participant samples, the authors reported higher levels of dioxin-like compounds in firefighters than in non-firefighters and higher levels of PCBs among current firefighters (Chernyak et al., 2012). [The Working Group noted that the study demonstrated an association between the toxicant body burden and the level of activity of enzymes involved in its biotransformation, mediated by the *AHRR* genotype.]

Two firefighters from Chicago, Illinois, USA, were reported with a diagnosis of chloracne relating to possible historical occupational exposures (Orris et al., 1986). Each case reported 23 years or 20 years of employment as a firefighter and participation in possible historical events, with 10 years and 15 years, respectively, since onset of symptoms. At the time of diagnosis, blood levels of PCBs were < 10 µg/L. [The Working Group noted that although the temporal relationship between possible occupational exposures and onset of symptoms might be plausible, for a disease mediated by AhR, no definitive etiological relationship could be established.]

[The Working Group noted that, overall, the three available studies (Beitel et al., 2020; Chernyak & Grassman, 2020; Ricaud et al., 2021) and the case report (Orris et al., 1986) all demonstrated AhR activation, measured through various end-points, with firefighting exposures. Although the studies were limited by small sample sizes and risk of recall bias (for the case report), collectively they pointed to agonistic binding and activation effects.]

(ii) Androgens and estrogens

Six studies investigated the levels of sex hormones in firefighters: one study was related to wildland critical training in prescribed burns (Christison et al., 2021), and five studies considered employment as a firefighter (Luria et al., 1982; Roy et al., 2003; Lit et al., 2010; Lofrano-Porto et al., 2020; Vinnikov et al., 2021), with two of these studies also investigating exposure to stress (Roy et al., 2003; Lit et al., 2010).

Christison et al. did not detect differences in morning plasma testosterone levels in 14 male and 2 female firefighters over 11 days of critical training with 7 days on prescribed burns, in Montana, USA. They reported a decreased testosterone:cortisol ratio after day 8; this is a marker for overreaching, which was correlated with muscle damage and soreness (Christison et al., 2021).

A cohort of 72 male probationary firefighters, from London, United Kingdom, was followed over 1 year, measured in five sessions, to investigate the within-individual relationship between recent stress exposure and testosterone levels (Roy et al., 2003). The five repeated session measurements were performed in the same place, same time of the day, and on the same day of the shift cycle, at 3-month intervals across the year. A decrease in morning plasma testosterone levels across the assessment sessions was observed, with higher prior stress associated with higher testosterone levels, whereas there was an increase in salivary cortisol levels (described below in Section 4.1.6(a)(iii) (Roy et al., 2003). [The Working Group noted that the observations suggested glucocorticoid-mediated testosterone suppression. The Working Group considered this study to be informative because of the repeated measurement design and use of probationary firefighters without previous firefighting exposures, adequate follow-up duration, reasonable sample size, with control for shift work, sampling timing, and (although including smokers) for smoking habits and intra-individual changes.]

Three cross-sectional studies reported total testosterone levels in male firefighters. Lofrano-Porto et al. (2020) reported a prevalence of 37% for low and borderline serum testosterone levels among 326 male career firefighters (stratified by reference values), from Florida, USA; this was associated with decreased left ventricular wall thickness. [The Working Group noted that the group with low testosterone levels was significantly older and had a higher body mass index (BMI) than did the group with testosterone levels that were within the reference range, whereas the group with borderline testosterone levels had a significantly lower age and BMI than did the group with low testosterone levels.] However, Vinnikov et al. (2021) reported normal blood testosterone levels for all 100 military firefighters, from Kazakhstan, from three occupational groups (firefighters, fire-truck drivers, and management and engineers), and no difference between firefighter groups, with higher testosterone levels associated with burnout risk as assessed by an inventory validated tool. [The Working Group noted that the groups were not matched for age or years in service, BMI data was not reported, and there was no non-firefighter control comparison.] Another cross-sectional study with 12 male firefighters as a healthy control group, from Ohio, USA, reported lower serum estradiol levels in firefighters than in male patients with acute infarction, and no difference between firefighters and male patients undergoing evaluation of chest pain with or without evidence of coronary artery disease (Luria et al., 1982). Additionally, BMI was significantly higher in firefighters than in the patients without notable coronary obstruction, and no differences were reported in BMI and age-adjusted total serum testosterone levels between the groups (Luria et al., 1982). [The Working Group noted that the comparison was limited to disease status (which may lead to uncertainties in the interpretation of

the results), used a small sample size, and had no exposure assessment.]

There was also no difference detected in saliva testosterone levels in seven firefighters from California, USA, sampled before and after a stress challenge (Lit et al., 2010). [The Working Group noted the sampling time span and small sample size.]

In total, six studies investigated testosterone levels in firefighters: two studies showed effects (Roy et al., 2003; Lofrano-Porto et al., 2020) and four studies showed unchanged levels (Luria et al., 1982; Lit et al., 2010; Christison et al., 2021; Vinnikov et al., 2021). [The Working Group noted that the studies with no effects were less informative, because of small sample sizes, lack of a control group, or non-matched or non-adequate sampling timings.]

(iii) Cortisol, adrenocorticotropic hormone, and catecholamines

Of seven studies investigating cortisol levels in scenarios involving live-fire drills, six studies reported increased cortisol levels (Smith et al., 2005; Sünram-Lea et al., 2012; Robinson et al., 2013; Kim et al., 2018; Christison et al., 2021; Smeets et al., 2021), with only one study reporting that levels were not significantly affected (Rosalky et al., 2017). [The Working Group noted that the staggered experiment start times, possible elevated anticipatory levels, loss of post-exposure samples, and difficulty in controlling the length of the exercise might have precluded the ability to observe effects in Rosalky et al. (2017).]

In firefighters (n = 325) from Republic of Korea, following four different night shift cycles, morning serum cortisol levels were higher after working a night shift than after working a day shift. (Lim et al., 2020).

Roy et al. (2003) observed (together with the testosterone decrease reported earlier in Section 4.1.6(a)(ii)) increased salivary cortisol levels after 1 year of follow-up of probationary firefighters. Sessions with higher daily stress before the assessment were associated with lower cortisol levels, suggesting downregulation of cortisol following an increment in stress exposure (Roy et al., 2003).

Cortisol levels also increased after physical exertion simulations in six studies without live fires in Australia, Italy, and the USA (Huang et al., 2009; Perroni et al., 2009; Webb et al., 2011; Wolkow et al., 2015b, 2017; McAllister et al., 2021). McAllister et al. investigated a time-restriction feeding regime and reported a shift in cortisol response and changes in inflammation markers among 13 firefighters following a simulated fire-ground challenge (McAllister et al., 2021). Wolkow et al. investigated the dual challenge of physical work and sleep restriction. Firefighters undertaking 3 days of physical work with 2 nights of sleep restriction had increased levels of salivary cortisol when compared with firefighters with 8 hours of sleep opportunity. Increased morning interleukin IL-6 levels in plasma were related to increased evening levels of salivary cortisol in the sleep-restricted group and decreased evening cortisol levels in the control group (Wolkow et al., 2015b). The authors reported that subjective self-reported mood and physical signs and symptoms were also related to cortisol levels (Wolkow et al., 2016a, b). In a study with a similar deployment design but for a dual challenge of physical exercise and hot ambient temperature, increases in cortisol and plasma IL-6 levels were observed, independently of conditions, suggesting that there was no effect of ambient temperature (Wolkow et al., 2017).

Mental stress alone was observed to increase cortisol levels in a pre/post trial (Roy et al., 1994, 1998; Roy, 2004), and two studies reported lower levels of cortisol after stress in firefighters than in control groups assigned to different tasks (Lit et al., 2010; Brand et al., 2011). [The Working Group noted that these studies were not informative because the comparison was only made with participants having a phobia (Brand et al., 2011) or because of small sample size and study design

(Lit et al., 2010).] Salivary cortisol levels associated with self-reported stress indicators were also observed in cross-sectional studies (Brody et al., 2000; Witteveen et al., 2010). [The Working Group noted that the study by Witteveen et al. (2010) presented limitations because of the saliva sampling design.] Repeated measurements in 136 firefighters and 142 primary school teachers showed lower morning, evening, and diurnal slope salivary cortisol levels, with overall cortisol output being lower in male firefighters than in male teachers (Susoliakova et al., 2014). [The Working Group noted that the groups were not matched, and mental stressors were not controlled for – firefighters were sampled on a day without an emergency call and teachers were sampled on their busiest day.]

The effect of dual challenge with physical and mental stress from a firefighting simulation exercise showed increased plasma cortisol levels, together with increased epinephrine and norepinephrine, after the dual challenge in comparison with physical exercise alone (Huang et al., 2010a; Webb et al., 2011).

Adrenocorticotropic hormone and catecholamines, which are less well-studied than cortisol, were also observed to be affected by live-fire training (Smith et al., 2005; Kim et al., 2018) and physical exercise (Diaz-Castro et al., 2020b), or by dual challenge (Huang et al., 2010a; Webb et al., 2011).

(iv) Peroxisome proliferator-activated receptor γ coactivator-1α, parathyroid hormone, thyroid-stimulating hormone, thyroxine, anti-müllerian hormone, and melatonin

A controlled trial of ubiquinol supplementation in a sample of 100 firefighters also reported increased levels of plasma peroxisome proliferatoractivated receptor γ coactivator-1α (PCG-1α), and parathyroid hormone, both after the physical challenge protocol and as an effect in the ubiquinol-supplemented group (Diaz-Castro et al., 2020b). [The Working Group noted that the study did not control for firefighters' occupational activity, and the physical challenge test may not have been representative of firefighters' physical exertion exposure.]

Trowbridge et al. investigated the associations between urinary excretion of flame retardant metabolites and plasma levels of thyroid-stimulating hormone (TSH) and thyroxine (T4) in a cross-sectional study comparing 84 female firefighters with 81 female office workers from the San Francisco Fire Department, USA. The authors observed a relationship between levels of flame retardant metabolites and T4 but not TSH: levels of bis(1,3-dichloro-2-propyl) phosphate (BDCPP) among firefighters were two-fold those among office workers and were associated with decreased T4 levels; this association was not observed among office workers (Trowbridge et al., 2022).

A randomized control trial involving 285 firefighters investigated the effects of repeated donations of plasma and blood on levels of PFAS and thyroid function hormones (Gasiorowski et al., 2022). The firefighters (current or former) with baseline PFOS levels of ≥ 5 ng/mL were assigned to repeatedly donate plasma or blood, or to be observed for 1 year. Plasma and blood donation both significantly decreased PFOS levels in firefighters compared with the observation-only group, and plasma donation had a larger treatment effect than did blood donation, but thyroid function (as measured by levels of TSH, triiodothyronine T3, and T4) was unchanged 1 year after repeated donations, compared with baseline (Gasiorowski et al., 2022).

The association between the occupation of firefighter and levels of anti-müllerian hormone, a clinical marker of ovarian reserve used to assess responsiveness to fertility treatment, was investigated in a cross-sectional study involving 106 female firefighters and 58 female non-firefighter controls (Davidson et al., 2022). Firefighters had lower levels of anti-müllerian hormone than did non-firefighters.

Kazemi et al. investigated salivary melatonin levels and self-reported sleepiness among firefighters at a petrochemical plant in the Islamic Republic of Iran who were following two different night shift cycles: 4 nights, 4 days, and 4 days off (rest days); or 7 nights, 7 days, and 7 days off. The melatonin circadian rhythm at night of firefighters showed a delayed peak in the last night of the 7-night shift and was associated with a delayed peak in sleepiness (Kazemi et al., 2018). [The Working Group noted that melatonin rhythm was only assessed in the last night of both shift cycles, with different lengths, and that changes may have been an adaptation to the night shift.]

(b) Human cells in vitro

No data were available to the Working Group.

(c) Experimental systems

(i) Non-human mammals in vivo

No data were available to the Working Group.

(ii) Non-human mammalian cells in vitro

One study evaluated estrogenic activity in extracts of firefighters' gloves and hoods in an estrogen screening assay in yeast; estrogenic and anti-estrogenic activity was measured in new and used gear; the outer layer of new gloves showed estrogen activity comparable to that of 1 nM estradiol (Stevenson et al., 2015; Table 4.11) [The Working Group noted that few samples of gear were analysed, and there was no information on characteristics of the equipment.]

Behnisch et al. investigated the thyroid hormone-disrupting effects of PFAS in technical mixtures of aqueous film-forming foams (AFFFs) using a cell reporter bioassay with a thyroid transporter transthyretin construct (TTR TRβ CALUX). The three AFFF mixtures tested showed thyroid disruptive potential, both with and without total oxidizable precursor treatment (for complete oxidation of precursors); higher activities were reported for the older AFFFs from 2013 than for AFFFs from 2019 (Behnisch et al., 2021; Table 4.11). [The Working Group noted that the AFFF samples constituted technical mixtures and not the foam itself, with unknown potential exposure concentrations, and were nevertheless tested at a dilution of 100 or 10 000 times.]

4.1.7 Evidence relevant to other key characteristics of carcinogens

(a) Causes immortalization

See Table 4.12.

Telomere length is an established marker of health and disease; reduced telomere length is observed with ageing, and increased telomere length is observed in malignant cells as part of the immortalization process in some cancers (Lansdorp, 2022). In terms of markers of cellular immortalization, only two epidemiological studies were available that assessed telomere length in samples from firefighters or firefighters in training, including one study that also conducted an assessment in vitro (Ma et al., 2020; Clarity et al., 2021).

(i) Exposed humans

Ma et al. (2020) examined the short-term impact of exposure to smoke from training fires on telomere length by comparing three samples from non-smoking conscripts attending a 3-day smoke-diving training course in Denmark. No statistically significant differences were reported in telomere length between sampling time-points (14 days before the training exercise, and immediately after and 7–14 days after the training exercise).

Clarity et al. (2021) assessed telomere length in 84 female firefighters who had worked for ≥ 5 years in California, USA, and in 79 female office workers. In this cross-sectional study, serum levels of 12 PFAS and urinary levels of 10 organophosphate flame retardants were quantified in both groups, and associations between widely

Table 4.11 End-points relevant to modulation of receptor-mediated effects in experimental systems in vitro

End-point	Test system	Detection	Positive control	Sample	Estrogenic activity (significance)[a]	Comments	Reference
Estrogenic activity (YES assay)	Yeast (engineered BJ2168 strain)	Luminescence assay (estrogenic activity) and haematocytometer (anti-estrogenic activity)	17β-estradiol	Extracts from firefighter gloves and hoods (new and with 8 wk use)	+, Hoods and outer and middle layers of new gloves with estrogenic activity ($P < 0.01$) +, Used gloves and hoods displayed low estrogenic and suggested stronger antiestrogenic activity ($P < 0.05$)	Few samples of gear analysed (1 new and 2 or 3 used); no information about characteristics of equipment	Stevenson et al. (2015)
Thyroid disruptive potential (TTR TRβ CALUX assay)	Human bone osteosarcoma epithelial cells (U2OS line) transfected with TRβ and luciferase reporter construct and combined with TTR-binding assay	Luminescence	PFOA	3 technical AFFF surfactant products from 2 different production years (2013 and 2019), tested with and without total oxidizable precursor treatment (all in triplicates)	+, All tested AFFF samples showed thyroid disruptive potential +, AFFF samples from 2013 showed higher assay activity than did samples from 2019	AFFF samples are technical mixtures and not the foam itself, nevertheless, they were diluted 100 or 10 000 times	Behnisch et al. (2021)

AFFF, aqueous film-forming foams; CALUX, chemical activated luciferase gene expression; PFOA, perfluorooctanoic acid; TRβ, thyroid receptor beta; TTR, thyroid hormone transporter transthyretin; YES, yeast estrogen screening.

[a] +, positive.

Table 4.12 End-points relevant to immortalization in exposed firefighters

End-point	Biosample, tissue, or cell type	Type of exposure, location, setting, study design	No. of exposed and controls	Response (significant)[a]	Covariates controlled	Comments[b]	Reference
Telomere length	PBMC	Exposure at firefighter training Denmark, pre/post training of smoke diving course	53 conscripts in training, sampled 3 times, before and after a 3-day smoke diving course	No changes	Sex, age, random effect for individual	Study has in vitro component that reports shorter telomere length in human cells exposed to PM; participants served as their own controls; small samples of 41 men, 12 women Exposure assessment: involvement in firefighter training tested as exposure appropriate for the effects assessments that were done in the pre/post study	Ma et al. (2020)
Telomere length	Peripheral blood	Employment as firefighter and specific chemicals California, USA, 2014–2015 Women Workers Biomonitoring Initiative, cross-sectional	84 firefighters, 79 office workers, all women	Positive association between PFAS (PFOS, PFOA, PFNA, PFDA) and ↑ telomere length; association between OPFR (BCEP) and ↓ telomere length	Age, dairy and egg consumption, urinary creatinine (varies by model)	Associations reported are when adjusting for age alone; associations were attenuated when adding additional covariates for all except PFOA Exposure assessment: chronic biomarkers PFAS and PBDEs appropriate for chronic outcome that was investigated; biomonitoring for short half-life OPFRs subject to confounding from other exposures	Clarity et al. (2021)

BCEtP, bis-2-chloroethyl phosphate; OPFRs, organophosphate flame retardants; PBMC, peripheral blood mononuclear cells; PFAS, per- and poly-fluoroalkyl substances; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid.

[a] +, statistically significant result(s) reported; no changes, no statistically significant results reported for any end-points of interest; (+), statistically significant result but study was of limited quality; ↑, increase; ↓, decrease.

[b] Factors to be considered for study quality included the methodology and design, reporting, and exposure assessment quality.

detected exposures (> 70%) and telomere length were examined in all participants and separately by occupational group. In general, the firefighters had longer telomeres than did the office workers. Among firefighters, levels of four PFAS (perfluorodecanoic acid, PFDA; perfluorononanoic acid, PFNA; perfluorooctanoic acid, PFOA; and perfluorooctanesulfonic acid, PFOS) were significantly associated with increased telomere length after adjusting for age; only the association for PFOA remained statistically significant after adjusting for additional confounders. One organophosphate flame retardant (bis-2-chloroethyl phosphate, BCEtP) was inversely associated with telomere length among firefighters. [The Working Group noted that strengths of the study included measurement of multiple exposure biomarkers in firefighters and in the control group. Limitations included lack of certainty that exposures were from the occupation and not from another source.]

[The Working Group noted that the differences in the two studies may be attributed, in part, to differences in the focal exposures – acute exposure to fire smoke during training versus chronic exposures to PFAS and organophosphate flame retardants.]

(ii) Human cells in vitro

Ma et al. (2020) treated a human lung adenocarcinoma cell line (A549) with suspended particles collected during their epidemiological study (described in Section 4.1.7(a)(ii)). Exposures were categorized as SP1 (particles from wood smoke training), SP2 (from wood smoke training that also included electrical cords and mattresses in the fire), and TDEP (from train diesel exposure). Cells were treated with each at three non-cytotoxic concentrations over 2–4 weeks. SP1 was significantly associated with decreased telomere length only at 2 weeks. When pooling results from all three exposures, there was a significant decrease in telomere length within 4 weeks. [The Working Group concluded that the effect was in the same direction as that observed in the epidemiological study, but results were only statistically significant in the in vitro study, in which exposures were limited to the collected PM.]

(b) Alters cell proliferation, cell death, or nutrient supply

Only one study relevant to firefighting was found in the literature for the key characteristic "alters cell proliferation, cell death, or nutrient supply". The study assessed cell proliferation and viability in immortalized human cells in vitro. Kafkoutsou et al. (2022) treated human embryonic kidney cells (HEK-293) with three different class B AFFFs. The foams were collected from fire departments in the USA and contained either PFOA or an unspecified C6-fluorosurfactant. Cells were treated with each foam at seven concentrations (up to 10% in media), with the vehicle as the control. Cell viability and cell proliferation were assessed (the latter with the CellTiter 96 AQueous One solution MTS assay) after 72 hours of exposure. For all three foams, there were decreases in both cell viability and cell proliferation with increasing exposure concentration; concentrations of > 3% consistently showed significant decreases for all foams. The PFOA-containing foam exhibited cytotoxicity at the lowest concentrations. [The Working Group noted that this finding may be relevant to kidney toxicity.]

(c) Multiple characteristics identified by transcriptomics or other experimental approaches

See Table 4.13.

This section describes other studies relevant to cancer mechanisms: oncoproteins (Ford et al., 1992), an oncogenic growth factor (Min et al., 2020), and transcriptomics (Gainey et al., 2018).

Table 4.13 End-points relevant to multiple characteristics (other potential biomarkers and susceptibility factors)

End-point	Biosample, tissue, or cell type	Type of the exposure, location, setting, study design	No. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments[b]	Reference
Proteins (2 growth factors and 7 oncoproteins)	Serum	Employment as firefighter USA (New York), New York City Fire Department, case–control	33 (selected from 226) firefighters, 16 controls (medical centre workers)	(+) ↑ TGFβ detection in firefighters (42%) compared with controls (0%)	Controls matched on age, sex, smoking status, race	Very small sample size; all men; method may have had low detection limit (no proteins detected except TGFβ)	Ford et al. (1992)
FGF-23, α-klotho, vitamin D	Serum	Employment as firefighter Republic of Korea, Sleep Panel Study (SLEPS), cross-sectional	450 (active firefighters including 81 day-only and 369 shift workers)	+ Shift work and job type associated with ↑ FGF-23 and α-klotho	Age, sex, BMI, LDL cholesterol (originally considered alcohol, smoking and exercise)	Strength: compared results across 5 job types and 5 shift types; 92% male participants; vitamin D was low among all firefighters	Min et al. (2020)

BMI, body mass index; FGF-23, fibroblast growth factor-23; LDL, low-density lipoprotein; TGFβ, transforming growth factor beta.

[a] +, statistically significant result(s) reported; no changes, no statistically significant results reported for any end-points of interest; (+) statistically significant result but study was of limited quality; ↑, increase.

[b] Factors to be considered for study quality included the methodology and design, reporting, and exposure assessment quality.

(i) Exposed humans

Ford et al. (1992) used immunoblotting to screen for nine serum oncoproteins and growth factors among a small sample of firefighters and controls (medical workers) from New York City, USA. Only transforming growth factor beta (TGFβ) was detected in any samples, and significantly more TGFβ was detected in firefighters (42%) than in controls (0%). [The Working Group noted that this marker is a regulator of cancer stemness and has been related to cancer risk and non-malignant respiratory disease in other studies (Bellomo et al., 2016; Saito et al., 2018).] The oncogene FGF-23, the tumour suppressor α-klotho, and vitamin D were measured in serum from firefighters (Min et al., 2020). [The Working Group noted that the focus of this study was circadian rhythm disruption among firefighters rather than other occupational exposures.]

(ii) Human cells in vitro

No data on human cells in vitro were available to the Working Group.

(iii) Experimental systems

Gainey et al. (2018) reported on a mouse model of fireground exposure, which demonstrated gene expression changes after exposure (also described in Section 4.1.5). The model was designed to test the acute impact of exposure during overhaul without SCBA protection. Male C57BL/6J mice were compared across three groups: control (never left animal facility), fireground exposure group (FG, stayed in the structure in a non-affected area), and overhaul group (OH, placed in area with overhaul). There were six mice in each group, and the experiment was repeated on three different days with new mice. RNA sequencing was performed on lung tissue collected 2 hours after overhaul. Of 16 261 genes detected, 1890 were significantly upregulated and 1962 were downregulated in the OH group compared with the FG group; this included 43 genes each with > 50% change in either direction. Differentially expressed genes were over-represented in 22 KEG (Kyoto Encyclopedia of Genes and Genomes) pathways, including chemical carcinogenesis, miRNAs in cancer, choline metabolism in cancer, and more.

4.2 Other relevant evidence

Studies reporting other evidence that may be relevant for carcinogenesis included assessment of hospital admissions from endocrine and metabolic disorders among firefighters, proteomics analyses after an exercise challenge, and a case series of allergic contact dermatitis in five firefighters (Ryu et al., 2021; Zhu et al., 2021; Patel & Nixon, 2022). However, the findings were deemed less informative and sporadic compared with the findings from other available studies.

References

Abreu A, Costa C, Pinho E Silva S, Morais S, do Carmo Pereira M, Fernandes A, et al. (2017). Wood smoke exposure of Portuguese wildland firefighters: DNA and oxidative damage evaluation. *J Toxicol Environ Health A*. 80(13–15):596–604. doi:10.1080/15287394.2017.1286896 PMID:28524757

Adetona AM, Adetona O, Gogal RM Jr, Diaz-Sanchez D, Rathbun SL, Naeher LP (2017). Impact of work task-related acute occupational smoke exposures on select proinflammatory immune parameters in wildland firefighters. *J Occup Environ Med*. 59(7):679–90. doi:10.1097/JOM.0000000000001053 PMID:28692002

Adetona AM, Martin WK, Warren SH, Hanley NM, Adetona O, Zhang JJ, et al. (2019). Urinary mutagenicity and other biomarkers of occupational smoke exposure of wildland firefighters and oxidative stress. *Inhal Toxicol*. 31(2):73–87. doi:10.1080/08958378.2019.1600079 PMID:30985217

Adetona O, Zhang JJ, Hall DB, Wang JS, Vena JE, Naeher LP (2013). Occupational exposure to woodsmoke and oxidative stress in wildland firefighters. *Sci Total Environ*. 449:269–75. doi:10.1016/j.scitotenv.2013.01.075 PMID:23434577

Al-Malki AL, Rezq AM, Al-Saedy MH (2008). Effect of fire smoke on some biochemical parameters in firefighters of Saudi Arabia. *J Occup Med Toxicol*. 3(1):33. doi:10.1186/1745-6673-3-33 PMID:19077241

Aldrich TK, Weakley J, Dhar S, Hall CB, Crosse T, Banauch GI, et al. (2016). Bronchial reactivity and lung function after World Trade Center exposure. *Chest*. 150(6):1333–40. doi:10.1016/j.chest.2016.07.005 PMID:27445092

Almeida AG, Duarte R, Mieiro L, Paiva AC, Rodrigues AM, Almeida MH, et al. (2007). [Pulmonary function in Portuguese firefighters]. *Rev Port Pneumol*. 13(3):349–64. [Portuguese] doi:10.1016/S0873-2159(15)30354-8 PMID:17632674

Andersen MHG, Saber AT, Clausen PA, Pedersen JE, Løhr M, Kermanizadeh A, et al. (2018a). Association between polycyclic aromatic hydrocarbon exposure and peripheral blood mononuclear cell DNA damage in human volunteers during fire extinction exercises. *Mutagenesis*. 33(1):105–15. doi:10.1093/mutage/gex021 PMID:29045708

Andersen MHG, Saber AT, Pedersen JE, Pedersen PB, Clausen PA, Løhr M, et al. (2018b). Assessment of polycyclic aromatic hydrocarbon exposure, lung function, systemic inflammation, and genotoxicity in peripheral blood mononuclear cells from firefighters before and after a work shift. *Environ Mol Mutagen*. 59(6):539–48. doi:10.1002/em.22193 PMID:29761929

Barceló-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK (2008). Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid. *Am J Clin Nutr*. 88(3):801–9. doi:10.1093/ajcn/88.3.801 PMID:18779299

Behnisch PA, Besselink H, Weber R, Willand W, Huang J, Brouwer A (2021). Developing potency factors for thyroid hormone disruption by PFASs using TTR-TRβ CALUX® bioassay and assessment of PFASs mixtures in technical products. *Environ Int*. 157:106791. doi:10.1016/j.envint.2021.106791 PMID:34364217

Beitel SC, Flahr LM, Hoppe-Jones C, Burgess JL, Littau SR, Gulotta J, et al. (2020). Assessment of the toxicity of firefighter exposures using the PAH CALUX bioassay. *Environ Int*. 135:105207. doi:10.1016/j.envint.2019.105207 PMID:31812113

Bellomo C, Caja L, Moustakas A (2016). Transforming growth factor β as regulator of cancer stemness and metastasis. *Br J Cancer*. 115(7):761–9. doi:10.1038/bjc.2016.255 PMID:27537386

Bergström CE, Eklund A, Sköld M, Tornling G (1997). Bronchoalveolar lavage findings in firefighters. *Am J Ind Med*. 32(4):332–6. doi:10.1002/(SICI)1097-0274(199710)32:4<332::AID-AJIM2>3.0.CO;2-W PMID:9258385

Bergström CE, Tornling G, Unge G (1988). Acquired progressive asthma in a fire-fighter. *Eur Respir J*. 1(5):469–70. PMID:3169218

Bodienkova GM, Ivanskaia TI (2003). [Nervous system pathology and disruption of immunoreactivity in firefighters]. *Gig Sanit*. (2):29–31.[Russian] PMID:12861686

Borges LP, Nascimento LC, Heimfarth L, Souza DRV, Martins AF, de Rezende Neto JM, et al. (2021). Estimated SARS-CoV-2 infection and seroprevalence in firefighters from a northeastern Brazilian state: a cross-sectional study. *Int J Environ Res Public Health*. 18(15):2–7. doi:10.3390/ijerph18158148 PMID:34360442

Brand S, Annen H, Holsboer-Trachsler E, Blaser A (2011). Intensive two-day cognitive-behavioral intervention decreases cortisol secretion in soldiers suffering from specific phobia to wear protective mask. *J Psychiatr Res*. 45(10):1337–45. doi:10.1016/j.jpsychires.2011.04.010 PMID:21600590

Brody S, Wagner D, Heinrichs M, James A, Hellhammer D, Ehlert U (2000). Social desirability scores are associated with higher morning cortisol levels in firefighters. *J Psychosom Res*. 49(4):227–8. doi:10.1016/S0022-3999(00)00169-0 PMID:11119778

Burgess JL, Brodkin CA, Daniell WE, Pappas GP, Keifer MC, Stover BD, et al. (1999). Longitudinal decline in measured firefighter single-breath diffusing capacity of carbon monoxide values. A respiratory surveillance dilemma. *Am J Respir Crit Care Med*. 159(1):119–24. doi:10.1164/ajrccm.159.1.9804153 PMID:9872828

Burgess JL, Fierro MA, Lantz RC, Hysong TA, Fleming JE, Gerkin R, et al. (2004). Longitudinal decline in lung function: evaluation of interleukin-10 genetic polymorphisms in firefighters. *J Occup Environ Med*. 46(10):1013–22. doi:10.1097/01.jom.0000141668.70006.52 PMID:15602175

Burgess JL, Nanson CJ, Bolstad-Johnson DM, Gerkin R, Hysong TA, Lantz RC, et al. (2001). Adverse respiratory effects following overhaul in firefighters. *J Occup Environ Med*. 43(5):467–73. doi:10.1097/00043764-200105000-00007 PMID:11382182

Burgess JL, Nanson CJ, Hysong TA, Gerkin R, Witten ML, Lantz RC (2002). Rapid decline in sputum IL-10 concentration following occupational smoke exposure. *Inhal Toxicol*. 14(2):133–40. doi:10.1080/089583701753403953 PMID:12122576

Burke M, Driscoll A, Heft-Neal S, Xue J, Burney J, Wara M (2021). The changing risk and burden of wildfire in the United States. *Proc Natl Acad Sci USA*. 118(2):e2011048118. doi:10.1073/pnas.2011048118 PMID:33431571

Buscarlet M, Provost S, Zada YF, Barhdadi A, Bourgoin V, Lépine G, et al. (2017). *DNMT3A* and *TET2* dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. *Blood*. 130(6):753–62. doi:10.1182/blood-2017-04-777029 PMID:28655780

Chastagnier M, Min S, Chaigneau M, Callais F, Festy B (1991). [Mutagenic activity of the condensates from thermal decomposition of different polyamides]. *Ann Pharm Fr*. 49(5):263–71. [French] PMID:1841527

Chernyak YI, Grassman JA (2020). Impact of AhRR (565C > G) polymorphism on dioxin dependent CYP1A2 induction. *Toxicol Lett*. 320:58–63. doi:10.1016/j.toxlet.2019.12.002 PMID:31805342

Chernyak YI, Shelepchikov AA, Brodsky ES, Grassman JA (2012). PCDD, PCDF, and PCB exposure in current and former firefighters from Eastern Siberia. *Toxicol Lett*. 213(1):9–14. doi:10.1016/j.toxlet.2011.09.021 PMID:21979175

Cherry N, Beach J, Galarneau JM (2021). Are inflammatory markers an indicator of exposure or effect in firefighters fighting a devastating wildfire? Follow-up of a cohort in Alberta, Canada. *Ann Work Expo Health*. 65(6):635–48. doi:10.1093/annweh/wxaa142 PMID:33620067

Chia KS, Jeyaratnam J, Chan TB, Lim TK (1990). Airway responsiveness of firefighters after smoke exposure. *Br J Ind Med*. 47(8):524–7. doi:10.1136/oem.47.8.524 PMID:2393631

Cho SJ, Echevarria GC, Kwon S, Naveed B, Schenck EJ, Tsukiji J, et al. (2014). One airway: biomarkers of protection from upper and lower airway injury after World Trade Center exposure. *Respir Med*. 108(1):162–70. doi:10.1016/j.rmed.2013.11.002 PMID:24290899

Christison KS, Gurney SC, Sol JA, Williamson-Reisdorph CM, Quindry TS, Quindry JC, et al. (2021). Muscle damage and overreaching during wildland firefighter critical training. *J Occup Environ Med*. 63(4):350–6. doi:10.1097/JOM.0000000000002149 PMID:33769401

Clarity C, Trowbridge J, Gerona R, Ona K, McMaster M, Bessonneau V, et al. (2021). Associations between polyfluoroalkyl substance and organophosphate flame retardant exposures and telomere length in a cohort of women firefighters and office workers in San Francisco. *Environ Health*. 20(1):97. doi:10.1186/s12940-021-00778-z PMID:34454526

Cleven KL, Ye K, Zeig-Owens R, Hena KM, Montagna C, Shan J, et al. (2019). Genetic variants associated with FDNY WTC-related sarcoidosis. *Int J Environ Res Public Health*. 16(10):E1830. doi:10.3390/ijerph16101830 PMID:31126090

Cordeiro TG, do Amaral JB, Pavao V, Cardoso RG, Voegels RL, Pezato PM, et al. (2021). Fire simulator exposure alters the innate epithelial response and inflammatory status in the airways of firefighters. *Rhinology*. 59(3):267–76. doi:10.4193/Rhin21.002 PMID:34051075

COSMIC (2022). Mutational Signatures (v3.3 - June 2022). Available from: https://cancer.sanger.ac.uk/signatures/, accessed November 2022.

Darcey DJ, Everson RB, Putman KL, Randerath K (1992). DNA adducts and exposure to burning oil. *Lancet*. 339(8791):489. doi:10.1016/0140-6736(92)91092-M PMID:1346835

Davidson S, Jahnke S, Jung AM, Burgess JL, Jacobs ET, Billheimer D, et al. (2022). Anti-mullerian hormone levels among female firefighters. *Int J Environ Res Public Health*. 19(10):19. doi:10.3390/ijerph19105981 PMID:35627519

de Oliveira Galvão MF, de Oliveira Alves N, Ferreira PA, Caumo S, de Castro Vasconcellos P, Artaxo P, et al. (2018). Biomass burning particles in the Brazilian Amazon region: mutagenic effects of nitro and oxy-PAHs and assessment of health risks. *Environ Pollut*. 233:960–70. doi:10.1016/j.envpol.2017.09.068 PMID:29031407

DeMarini DM, Linak WP (2022). Mutagenicity and carcinogenicity of combustion emissions are impacted more by combustor technology than by fuel composition: a brief review. *Environ Mol Mutagen*. 63(3):135–50. doi:10.1002/em.22475 PMID:35253926

Demling R, Lalonde C, Picard L, Blanchard J (1994). Changes in lung and systemic oxidant and antioxidant activity after smoke inhalation. *Shock*. 1(2):101–7. doi:10.1097/00024382-199402000-00004 PMID:7749927

Demling RH, LaLonde C (1990). Moderate smoke inhalation produces decreased oxygen delivery, increased oxygen demands, and systemic but not lung parenchymal lipid peroxidation. *Surgery*. 108(3):544–52. PMID:2396198

Diaz-Castro J, Mira-Rufino PJ, Moreno-Fernandez J, Chirosa I, Chirosa JL, Guisado R, et al. (2020b). Ubiquinol supplementation modulates energy metabolism and bone turnover during high intensity exercise. *Food Funct*. 11(9):7523–31. doi:10.1039/D0FO01147A PMID:32797125

Diaz-Castro J, Moreno-Fernandez J, Chirosa I, Chirosa LJ, Guisado R, Ochoa JJ (2020a). Beneficial effect of ubiquinol on hematological and inflammatory signalling during exercise. *Nutrients*. 12(2):E424. doi:10.3390/nu12020424 PMID:32041223

Epis MR, Giles KM, Barker A, Kendrick TS, Leedman PJ (2009). miR-331–3p regulates ERBB-2 expression and androgen receptor signalling in prostate cancer. *J Biol Chem*. 284(37):24696–704. doi:10.1074/jbc.M109.030098 PMID:19584056

Fent KW, Toennis C, Sammons D, Robertson S, Bertke S, Calafat AM, et al. (2019). Firefighters' and instructors' absorption of PAHs and benzene during training exercises. *Int J Hyg Environ Health*. 222(7):991–1000. doi:10.1016/j.ijheh.2019.06.006 PMID:31272797

Ferguson MD, Semmens EO, Dumke C, Quindry JC, Ward TJ (2016). Measured pulmonary and systemic markers of inflammation and oxidative stress following wildland firefighter simulations. *J Occup Environ Med*. 58(4):407–13. doi:10.1097/JOM.0000000000000688 PMID:27058482

Fireman EM, Lerman Y, Ganor E, Greif J, Fireman-Shoresh S, Lioy PJ, et al. (2004). Induced sputum assessment in New York City firefighters exposed to World Trade Center dust. *Environ Health Perspect*. 112(15):1564–9. doi:10.1289/ehp.7233 PMID:15531443

Ford J, Smith S, Luo JC, Friedman-Jimenez G, Brandt-Rauf P, Markowitz S, et al. (1992). Serum growth factors and oncoproteins in firefighters. *Occup Med (Lond)*. 42(1):39–42. doi:10.1093/occmed/42.1.39 PMID:1533320

Gainey SJ, Horn GP, Towers AE, Oelschlager ML, Tir VL, Drnevich J, et al. (2018). Exposure to a firefighting overhaul environment without respiratory protection increases immune dysregulation and lung disease risk. *PLoS One*. 13(8):e0201830. doi:10.1371/journal.pone.0201830 PMID:30130361

Gasiorowski R, Forbes MK, Silver G, Krastev Y, Hamdorf B, Lewis B, et al. (2022). Effect of plasma and blood donations on levels of perfluoroalkyl and polyfluoroalkyl substances in firefighters in Australia a randomized clinical trial. *JAMA Netw Open*. 5(4):e226257. doi:10.1001/jamanetworkopen.2022.6257 PMID:35394514

Gaughan DM, Christiani DC, Hughes MD, Baur DM, Kobzik L, Wagner GR, et al. (2014b). High hsCRP is associated with reduced lung function in structure firefighters. *Am J Ind Med*. 57(1):31–7. doi:10.1002/ajim.22260 PMID:24115029

Gaughan DM, Siegel PD, Hughes MD, Chang CY, Law BF, Campbell CR, et al. (2014a). Arterial stiffness, oxidative stress, and smoke exposure in wildland firefighters. *Am J Ind Med*. 57(7):748–56. doi:10.1002/ajim.22331 PMID:24909863

Gianniou N, Giannakopoulou C, Dima E, Kardara M, Katsaounou P, Tsakatikas A, et al. (2018). Acute effects of smoke exposure on airway and systemic inflammation in forest firefighters. *J Asthma Allergy*. 11:81–8. doi:10.2147/JAA.S136417 PMID:29719412

Gianniou N, Katsaounou P, Dima E, Giannakopoulou CE, Kardara M, Saltagianni V, et al. (2016). Prolonged occupational exposure leads to allergic airway sensitization and chronic airway and systemic inflammation in professional firefighters. *Respir Med*. 118:7–14. doi:10.1016/j.rmed.2016.07.006 PMID:27578465

Goodrich JM, Calkins MM, Caban-Martinez AJ, Stueckle T, Grant C, Calafat AM, et al. (2021a). Per- and polyfluoroalkyl substances, epigenetic age and DNA methylation: a cross-sectional study of firefighters. *Epigenomics*. 13(20):1619–36. doi:10.2217/epi-2021-0225 PMID:34670402

Goodrich JM, Furlong MA, Caban-Martinez AJ, Jung AM, Batai K, Jenkins T, et al. (2021b). Differential DNA methylation by Hispanic ethnicity among firefighters in the United States. *Epigenet Insights*. 14:25168657211006159.doi:10.1177/25168657211006159 PMID:35036834

Goodrich JM, Jung AM, Furlong MA, Beitel S, Littau S, Gulotta J, et al. (2022). Repeat measures of DNA methylation in an inception cohort of firefighters. *Occup Environ Med*. doi:10.1136/oemed-2021-108153 PMID:35332072

Greven F, Krop E, Burger N, Kerstjens H, Heederik D (2011a). Serum pneumoproteins in firefighters. *Biomarkers*. 16(4):364–71. doi:10.3109/1354750X.2011.578218 PMID:21595570

Greven F, Krop E, Spithoven J, Rooyackers J, Kerstjens H, Heederik D (2011b). Lung function, bronchial hyperresponsiveness, and atopy among firefighters. *Scand J Work Environ Health*. 37(4):325–31. doi:10.5271/sjweh.3153 PMID:21340442

Greven FE, Krop EJ, Spithoven JJ, Burger N, Rooyackers JM, Kerstjens HA, et al. (2012). Acute respiratory effects in firefighters. *Am J Ind Med*. 55(1):54–62. doi:10.1002/ajim.21012 PMID:21959832

Greven FE, Rooyackers JM, Kerstjens HA, Heederik DJ (2011c). Respiratory symptoms in firefighters. *Am J Ind Med*. 54(5):350–5. doi:10.1002/ajim.20929 PMID:21246589

Gündüzöz M, Birgin İritaş S, Tutkun L, Büyükşekerci M, Pinar Çetintepe S, Bal C, et al. (2018). A new potential biomarker in early diagnosis of firefighter lung function impairment: dynamic thiol/disulphide homeostasis. *Cent Eur J Public Health*. 26(3):190–4. doi:10.21101/cejph.a4972 PMID:30419620

Gurney SC, Christison KS, Williamson-Reisdorph CM, Sol JA, Quindry TS, Quindry JC, et al. (2021). Alterations in metabolic and cardiovascular risk factors during critical training in wildland firefighters. *J Occup Environ Med*. 63(7):594–9. doi:10.1097/JOM.0000000000002191 PMID:34184652

Hargrove MM, Kim YH, King C, Wood CE, Gilmour MI, Dye JA, et al. (2019). Smoldering and flaming biomass wood smoke inhibit respiratory responses in mice. *Inhal Toxicol*. 31(6):236–47. doi:10.1080/08958378.2019.1654046

Hejl AM, Adetona O, Diaz-Sanchez D, Carter JD, Commodore AA, Rathbun SL, et al. (2013). Inflammatory effects of woodsmoke exposure among wildland firefighters working at prescribed burns at the Savannah River Site, SC. *J Occup Environ Hyg*. 10(4):173–80. doi:10.1080/15459624.2012.760064 PMID:23363434

Hena KM, Yip J, Jaber N, Goldfarb D, Fullam K, Cleven K, et al.; FDNY Sarcoidosis Clinical Research Group (2018). Clinical course of sarcoidosis in World Trade Center-exposed firefighters. *Chest*. 153(1):114–23. doi:10.1016/j.chest.2017.10.014 PMID:29066387

Hengstler JG, Fuchs J, Bolm-Audorff U, Meyer S, Oesch F (1995). Single-strand breaks in deoxyribonucleic acid in fire fighters accidentally exposed to *o*-nitroanisole and other chemicals. *Scand J Work Environ Health*. 21(1):36–42. doi:10.5271/sjweh.6 PMID:7784863

Herbert R, Moline J, Skloot G, Metzger K, Baron S, Luft B, et al. (2006). The World Trade Center disaster and the health of workers: five-year assessment of a unique medical screening program. *Environ Health Perspect*. 114(12):1853–8. doi:10.1289/ehp.9592 PMID:17185275

Hong YC, Park HS, Ha EH (2000). Influence of genetic susceptibility on the urinary excretion of 8-hydroxydeoxyguanosine of firefighters. *Occup Environ Med*. 57(6):370–5. doi:10.1136/oem.57.6.370 PMID:10810125

Hu B, Ying X, Wang J, Piriyapongsa J, Jordan IK, Sheng J, et al. (2014). Identification of a tumor-suppressive human-specific microRNA within the FHIT tumor-suppressor gene. *Cancer Res*. 74(8):2283–94. doi:10.1158/0008-5472.CAN-13-3279 PMID:24556720

Huang CJ, Garten RS, Wade C, Webb HE, Acevedo EO (2009). Physiological responses to simulated stair climbing in professional firefighters wearing rubber and leather boots. *Eur J Appl Physiol*. 107(2):163–8. doi:10.1007/s00421-009-1092-8 PMID:19543910

Huang CJ, Webb HE, Garten RS, Kamimori GH, Acevedo EO (2010b). Psychological stress during exercise: lymphocyte subset redistribution in firefighters. *Physiol Behav*. 101(3):320–6. doi:10.1016/j.physbeh.2010.05.018 PMID:20570686

Huang CJ, Webb HE, Garten RS, Kamimori GH, Evans RK, Acevedo EO (2010a). Stress hormones and immunological responses to a dual challenge in professional firefighters. *Int J Psychophysiol*. 75(3):312–8. doi:10.1016/j.ijpsycho.2009.12.013 PMID:20079388

IARC (1997). Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. *IARC Monogr Eval Carcinog Risks Hum*. 69:1–666. Available from: https://publications.iarc.fr/87 PMID:9379504

IARC (2006). Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxypropan-2-ol. *IARC Monogr Eval Carcinog Risks Hum*. 88:1–478. Available from: https://publications.iarc.fr/106 PMID:17366697

IARC (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval Carcinog Risks Hum*. 92:1–853. Available from: https://publications.iarc.fr/110 PMID:21141735

IARC (2012a). Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum*. 100C:1–501. Available from: https://publications.iarc.fr/120 PMID:23189751

IARC (2012b). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*. 100F:1–599. Available from: https://publications.iarc.fr/123 PMID:23189753

IARC (2012c). Radiation. *IARC Monogr Eval Carcinog Risks Hum*. 100D:1–341. Available from: https://publications.iarc.fr/121 PMID:23189752

IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*. 105:1–703. Available from: https://publications.iarc.fr/129 PMID:26442290

IARC (2015). Polychlorinated biphenyls and polybrominated biphenyls. *IARC Monogr Eval Carcinog Risks Hum*. 107:1–502. Available from: https://publications.iarc.fr/131 PMID:29905442

IARC (2016). Outdoor air pollution. *IARC Monogr Eval Carcinog Risks Hum*. 109:1–448. Available from: https://publications.iarc.fr/538 PMID:29905447

IARC (2018). Benzene. *IARC Monogr Eval Carcinog Risks Hum*. 120:1–301. Available from: https://publications.iarc.fr/576 PMID:31769947

IARC (2019). Styrene, styrene-7,8-oxide, and quinoline. *IARC Monogr Eval Carcinog Risks Hum*. 121:1–345. Available from: https://publications.iarc.fr/582 PMID:31967769

IARC (2020). Night shift work. *IARC Monogr Identif Carcinog Hazard Hum*. 124:1–371. Available from: https://publications.iarc.fr/593 PMID:33656825

IARC (2021). Acrolein, crotonaldehyde, and arecoline. *IARC Monogr Identif Carcinog Hazard Hum*. 128:1–335. Available from: https://publications.iarc.fr/602 PMID:36924508

Jasper AE, McIver WJ, Sapey E, Walton GM (2019). Understanding the role of neutrophils in chronic inflammatory airway disease. *F1000Res*. 8:F1000 Rev-557 doi:10.12688/f1000research.18411.1 PMID:31069060

Jasra S, Giricz O, Zeig-Owens R, Pradhan K, Goldfarb DG, Barreto-Galvez A, et al. (2022). High burden of clonal hematopoiesis in first responders exposed to the World Trade Center disaster. *Nat Med*. 28(3):468–71. doi:10.1038/s41591-022-01708-3 PMID:35256801

Jeong KS, Zhou J, Griffin SC, Jacobs ET, Dearmon-Moore D, Zhai J, et al. (2018). MicroRNA changes in firefighters. *J Occup Environ Med*. 60(5):469–74. doi:10.1097/JOM.0000000000001307 PMID:29465512

Josyula AB, Kurzius-Spencer M, Littau SR, Yucesoy B, Fleming J, Burgess JL (2007). Cytokine genotype and phenotype effects on lung function decline in firefighters. *J Occup Environ Med*. 49(3):282–8. doi:10.1097/JOM.0b013e3180322584 PMID:17351514

Jung AM, Jahnke SA, Dennis LK, Bell ML, Burgess JL, Jitnarin N, et al. (2021a). Occupational factors and miscarriages in the US fire service: a cross-sectional analysis of women firefighters. *Environ Health*. 20(1):116. doi:10.1186/s12940-021-00800-4 PMID:34749749

Jung AM, Zhou J, Beitel SC, Littau SR, Gulotta JJ, Wallentine DD, et al. (2021b). Longitudinal evaluation of whole blood miRNA expression in firefighters. *J Expo Sci Environ Epidemiol*. 31(5):900–12. doi:10.1038/s41370-021-00306-8 PMID:33603099

Kafkoutsou AL, Yang YP, Zeynaloo E, Deo SK, Solle NS, Kobetz EN, et al. (2022). Impact of firefighting aqueous film-forming foams on human cell proliferation and cellular mortality. *J Occup Environ Med*. 64(5):e340–4. doi:10.1097/JOM.0000000000002527 PMID:35250009

Kazemi R, Zare S, Hemmatjo R (2018). Comparison of melatonin profile and alertness of firefighters with different work schedules. *J Circadian Rhythms*. 16(1):1. doi:10.5334/jcr.155 PMID:30210561

Keir JLA, Akhtar US, Matschke DMJ, Kirkham TL, Chan HM, Ayotte P, et al. (2017). Elevated exposures to polycyclic aromatic hydrocarbons and other organic mutagens in Ottawa firefighters participating in emergency, on-shift fire suppression. *Environ Sci Technol*. 51(21):12745–55. doi:10.1021/acs.est.7b02850 PMID:29043785

Kern DG, Neill MA, Wrenn DS, Varone JC (1993). Investigation of a unique time-space cluster of sarcoidosis in firefighters. *Am Rev Respir Dis*. 148(4 Pt 1):974–80. doi:10.1164/ajrccm/148.4_Pt_1.974 PMID:8214953

Kim SC, Lee HJ, Shin DM, Ku BS, Oh JH, Cho BJ, et al. (2018). Cardiovascular risk in fire academy instructors during live-fire simulation activity. *Ann Burns Fire Disasters*. 31(4):313–21. PMID:30983932

Kuan PF, Mi Z, Georgopoulos P, Hashim D, Luft BJ, Boffetta P (2019). Enhanced exposure assessment and genome-wide DNA methylation in World Trade Center disaster responders. *Eur J Cancer Prev*. 28(3):225–33. doi:10.1097/CEJ.0000000000000460 PMID:30001286

Kudaeva IV, Budarina LA (2005). [Features of biochemical parameters in firemen]. *Med Tr Prom Ekol*. 12(12):32–7. [Russian] PMID:16430120

Kudaeva IV, Budarina LA (2007). [Biochemical criteria of occupationally related diseases formation in firemen]. *Med Tr Prom Ekol*. 6(6):12–8. [Russian] PMID:17695263

Kwon S, Lee M, Crowley G, Schwartz T, Zeig-Owens R, Prezant DJ, et al. (2021). Dynamic metabolic risk profiling of World Trade Center Lung Disease: a longitudinal cohort study. *Am J Respir Crit Care Med*. 204(9):1035–47. doi:10.1164/rccm.202006-2617OC PMID:34473012

Kwon S, Weiden MD, Echevarria GC, Comfort AL, Naveed B, Prezant DJ, et al. (2013). Early elevation of serum MMP-3 and MMP-12 predicts protection from World Trade Center-lung injury in New York City Firefighters: a nested case-control study. *PLoS One*. 8(10):e76099. doi:10.1371/journal.pone.0076099 PMID:24146820

Lam R, Haider SH, Crowley G, Caraher EJ, Ostrofsky DF, Talusan A, et al. (2020). Synergistic effect of WTC-particulate matter and lysophosphatidic acid exposure and the role of RAGE: in-vitro and translational assessment. *Int J Environ Res Public Health*. 17(12):E4318. doi:10.3390/ijerph17124318 PMID:32560330

Lansdorp PM (2022). Telomeres, aging, and cancer: the big picture. *Blood*. 139(6):813–21. doi:10.1182/blood.2021014299 PMID:35142846

Leonard SS, Castranova V, Chen BT, Schwegler-Berry D, Hoover M, Piacitelli C, et al. (2007). Particle size-dependent radical generation from wildland fire smoke. *Toxicology*. 236(1–2):103–13. doi:10.1016/j.tox.2007.04.008 PMID:17482744

Li Q, Hirata Y, Kawada T, Minami M (2004). Elevated frequency of sister chromatid exchanges of lymphocytes in sarin-exposed victims of the Tokyo sarin disaster 3 years after the event. *Toxicology*. 201(1–3):209–17. doi:10.1016/j.tox.2004.04.014 PMID:15297034

Lim GY, Jang TW, Sim CS, Ahn YS, Jeong KS (2020). Comparison of cortisol level by shift cycle in Korean firefighters. *Int J Environ Res Public Health*. 17(13):17. doi:10.3390/ijerph17134760 PMID:32630691

Lin H-P, Ho H-M, Chang C-W, Yeh S-D, Su Y-W, Tan T-H, et al. (2019). DUSP22 suppresses prostate cancer proliferation by targeting the EGFR-AR axis. *FASEB J*. 33(12):14653–67. doi:10.1096/fj.201802558RR PMID:31693867

Liou SH, Jacobson-Kram D, Poirier MC, Nguyen D, Strickland PT, Tockman MS (1989). Biological monitoring of fire fighters: sister chromatid exchange and polycyclic aromatic hydrocarbon-DNA adducts in peripheral blood cells. *Cancer Res*. 49(17):4929–35. PMID:2503247

Lit L, Boehm D, Marzke S, Schweitzer J, Oberbauer AM (2010). Certification testing as an acute naturalistic stressor for disaster dog handlers. *Stress*. 13(5):392–401. doi:10.3109/10253891003667896 PMID:20666644

Lofrano-Porto A, Soares EMKVK, Matias A, Porto LGG, Smith DL (2020). Borderline-low testosterone levels are associated with lower left ventricular wall thickness in firefighters: An exploratory analysis. *Andrology*. 8(6):1753–61. doi:10.1111/andr.12860 PMID:32633472

Loke J, Farmer W, Matthay RA, Putman CE, Smith GJ (1980). Acute and chronic effects of fire fighting on pulmonary function. *Chest*. 77(3):369–73. doi:10.1378/chest.77.3.369 PMID:7357940

Loupasakis K, Berman J, Jaber N, Zeig-Owens R, Webber MP, Glaser MS, et al. (2015). Refractory sarcoid arthritis in World Trade Center-exposed New York City firefighters: a case series. *J Clin Rheumatol*. 21(1):19–23. doi:10.1097/RHU.0000000000000185 PMID:25539429

Luria MH, Johnson MW, Pego R, Seuc CA, Manubens SJ, Wieland MR, et al. (1982). Relationship between sex hormones, myocardial infarction, and occlusive coronary disease. *Arch Intern Med*. 142(1):42–4. doi:10.1001/archinte.1982.00340140044011 PMID:7053736

Ma Y, Bellini N, Scholten RH, Andersen MHG, Vogel U, Saber AT, et al. (2020). Effect of combustion-derived particles on genotoxicity and telomere length: a study on human cells and exposed populations. *Toxicol Lett*. 322:20–31. doi:10.1016/j.toxlet.2020.01.002 PMID:31923465

Ma Z, Qiu X, Wang D, Li Y, Zhang B, Yuan T, et al. (2015). MiR-181a-5p inhibits cell proliferation and migration by targeting Kras in non-small cell lung cancer A549 cells. *Acta Biochim Biophys Sin (Shanghai)*. 47(8):630–8. doi:10.1093/abbs/gmv054 PMID:26124189

Macedo RCS, Vieira A, Marin DP, Otton R (2015). Effects of chronic resveratrol supplementation in military firefighters undergo a physical fitness test–a placebo-controlled, double blind study. *Chem Biol Interact*. 227:89–95. doi:10.1016/j.cbi.2014.12.033 PMID:25572586

Main LC, Wolkow A, Raines J, Della Gatta P, Snow R, Aisbett B (2013). The stress of fire fighting - implications for long term health outcomes. Proceedings of the 2012 AFAC & Bushfire CRC Conference Research Forum, Perth, Australia, pp. 160–169.

Main LC, Wolkow AP, Tait JL, Della Gatta P, Raines J, Snow R, et al. (2020). Firefighter's acute inflammatory response to wildfire suppression. *J Occup Environ Med*. 62(2):145–8. doi:10.1097/JOM.0000000000001775 PMID:31764604

McAllister MJ, Basham SA, Smith JW, Waldman HS, Krings BM, Mettler JA, et al. (2018). Effects of environmental heat and antioxidant ingestion on blood markers of oxidative stress in professional firefighters performing structure fire exercises. *J Occup Environ Med*. 60(11):e595–601. doi:10.1097/JOM.0000000000001452 PMID:30252723

McAllister MJ, Gonzalez AE, Waldman HS (2020). Impact of time restricted feeding on markers of cardiometabolic health and oxidative stress in resistance-trained firefighters. *J Strength Cond Res*. Publish Ahead of Print: doi:10.1519/JSC.0000000000003860

McAllister MJ, Gonzalez AE, Waldman HS (2021). Time restricted feeding reduces inflammation and cortisol response to a firegrounds test in professional firefighters. *J Occup Environ Med*. 63(5):441–7. doi:10.1097/JOM.0000000000002169 PMID:33928938

Min J, Jang TW, Ahn YS, Sim CS, Jeong KS (2020). Association between shift work and biological factors including FGF-23, klotho, and serum 25-(OH) vitamin D3 among Korean firefighters: a cross-sectional study. *Sleep*. 43(10):zsaa075. doi:10.1093/sleep/zsaa075 PMID:32347311

Montague BT, Wipperman MF, Hooper AT, Hamon SC, Crow R, Elemo F, et al. (2022). Anti-SARS-CoV-2 IgA identfies asymptomatic infection in first responders. *J Infect Dis*. 225(4):578–86. doi:10.1093/infdis/jiab524 PMID:34636907

Morales-Bárcenas R, Chirino YI, Sánchez-Pérez Y, Osornio-Vargas ÁR, Melendez-Zajgla J, Rosas I, et al. (2015). Particulate matter (PM_{10}) induces metalloprotease activity and invasion in airway epithelial cells. *Toxicol Lett*. 237(3):167–73. doi:10.1016/j.toxlet.2015.06.001 PMID:26047787

Mosakhani N, Sarhadi VK, Borze I, Karjalainen-Lindsberg ML, Sundström J, Ristamäki R, et al. (2012). MicroRNA profiling differentiates colorectal cancer according to KRAS status. *Genes Chromosomes Cancer*. 51(1):1–9. doi:10.1002/gcc.20925 PMID:21922590

Nishikawa H, Sakaguchi S (2014). Regulatory T cells in cancer immunotherapy. *Curr Opin Immunol*. 27:1–7. doi:10.1016/j.coi.2013.12.005 PMID:24413387

Nolan A, Kwon S, Cho SJ, Naveed B, Comfort AL, Prezant DJ, et al. (2014). MMP-2 and TIMP-1 predict healing of WTC-lung injury in New York City firefighters. *Respir Res*. 15(1):5. doi:10.1186/1465-9921-15-5 PMID:24447332

Nolan A, Naveed B, Comfort AL, Ferrier N, Hall CB, Kwon S, et al. (2012). Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust. *Chest*. 142(2):412–8. doi:10.1378/chest.11-1202 PMID:21998260

Oliveira M, Costa S, Vaz J, Fernandes A, Slezakova K, Delerue-Matos C, et al. (2020). Firefighters exposure to fire emissions: Impact on levels of biomarkers of exposure to polycyclic aromatic hydrocarbons and genotoxic/oxidative-effects. *J Hazard Mater*. 383:121179. doi:10.1016/j.jhazmat.2019.121179 PMID:31522064

Orris P, Worobec S, Kahn G, Hryhorczuk D, Hessl S (1986). Chloracne in firefighters. *Lancet*. 1(8474):210–1. doi:10.1016/S0140-6736(86)90683-5 PMID:2868232

Ouyang B, Baxter CS, Lam HM, Yeramaneni S, Levin L, Haynes E, et al. (2012). Hypomethylation of dual specificity phosphatase 22 promoter correlates with duration of service in firefighters and is inducible by low-dose benzo[*a*]pyrene. *J Occup Environ Med*. 54(7):774–80. doi:10.1097/JOM.0b013e31825296bc PMID:22796920

Ozen M, Karatas OF, Gulluoglu S, Bayrak OF, Sevli S, Guzel E, et al. (2015). Overexpression of miR-145-5p inhibits proliferation of prostate cancer cells and reduces SOX2 expression. *Cancer Invest*. 33(6):251–8. doi:10.3109/07357907.2015.1025407 PMID:25951106

Park E, Lee YJ, Lee SW, Bang CH, Lee G, Lee JK, et al. (2016). Changes of oxidative/antioxidative parameters and DNA damage in firefighters wearing personal protective equipment during treadmill walking training. *J Phys Ther Sci*. 28(11):3173–7. doi:10.1589/jpts.28.3173 PMID:27942144

Patel K, Nixon R (2022). Allergic contact dermatitis from black rubber in firefighters' masks: a case series. *Contact Dermat*. 86(2):136–7. doi:10.1111/cod.13993 PMID:34676559

Perna L, Zhang Y, Mons U, Holleczek B, Saum KU, Brenner H (2016). Epigenetic age acceleration predicts cancer, cardiovascular, and all-cause mortality in a German case cohort. *Clin Epigenetics*. 8(1):64. doi:10.1186/s13148-016-0228-z PMID:27274774

Perroni F, Tessitore A, Cibelli G, Lupo C, D'Artibale E, Cortis C, et al. (2009). Effects of simulated firefighting on the responses of salivary cortisol, alpha-amylase and psychological variables. *Ergonomics*. 52(4):484–91. doi:10.1080/00140130802707873 PMID:19401900

Peters B, Ballmann C, Quindry T, Zehner EG, McCroskey J, Ferguson M, et al. (2018). Experimental woodsmoke exposure during exercise and blood oxidative stress.

J Occup Environ Med. 60(12):1073–81. doi:10.1097/JOM.0000000000001437 PMID:30188494

Ray MR, Basu C, Mukherjee S, Roychowdhury S, Lahiri T (2005). Micronucleus frequencies and nuclear anomalies in exfoliated buccal epithelial cells of firefighters. *Int J Hum Genet*. 05(01):45–8. doi:10.1080/09723757.2005.11885915

Ricaud G, Lim D, Bernier J (2021). Environmental exposition to aromatic hydrocarbon receptor ligands modulates the CD4(+) T lymphocyte subpopulations profile. *Expo Health*. 13(3):307–22. doi:10.1007/s12403-021-00385-w

Robinson SJ, Leach J, Owen-Lynch PJ, Sünram-Lea SI (2013). Stress reactivity and cognitive performance in a simulated firefighting emergency. *Aviat Space Environ Med*. 84(6):592–9. doi:10.3357/ASEM.3391.2013 PMID:23745287

Rosalky DS, Hostler D, Webb HE (2017). Work duration does not affect cortisol output in experienced firefighters performing live burn drills. *Appl Ergon*. 58:583–91. doi:10.1016/j.apergo.2016.04.008 PMID:27146634

Rothman N, Correa-Villaseñor A, Ford DP, Poirier MC, Haas R, Hansen JA, et al. (1993). Contribution of occupation and diet to white blood cell polycyclic aromatic hydrocarbon–DNA adducts in wildland firefighters. *Cancer Epidemiol Biomarkers Prev*. 2(4):341–7. PMID:8348057

Rothman N, Shields PG, Poirier MC, Harrington AM, Ford DP, Strickland PT (1995). The impact of glutathione *S*-transferase M1 and cytochrome P450 1A1 genotypes on white-blood-cell polycyclic aromatic hydrocarbon–DNA adduct levels in humans. *Mol Carcinog*. 14(1):63–8. doi:10.1002/mc.2940140111 PMID:7546226

Roy M, Kirschbaum C, Steptoe A (2003). Intraindividual variation in recent stress exposure as a moderator of cortisol and testosterone levels. *Ann Behav Med*. 26(3):194–200. doi:10.1207/S15324796ABM2603_04 PMID:14644695

Roy MP (2004). Patterns of cortisol reactivity to laboratory stress. *Horm Behav*. 46(5):618–27. doi:10.1016/j.yhbeh.2004.06.015 PMID:15555504

Roy MP, Steptoe A, Kirschbaum C (1994). Association between smoking status and cardiovascular and cortisol stress responsivity in healthy young men. *Int J Behav Med*. 1(3):264–83. doi:10.1207/s15327558ijbm0103_6 PMID:16250801

Roy MP, Steptoe A, Kirschbaum C (1998). Life events and social support as moderators of individual differences in cardiovascular and cortisol reactivity. *J Pers Soc Psychol*. 75(5):1273–81. doi:10.1037/0022-3514.75.5.1273 PMID:9866187

Ryu S, Lee YJ, Jang EC, Kwon SC, Kim K, Ahn YS, et al. (2021). Hospital admissions due to endocrine diseases in Korean male firefighters. *Ann Occup Environ Med*. 33(1):e32. doi:10.35371/aoem.2021.33.e32 PMID:34868602

Saito A, Horie M, Nagase T (2018). TGF-β signalling in lung health and disease. *Int J Mol Sci*. 19(8):2460. doi:10.3390/ijms19082460 PMID:30127261

Santos JAR, Fernandes RJ, Zacca R (2020). Multimicronutrient supplementation and immunoglobulin response in well-fed firefighters. *Sports Med Int Open*. 5(1):E1–7.doi:10.1055/a-1296-1486 PMID:33376770

Singh A, Liu C, Putman B, Zeig-Owens R, Hall CB, Schwartz T, et al. (2018). Predictors of asthma/COPD overlap in FDNY firefighters with World Trade Center Dust exposure: a longitudinal study. *Chest*. 154(6):1301–10. doi:10.1016/j.chest.2018.07.002 PMID:30028968

Smeets MM, Vandenbossche P, Duijst WL, Mook WNV, Leers MPG (2021). Validation of a new method for saliva cortisol testing to assess stress in first responders. *Emerg Med J*. 38(4):297–302. doi:10.1136/emermed-2019-209205 PMID:33574024

Smith DL, Dyer K, Petruzzello SJ (2004). Blood chemistry and immune cell changes during 1 week of intensive firefighting training. *J Therm Biol*. 29(7–8):725–9. doi:10.1016/j.jtherbio.2004.08.046

Smith DL, Friedman NMG, Bloom SI, Armero WL, Pence BD, Cook MD, et al. (2019). Firefighting induces acute inflammatory responses that are not relieved by aspirin in older firefighters. *J Occup Environ Med*. 61(7):617–22. doi:10.1097/JOM.0000000000001626 PMID:31090673

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*. 124(6):713–21. doi:10.1289/ehp.1509912 PMID:26600562

Smith DL, Petruzzello SJ, Chludzinski MA, Reed JJ, Woods JA (2005). Selected hormonal and immunological responses to strenuous live-fire firefighting drills. *Ergonomics*. 48(1):55–65. doi:10.1080/00140130412331303911 PMID:15764306

Sotos-Prieto M, Christophi C, Black A, Furtado JD, Song Y, Magiatis P, et al. (2019). Assessing validity of self-reported dietary intake within a Mediterranean diet cluster randomized controlled trial among US firefighters. *Nutrients*. 11(9):E2250. doi:10.3390/nu11092250 PMID:31546768

Stevenson M, Alexander B, Baxter CS, Leung YK (2015). Evaluating endocrine disruption activity of deposits on firefighting gear using a sensitive and high throughput screening method. *J Occup Environ Med*. 57(12):e153–7. doi:10.1097/JOM.0000000000000577 PMID:26641839

Sünram-Lea SI, Owen-Lynch J, Robinson SJ, Jones E, Hu H (2012). The effect of energy drinks on cortisol levels, cognition and mood during a fire-fighting exercise. *Psychopharmacology (Berl)*. 219(1):83–97. doi:10.1007/s00213-011-2379-0 PMID:21710168

Susoliakova O, Smejkalova J, Bicikova M, Potuznikova D, Hodacova L, Grimby-Ekman A, et al. (2014). Salivary cortisol in two professions: daily cortisol profiles in

school teachers and firefighters. *Neuro Endocrinol Lett*. 35(4):314–21. PMID:25038601

Swiston JR, Davidson W, Attridge S, Li GT, Brauer M, van Eeden SF (2008). Wood smoke exposure induces a pulmonary and systemic inflammatory response in firefighters. *Eur Respir J*. 32(1):129–38. doi:10.1183/09031936.00097707 PMID:18256060

Trowbridge J, Gerona R, McMaster M, Ona K, Clarity C, Bessonneau V, et al. (2022). Organophosphate and organohalogen flame-retardant exposure and thyroid hormone disruption in a cross-sectional study of female firefighters and office workers from San Francisco. *Environ Sci Technol*. 56(1):440–50. doi:10.1021/acs.est.1c05140 PMID:34902963

Tsukiji J, Cho SJ, Echevarria GC, Kwon S, Joseph P, Schenck EJ, et al. (2014). Lysophosphatidic acid and apolipoprotein A1 predict increased risk of developing World Trade Center-lung injury: a nested case–control study. *Biomarkers*. 19(2):159–65. doi:10.3109/1354750X.2014.891047 PMID:24548082

Viau CJ, Lockard JM, Enoch HG, Sabharwal PS (1982). Comparison of the genotoxic activities of extracts from ambient and forest fire polluted air. *Environ Mutagen*. 4:37–43. doi:10.1002/em.2860040106 PMID:7040069

Vinnikov D, Romanova Z, Kapanova G, Raushanova A, Kalmakhanov S, Zhigalin A (2021). Testosterone and occupational burnout in professional male firefighters. *BMC Public Health*. 21(1):397. doi:10.1186/s12889-021-10446-z PMID:33622299

Walker A, Beatty HEW, Zanetti S, Rattray B (2017). Improving body composition may reduce the immune and inflammatory responses of firefighters working in the heat. *J Occup Environ Med*. 59(4):377–83. doi:10.1097/JOM.0000000000000980 PMID:28628047

Walker A, Keene T, Argus C, Driller M, Guy JH, Rattray B (2015). Immune and inflammatory responses of Australian firefighters after repeated exposures to the heat. *Ergonomics*. 58(12):2032–9. doi:10.1080/00140139.2015.1051596 PMID:26082313

Wang Y, Xin H, Han Z, Sun H, Gao N, Yu H (2015). MicroRNA-374a promotes esophageal cancer cell proliferation via Axin2 suppression. *Oncol Rep*. 34(4):1988–94. doi:10.3892/or.2015.4182 PMID:26252180

Wang Z, Chen B, Fu Y, Ou C, Rong Q, Kong X, et al. (2022). Eosinophilia and lung cancer: analysis from real-world data and Mendelian randomization study. *Front Med (Lausanne)*. 9:830754. doi:10.3389/fmed.2022.830754 PMID:35355607

Watkins ER, Hayes M, Watt P, Renshaw D, Richardson AJ (2021). Extreme occupational heat exposure is associated with elevated haematological and inflammatory markers in fire service instructors. *Exp Physiol*. 106(1):233–43. doi:10.1113/EP088386 PMID:32462715

Watkins ER, Hayes M, Watt P, Richardson AJ (2019a). The acute effect of training fire exercises on fire service instructors. *J Occup Environ Hyg*. 16(1):27–40. doi:10.1080/15459624.2018.1531132 PMID:30277854

Watkins ER, Hayes M, Watt P, Richardson AJ (2019b). Heat tolerance of fire service instructors. *J Therm Biol*. 82:1–9. doi:10.1016/j.jtherbio.2019.03.005 PMID:31128636

Watt PW, Willmott AG, Maxwell NS, Smeeton NJ, Watt E, Richardson AJ (2016). Physiological and psychological responses in fire instructors to heat exposures. *J Therm Biol*. 58:106–14. doi:10.1016/j.jtherbio.2016.04.008 PMID:27157340

Webb HE, Garten RS, McMinn DR, Beckman JL, Kamimori GH, Acevedo EO (2011). Stress hormones and vascular function in firefighters during concurrent challenges. *Biol Psychol*. 87(1):152–60. doi:10.1016/j.biopsycho.2011.02.024 PMID:21382435

Weiden MD, Naveed B, Kwon S, Cho SJ, Comfort AL, Prezant DJ, et al. (2013). Cardiovascular biomarkers predict susceptibility to lung injury in World Trade Center dust-exposed firefighters. *Eur Respir J*. 41(5):1023–30. doi:10.1183/09031936.00077012 PMID:22903969

Witteveen AB, Huizink AC, Slottje P, Bramsen I, Smid T, van der Ploeg HM (2010). Associations of cortisol with posttraumatic stress symptoms and negative life events: a study of police officers and firefighters. *Psychoneuroendocrinology*. 35(7):1113–8. doi:10.1016/j.psyneuen.2009.12.013 PMID:20083359

Wolkow A, Aisbett B, Ferguson SA, Reynolds J, Main LC (2016a). Psychophysiological relationships between a multi-component self-report measure of mood, stress and behavioural signs and symptoms, and physiological stress responses during a simulated firefighting deployment. *Int J Psychophysiol*. 110:109–18. doi:10.1016/j.ijpsycho.2016.10.015 PMID:27984046

Wolkow A, Aisbett B, Jefferies S, Main LC (2017). Effect of heat exposure and simulated physical firefighting work on acute inflammatory and cortisol responses. *Ann Work Expo Health*. 61(5):600–3. doi:10.1093/annweh/wxx029 PMID:28383724

Wolkow A, Aisbett B, Reynolds J, Ferguson SA, Main LC (2015b). Relationships between inflammatory cytokine and cortisol responses in firefighters exposed to simulated wildfire suppression work and sleep restriction. *Physiol Rep*. 3(11):3. doi:10.14814/phy2.12604 PMID:26603450

Wolkow A, Aisbett B, Reynolds J, Ferguson SA, Main LC (2016b). Acute psychophysiological relationships between mood, inflammatory and cortisol changes in response to simulated physical firefighting work and sleep restriction. *Appl Psychophysiol Biofeedback*. 41(2):165–80. doi:10.1007/s10484-015-9329-2 PMID:26698865

Wolkow A, Ferguson SA, Vincent GE, Larsen B, Aisbett B, Main LC (2015a). The impact of sleep restriction and simulated physical firefighting work on acute inflammatory stress responses. *PLoS One*. 10(9):e0138128. doi:10.1371/journal.pone.0138128 PMID:26378783

Wright-Beatty HE, McLellan TM, Larose J, Sigal RJ, Boulay P, Kenny GP (2014). Inflammatory responses of older firefighters to intermittent exercise in the heat. *Eur J Appl Physiol*. 114(6):1163–74. doi:10.1007/s00421-014-2843-8 PMID:24563092

Wu CM, Adetona A, Song CC, Naeher L, Adetona O (2020b). Measuring acute pulmonary responses to occupational wildland fire smoke exposure using exhaled breath condensate. *Arch Environ Occup Health*. 75(2):65–9. doi:10.1080/19338244.2018.1562413 PMID:30668286

Wu CM, Warren SH, DeMarini DM, Song CC, Adetona O (2020a). Urinary mutagenicity and oxidative status of wildland firefighters working at prescribed burns in a midwestern US forest. *Occup Environ Med*. 78(5):315–22. doi:10.1136/oemed-2020-106612 PMID:33139344

Yucesoy B, Kurzius-Spencer M, Johnson VJ, Fluharty K, Kashon ML, Guerra S, et al. (2008). Association of cytokine gene polymorphisms with rate of decline in lung function. *J Occup Environ Med*. 50(6):642–8. doi:10.1097/JOM.0b013e31816515e1 PMID:18545091

Yun JA, Jeong KS, Ahn YS, Han Y, Choi KS (2021). The interaction of inflammatory markers and alcohol-use on cognitive function in Korean male firefighters. *Psychiatry Investig*. 18(3):205–13. doi:10.30773/pi.2020.0101 PMID:33685038

Zeig-Owens R, Singh A, Aldrich TK, Hall CB, Schwartz T, Webber MP, et al. (2018). Blood leukocyte concentrations, FEV_1 decline, and airflow limitation. A 15-year longitudinal study of World Trade Center-exposed firefighters. *Ann Am Thorac Soc*. 15(2):173–83. doi:10.1513/AnnalsATS.201703-276OC PMID:29099614

Zhao D, Sui Y, Zheng X (2016). MiR-331–3p inhibits proliferation and promotes apoptosis by targeting HER2 through the PI3K/Akt and ERK1/2 pathways in colorectal cancer. *Oncol Rep*. 35(2):1075–82. doi:10.3892/or.2015.4450 PMID:26718987

Zhou J, Jenkins TG, Jung AM, Jeong KS, Zhai J, Jacobs ET, et al. (2019). DNA methylation among firefighters. *PLoS One*. 14(3):e0214282. doi:10.1371/journal.pone.0214282 PMID:30913233

Zhu T, Hu Y, Hwang J, Zhao D, Huang L, Qiao L, et al. (2021). Urinary proteomics of simulated firefighting tasks and its relation to fitness parameters. *Int J Environ Res Public Health*. 18(20):10618. doi:10.3390/ijerph182010618 PMID:34682364

5. SUMMARY OF DATA REPORTED

5.1 Exposure characterization

Occupational exposure as a firefighter is complex and highly heterogeneous and includes chemical, physical, biological, and psychosocial hazards resulting from fires and non-fire events and environments. Firefighters have various roles and responsibilities, training requirements, resources, and employer types (including volunteer agencies) that may vary widely across countries and change over their careers. Firefighters respond to various types of fire (e.g. structure, wildland, and vehicle fires) and other events (e.g. vehicle accidents, medical incidents, hazardous material releases, floods, and building collapses). Variability among these work factors may have an impact on the magnitude and composition of occupational exposures.

Firefighters may be exposed to compounds in fire effluents and in diesel and gasoline engine exhaust (e.g. polycyclic aromatic hydrocarbons, volatile organic compounds, halogenated compounds, metals, and particulates), building materials and furnishings (e.g. asbestos, silica, synthetic fibres, and flame retardants), chemicals used during firefighting and training (e.g. perfluoroalkyl substances in firefighting foams), and other hazards (e.g. heat stress, dehydration, shift work, infectious agents, and ultraviolet and other radiation). The full spectrum of chemicals to which firefighters are exposed has not been completely characterized. The types and intensity of exposure from fire effluents depend on the materials being burned, ventilation conditions, and duration of the shift or exposure. Structures today contain numerous synthetic materials (e.g. foams, plastics, and glues) that allow fires to spread faster and produce a greater variety of hazardous compounds than in past decades.

Fire instructors may be repeatedly exposed to combustion products when they oversee live-fire training exercises (which may include wood, straw, or engineered wood products as fuel). Multiple training exercises are possible during a day or week of training, and instructors may be involved in several weeks of training each year.

Wildfire responses last longer than responses to many other types of fire and may require firefighters to remain near the fire for several days or weeks. Wildland firefighters may be deployed to multiple wildfires in a year or season, with short rest periods between each response. Wildland or vegetation fires are increasingly encroaching on urban areas (known as the wildland–urban interface, WUI). As such, firefighters battling WUI fires may be exposed to effluents from vegetation fires and from structure or vehicle fires.

Biological uptake of fire effluents may occur via inhalation and dermal absorption and is also possible via ingestion. Effective assessment of firefighters' exposures must consider a host of variables that collectively govern absorption,

distribution, metabolism, and excretion (e.g. chemical properties, duration of exposure, site of contact, use of personal protective equipment (PPE), role in fire suppression, and individual characteristics such as sex or level of hydration). Certain persistent organic pollutants may bioaccumulate. The metabolism and excretion of substances in fire effluents affect the levels of substances and/or their metabolites in biological samples (e.g. blood, urine, and exhaled breath). The advantage of biomonitoring is that it integrates the exposure from all routes of entry.

Firefighters principally rely on PPE to reduce their exposures. A well-fitting self-contained breathing apparatus (SCBA) provides protection against inhalation of airborne chemicals and is primarily worn by firefighters during fire suppression activities involving structures or vehicles. However, SCBA may not be worn in all settings with potential exposures (e.g. during overhaul, pump operation and command, or handling of contaminated PPE). Effective respiratory protection is less commonly worn during wildland firefighting than during firefighting conducted in the municipal setting.

Dermal absorption of chemicals may occur even in firefighters wearing PPE because of the limitations of the design, fit, and maintenance or decontamination of PPE. Contamination on PPE may also transfer to firefighters' skin and/or work surfaces during doffing (removal) or other handling of used PPE, potentially leading to dermal absorption or ingestion. The implementation of exposure-control measures (including PPE) may vary widely throughout the fire service, particularly in under-resourced regions or areas of the world.

Exposure components, firefighter duties, and PPE use have changed over the time period covered by the studies in the present monograph.

5.2 Cancer in humans

Since the previous evaluation by the *IARC Monographs* programme in 2007, many new studies have been published that assessed the carcinogenicity of occupational exposure as a firefighter. All available studies were considered in the present evaluation. However, some of these studies were based only on cases of cancer observed either in cancer registries or on death certificates (compared with other causes of cancer or mortality). These event-only studies were found to be less informative for the evaluation, given the potential for selection bias to influence the study results. There was also poor reporting of occupation in cancer registries and on death certificates, which could lead to differential exposure misclassification and bias in either direction. Accordingly, more weight was given to cohort studies in the evaluation. These studies in general did not adjust for confounding factors other than sex (or gender), age, and calendar period. For studies with repeated follow-up or substantial overlap, only the most recent update or most informative publication (e.g. based on exposure assessment quality) was used. The cohort studies deemed most informative for the evaluation were conducted in Australia, Canada, Denmark, Finland, Iceland, Norway, the Republic of Korea, Sweden, and the USA.

The exposure definition used by most of the available studies was ever having worked as a firefighter, without additional information about firefighting exposure or activities. Several studies further classified firefighters according to job duties (e.g. excluding those with administrative jobs) and/or evaluated duration of employment as a firefighter. Only a few studies reported more detailed exposure metrics, such as number of fire runs. These studies were deemed most informative and were given more weight in the evaluation.

Several published meta-analyses of cancer risk among firefighters were available; however, they did not incorporate estimates from the most recent studies. Consequently, the Working Group conducted a meta-analysis to produce a common estimate for cancer sites found to be elevated in previous meta-analyses or in the highest-quality individual studies, including mesothelioma, malignant melanoma of the skin (hereafter referred to as melanoma), and cancers of the urinary bladder, testis, prostate, colon, brain, lung, thyroid, stomach, and kidney, non-Hodgkin lymphoma (NHL), and all cancers combined.

In examining the evidence for cancer in humans, consideration was given to potential sources of bias, such as exposure misclassification, selection bias, surveillance bias, healthy-worker hire and survivor bias, and confounding. Exposure misclassification for the intensity and duration of specific exposures within firefighting (e.g. smoke exposure or other chemical hazards) was presumed to be high, given the lack of information in the available studies. For selection bias, the main factor of concern was the healthy-worker (hire) effect, which could be substantial among firefighters, given the screening for physical fitness for duty that occurs before hire. This would tend to reduce cancer risk estimates among firefighters compared with the general population, especially in the years shortly after hire. Healthy-worker survivor bias (in which departure of some members of the workforce for exposure-related reasons occurs) may also be substantial among firefighters and would cause attenuation of risk estimates, especially for analyses based on duration of employment. Similar effects may be seen in volunteer firefighters.

Tobacco smoking was not considered to be a strong positive confounder, given the evidence that firefighters may smoke less than the general population and the deficit in lung cancer incidence observed among firefighters compared with the general population in most of the studies. The potential for other exposures or risk factors encountered in everyday life (including obesity, physical activity, alcohol consumption, and sun exposure) to confound the association with occupational exposure was a factor considered for individual confounders and cancer sites, but little information was available to judge the magnitude or direction of such confounding. Exposures of firefighters to carcinogens (e.g. asbestos, sun exposure) outside firefighting may cause confounding of the association between exposure as a firefighter and certain cancers (e.g. mesothelioma, melanoma); however, only sparse information was available regarding such exposures.

A major consideration was the possibility of surveillance bias, whereby firefighters may be more likely than the reference population to undergo regular medical examination or cancer screening, and thus more likely to have cancers detected that would not otherwise have been identified or would have been detected at an earlier stage than in the reference population. This bias could inflate the estimates of cancer risk among firefighters, particularly compared with the general population. Surveillance bias is of less concern for cancer sites for which there is no screening or early detection method, or for which survivability is low.

Mesothelioma has only recently been reported in cohorts of firefighters for several reasons: specific International Classification of Diseases (ICD) codes became available only in the late 1990s with the addition of the 10th revision (ICD-10); the accuracy of diagnosis has increased; and cohorts have been followed-up for long periods of time (necessary given the long latency between asbestos exposure and mesothelioma occurrence). Seven of the higher-quality studies (i.e. those in which there was an absence of potential for a strong bias) examined the incidence of mesothelioma (fewer studies examined mortality) among cohorts mainly comprising

career municipal firefighters. In all except one of the studies (the Danish cohort), an elevated risk of mesothelioma was observed among firefighters. In the meta-analysis conducted by the Working Group, a meta-rate ratio (meta-RR) of 1.58 (95% confidence interval, CI, 1.14–2.20) was observed. Removing the Danish study reduced the overall heterogeneity and increased the meta-RR to 1.70 (95% CI, 1.30–2.22). Although an inverse association was observed with duration of employment in the meta-regression, the Working Group accorded less weight to these results, given the small number of studies for which duration was available, the potential influence of the healthy-worker survivor bias, and because duration is a poor surrogate for exposure. Moreover, studies with duration-based analyses did not consider the long latency between exposure and mesothelioma occurrence. Overall, on the basis of the consistency of the findings across the studies, the magnitude of the meta-estimate of association, the low likelihood for bias or confounding as an explanation for these findings, and the plausibility of exposure of firefighters to asbestos in the course of their duties, the Working Group concluded that a positive association was seen for mesothelioma in the body of evidence and that chance, bias, and confounding could be ruled out with reasonable confidence.

Ten higher-quality studies examined the incidence of bladder cancer among firefighters. A modest but relatively precise association was observed in the meta-analysis (meta-RR, 1.16; 95% CI, 1.08–1.26), with low heterogeneity across the studies. This estimate was supported by the results of other higher-quality studies of cancer incidence that used a slightly expanded definition of bladder cancer. The findings on bladder cancer incidence were supported by observed excess risk in the mortality studies, which were fewer in number and had less precision. Most of the studies with quantitative estimates of fire responses or exposed days did not find positive trends for bladder cancer incidence. However, in a study in the USA in which internal exposure–response estimates were adjusted for employment duration, evidence of a positive association was observed, suggesting that the healthy-worker survivor bias may have influenced findings in the other studies, which did not conduct such an adjustment. Two studies also observed an excess of incident bladder cancer among female firefighters. Taking into account all the evidence, and noting the many known or suspected bladder carcinogens to which firefighters are exposed, the Working Group concluded that a positive association was observed in the body of evidence for bladder cancer, and that chance, bias, and confounding could reasonably be ruled out as explanations for these findings.

The incidence of testicular cancer was examined in 11 higher-quality cohort studies. In eight of the studies, increased but imprecise estimates were found in firefighters compared with the general population. The meta-RR was 1.37 (95% CI, 1.03–1.82) and exhibited high heterogeneity across the studies. The one available study did not find an association between duration of employment and testicular cancer incidence, although the Working Group did not consider this finding to be highly informative because of a possible healthy-worker survivor bias. No standardized screening methods are available, and most testicular cancers are found by self or medical examination. On the basis of tumour behaviour and progression, early detection is not likely to explain the excess risk. Given that there was limited information on plausible exposures for testicular cancer, only modest effects were observed, there was significant heterogeneity in results among relevant studies, and findings were inconsistent across available exposure contrasts, chance and bias could not be reasonably ruled out as alternative explanations for the observed excess risk.

Twenty-one cohort studies examined the risk of NHL among firefighters. Interpretation of these findings was complicated by the

heterogeneous and evolving diagnostic criteria for NHL. Although all the studies excluded multiple myeloma and lymphocytic leukaemia in their definition, there was still variability in the diagnostic codes included in each study. In the meta-analysis, overall meta-RRs of 1.12 (95% CI, 1.01–1.25) and 1.20 (95% CI, 1.03–1.40) were observed for NHL incidence (13 studies) and mortality (4 studies), respectively. These results were robust across the sensitivity analyses in the meta-analyses, including in a study among female volunteer firefighters. Only a few of the individual studies found any evidence of an association between duration of employment as a firefighter and incidence of NHL. The Working Group concluded that many factors made the evaluation of occupation as a firefighter and NHL challenging, including the inconsistent definitions of NHL and etiological differences in NHL subtypes. Small elevations in both NHL incidence and mortality across several well-designed studies were observed; however, the role of chance, bias, or confounding could not be ruled out.

Twenty studies with good or satisfactory exposure assessment examined the incidence or mortality of prostate cancer among cohorts mainly comprising career municipal firefighters. Nine of these studies identified an elevated risk of prostate cancer among male firefighters. In the meta-analysis conducted by the Working Group, a meta-RR of 1.21 (95% CI, 1.12–1.32) but with high heterogeneity was observed for incidence studies. For mortality studies, the meta-RR was 1.07 (95% CI, 0.95–1.20). The Working Group considered it likely that the elevated incidence rates for prostate cancer arose in part from increased surveillance in the firefighter groups compared with the general population. Overall, the Working Group found that there was evidence suggesting that the risk of cancer of the prostate is positively associated with occupational exposure as a firefighter. However, the possibility of detection bias, the lack of a consistent relationship to any of the included exposure metrics, and weak results in the mortality studies (which would be less susceptible to surveillance bias) meant that chance, bias, and confounding could not be ruled out with reasonable confidence.

In the meta-analysis performed by the Working Group, an excess was observed for incidence of melanoma (meta-RR, 1.36; 95% CI, 1.15–1.62; 12 studies), but not for mortality (meta-RR, 1.05; 95% CI, 0.48–2.30; 4 studies). Some heterogeneity in the risk estimates was observed for melanoma incidence. Of the four cohort studies that included an exposure assessment categorized as "good" and that reported estimates for melanoma incidence, three reported an excess risk. Although firefighters may be occupationally exposed to solar radiation, potential confounding due to non-occupational sources of exposure or individual susceptibility could not be ruled out. There was also a possibility that these findings might be explained by surveillance bias in these studies. Overall, the Working Group concluded that a positive association was seen between occupational exposure as a firefighter and melanoma; however, the contribution of surveillance bias, confounding, and chance could not be ruled out with reasonable confidence.

There were a number of cohort studies that evaluated cancer of the colon among firefighters. These studies had mixed results. In the meta-analysis performed by the Working Group, an excess was observed for incidence of cancer of the colon (meta-RR, 1.19; 95% CI, 1.07–1.32; 10 studies), but not for mortality (meta-RR, 1.03; 95% CI, 0.78–1.37; 9 studies). Because of the increased risk in incidence and not mortality, surveillance bias was considered possible. Firefighters are required to have a high level of physical fitness to enter their profession and may have a higher level of leisure physical activity, which has been associated with a decreased risk of colon cancer, but little is known about this and other non-occupational risk factors among firefighters. Overall, the

Working Group concluded that a positive association was seen between occupational exposure as a firefighter and colon cancer; however, chance, bias, and confounding could not be ruled out with reasonable confidence.

Because firefighters are exposed to many known lung carcinogens, the risk of lung cancer is of explicit interest. Thirty-four studies provided information on the incidence or mortality of cancer of the lung among mainly career municipal firefighters. For both incidence and mortality, most of the studies had relative risk estimates of < 1. In the meta-analysis conducted by the Working Group, a decreased incidence meta-RR (with high heterogeneity) was observed (meta-RR, 0.85; 95% CI, 0.75–0.96). For mortality, no effect was observed (meta-RR, 0.96; 95% CI, 0.86–1.06). Given the potentially lower rates of smoking among firefighters than in the general population, negative confounding by smoking may have led to lower rates of lung cancer among firefighters. Overall, the Working Group found little evidence that risk of cancer of the lung is positively associated with occupational exposure as a firefighter.

The Working Group reviewed 20 studies that reported results for thyroid cancer incidence or mortality in firefighters. In the meta-analysis conducted by the Working Group, an overall increased incidence of thyroid cancer was observed in firefighters compared with the general population (meta-RR, 1.28; 95% CI, 1.02–1.61). However, the meta-RR was attenuated in most sensitivity analyses. The Working Group noted the strong possibility of surveillance bias contributing to the elevated rate of thyroid cancer incidence. Furthermore, the studies with a more robust exposure assessment tended to report a lower risk of thyroid cancer than those with a weaker exposure assessment. As a result, the Working Group determined that no causal conclusion could be reached for occupational exposure as a firefighter and thyroid cancer.

For other cancer sites, including the brain, stomach, larynx, kidney, leukaemia, and multiple myeloma, the Working Group concluded that the findings were either too close to the null, inconsistent, or subject to major concern about surveillance bias to permit a causal conclusion to be reached.

For the incidence of all cancers combined, the Working Group noted a slightly higher rate among firefighters than in the general population but concluded that the excess was probably attributable to positive findings for the cancer sites described above.

5.3 Cancer in experimental animals

No data were available to the Working Group.

5.4 Mechanistic evidence

In examining the mechanistic evidence from studies in humans, consideration was given to aspects of the study quality (such as study design, availability of pre-exposure samples, quality of matched controls, sample size, and appropriateness of sample collection timing and end-point selection), and whether causal associations could be established between occupational exposure as a firefighter and the mechanistic end-points.

The Working Group considered studies on mechanistic evidence of carcinogenicity from exposures associated with structure fires, wildland fires, employment as a firefighter, catastrophic events, and other aspects related to occupational exposure as a firefighter. The evaluation was based on the totality of the evidence from exposures associated with structure fires, wildland fires, and employment as a firefighter because of similarities in the mechanistic evidence across these exposure types. There was also similar mechanistic evidence from studies on first responders to the World Trade Center disaster, including firefighters.

There is consistent and coherent evidence that occupational exposure as a firefighter exhibits five key characteristics of carcinogens: it is genotoxic; induces epigenetic alterations; induces oxidative stress; induces chronic inflammation; and modulates receptor-mediated effects.

Occupational exposure as a firefighter is genotoxic. In exposed humans, the body of evidence was consistent and coherent, with several studies reporting genotoxic effects across three categories of exposure, specifically structure fires, wildland fires, and employment as a firefighter.

Increased DNA damage in blood cells was found for both municipal and wildland firefighters. In municipal firefighters, the level of DNA damage was found to be positively correlated with concentrations of urinary 1-hydroxypyrene, skin pyrene, and skin total polycyclic aromatic hydrocarbons (PAHs). Increased urinary mutagenicity was observed in firefighters who were exposed to structure fires and wildland fires, with the wildland firefighting study finding that urinary mutagenicity was associated with duration of smoke exposure as well as the firefighting task. One study found a significant increase in the frequency of PAH–DNA adducts in blood from municipal firefighters, after controlling for confounders. One study found an increase in micronucleus frequency in buccal epithelial cells of municipal firefighters; this effect was also significant when stratifying by years of service, with the firefighters who had served 20 years or longer having a higher micronucleus frequency than those who had served less than 20 years. Some studies reported negative findings; however, these studies had design issues that may have limited their ability to detect a positive result. In one of the studies that did not find a statistically significant increase in genotoxicity, a significant positive association was observed between urinary mutagenicity and urinary 1-hydroxypyrene.

Consistent and coherent evidence for genotoxicity also comes from experimental systems, including human cells in vitro. Specifically, extracted organic material from particulate matter from biomass burning in the Amazon during both the dry and wet seasons induced micronuclei in a human lung cell line and frameshift mutations in *Salmonella typhimurium* with and without metabolic activation. In other studies, organic extracts of combustion emissions relevant to occupational exposure as a firefighter induced base-pair substitution and frameshift mutations in *S. typhimurium*.

Occupational exposure as a firefighter induces epigenetic alterations. Consistent and coherent evidence came from four studies in exposed humans showing alterations in blood DNA methylation at loci in cancer-related genes. One epigenome-wide association study followed new recruits for 2 years and observed persistent and cumulative changes in DNA methylation. Enriched pathways among the methylated loci included cancer-related pathways. This study observed that DNA methylation alterations were associated with proxies for cumulative exposure, including number of fire-runs and total fire-hours. In two cross-sectional epigenome-wide association studies, it was also observed that DNA methylation alterations in firefighters were associated either with years of service or with concentrations of perfluoroalkyl substances in the blood. One study using a targeted gene analysis found a gene-specific DNA methylation alteration in firefighters that was correlated with years of service. In addition, decreases in expression of tumour suppressor microRNAs (miRNAs) and increases in expression of oncogenic microRNAs were observed in blood samples from firefighters. In two studies of the same population, nine altered miRNAs were reported when comparing incumbent firefighters with new recruits, and altered expression of three of these miRNAs was replicated when comparing new recruits at baseline with follow-up 2 years later. Nine additional

miRNAs were identified that were associated with employment duration in a longitudinal study of new recruits.

Occupational exposure as a firefighter induces oxidative stress. There is consistent and coherent evidence from several studies for the induction of oxidative stress in exposed humans. Oxidative DNA damage, determined by formamidopyrimidine DNA glycosylase (Fpg)-sensitive sites using the comet assay, was detected in blood samples from firefighters exposed to structure fires. These results correlated positively with PAH concentrations on skin wipes from the neck. In addition, oxidative DNA damage induced by exposure to forest fires was correlated positively with urinary 2-hydroxyfluorene and 1-hydroxypyrene levels. Another study demonstrated increases in markers of oxidative stress, specifically, oxidized guanine species and 8-isoprostane, in the urine after wildland fire exposure. A positive correlation was also reported between pre- and post-exposure changes in malondialdehyde level and black carbon exposure. A few studies did not observe significant alterations in levels of oxidative stress markers, possibly due to inappropriate sample collection time-points and lack of control for confounding factors.

Further suggestive evidence for oxidative stress was provided by three studies in mammalian experimental systems, two in vivo and one in vitro. Adult sheep exposed to cooled smoke from burned cotton towelling exhibited alterations in several oxidative stress markers in various tissues compared with controls. Levels of hydrogen peroxide and malondialdehyde were increased in mouse peritoneal monocytes in vitro exposed to particulate matter in smoke samples collected from wildland fires compared with clean air samples. Furthermore, this particulate matter exposure was found to induce oxidative DNA damage in an acellular system.

Occupational exposure as a firefighter induces chronic inflammation. There is evidence for exposure-related increases in numerous inflammatory markers. A few studies showed persistent airway and systemic inflammation up to 1–3 months after exposure, including exposure-related increases in inflammatory markers such as interleukins IL-6 and IL-8. In addition, several studies in firefighters reported declines in lung function with associated changes in inflammatory markers (e.g. IL-6, IL-8), and a few studies reported bronchial hyperreactivity, suggestive of lung injury and chronic inflammation. Also, one cross-sectional study showed an association between bronchial hyperreactivity and the number of fire exposures during the previous 12 months. Many of these studies had design limitations in the lack of availability of pre-exposure samples, the quality of matched controls, the sample size, and the appropriateness of sample collection timing. Nonetheless, the cumulative evidence across studies showed the presence of long-lasting inflammation in firefighters (e.g. fire instructors) who experience frequent repeated exposures with minimal recovery time periods. Furthermore, there was overwhelming evidence from studies reporting acute inflammation measured by several inflammatory markers, such as increases in IL-6 and/or IL-8, in the blood and airways. These data are consistent across a range of exposure types, including structure fires, wildland fires, and employment as a firefighter.

Occupational exposure as a firefighter modulates receptor-mediated effects. In exposed humans after different exposures (pre-/post-exposure measurement in live-fire drill, employment length, and firefighting history), three studies consistently and coherently demonstrated activation of the aryl hydrocarbon receptor. Two of these studies showed aryl hydrocarbon receptor agonistic effects, and one study showed an association with increased downstream metabolic enzyme activity, modified by genotype. Further supportive evidence in humans came from observations of altered levels of testosterone, cortisol, adrenocorticotropic hormone, catecholamines,

and thyroxine. There was suggestive evidence for modulation of receptor-mediated effects in two different studies in experimental systems in vitro. One study on technical mixtures of firefighting foam showed thyroid-disrupting potential in a human bone osteosarcoma epithelial cell line. In a second study, extracts from firefighters' gloves and hoods gave positive results in a yeast estrogenic assay.

For the other key characteristics of carcinogens, there was a paucity of data or no data were available.

6. EVALUATION AND RATIONALE

6.1 Cancer in humans

There is *sufficient* evidence in humans for the carcinogenicity of occupational exposure as a firefighter. Occupational exposure as a firefighter causes mesothelioma and cancer of the bladder. Positive associations have been observed between occupational exposure as a firefighter and cancers of the colon, prostate, and testis, and malignant melanoma of the skin and non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

There is *inadequate* evidence in experimental animals regarding the carcinogenicity of occupational exposure as a firefighter.

6.3 Mechanistic evidence

There is *strong* evidence that occupational exposure as a firefighter exhibits key characteristics of carcinogens in exposed humans.

6.4 Overall evaluation

Occupational exposure as a firefighter is *carcinogenic to humans (Group 1).*

6.5 Rationale

The Group 1 determination for occupational exposure as a firefighter is based on *sufficient* evidence for cancer in humans. This *sufficient* evidence was observed for mesothelioma and cancer of the bladder, based on findings from many well-conducted cohort studies in multiple countries in Asia, Europe, North America, and Oceania comparing the cancer incidence or mortality experience of firefighters with that of the general population. The Working Group noted consistent positive associations for these cancers in the body of epidemiological evidence, including among the most informative studies based on consideration of exposure assessment quality, length of follow-up, and other study attributes. Furthermore, the positive findings were supported by the plausibility of exposure of firefighters to agents known to cause mesothelioma and bladder cancer (e.g. asbestos, and polycyclic aromatic hydrocarbons and other combustion products, respectively). For cancers of the colon, prostate, and testis, and for melanoma and non-Hodgkin lymphoma, the Working Group concluded that the evidence is *limited*: positive associations were observed in the body of evidence for firefighters, but chance, bias, and/or confounding could not be ruled out with reasonable confidence because of inconsistent associations, concerns about surveillance

bias (whereby firefighters might be subject to more frequent screening or medical examinations than are the general population), possible confounding, and/or the lack of exposure to known causes of these cancers. For other cancer sites, the evidence is *inadequate*.

There is also *strong* evidence that occupational exposure as a firefighter exhibits multiple key characteristics of carcinogens. Occupational exposure as a firefighter is genotoxic; it induces epigenetic alterations; it induces oxidative stress; it induces chronic inflammation; and it modulates receptor-mediated effects. A minority of the Working Group considered that the evidence for chronic inflammation was only suggestive; however, the majority opinion of the Working Group was that the evidence was consistent and coherent for this key characteristic. The evidence that occupational exposure as a firefighter exhibits these key characteristics came primarily from studies in humans exposed to different types of fire (i.e. structure, training, and wildland), as well as exposure measured as occupation (including volunteers) as a firefighter. Evidence regarding cancer in experimental animals is *inadequate* because no studies were available to the Working Group.

On the basis of the available evidence, the Group 1 evaluation for occupational exposure as a firefighter should be presumed to apply to all categories and types of firefighter, and to men and women.

LIST OF ABBREVIATIONS

AAS	atomic absorption spectrophotometry
AAS-HG	atomic absorption spectrophotometry-hydride vapour generator method
AFFF	aqueous film-forming foam
AhR	aryl hydrocarbon receptor
AHRR	aryl hydrocarbon receptor repressor
AMPK	AMP-activated protein kinase
AOPP	advanced oxidation protein products
APF	assigned protection factor
APGC-MS/MS	atmospheric pressure gas chromatography-tandem mass spectrometry
ApoA1	apolipoprotein-AI
ARR	adjusted relative risk
B[*a*]P	benzo[*a*]pyrene
BBLV	binding biological limit value
BCEtP	bis-2-chloroethyl phosphate
BDCPP	bis(1,3-dichloro-2-propyl) phosphate
BEI	biological exposure index
BEV	battery electric vehicle
BLV	biological limit value
BMI	body mass index
BTEX	benzene, toluene, ethylbenzene, and xylene
CanCHEC	Canadian Census Health and Environment Cohort
CAT	catalase
CC16	Club cell secretory protein
CD	conjugated diene
CFHS	Career Firefighter Health Study
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COSMIC	Catalogue Of Somatic Mutations In Cancer
CT	computerized tomography
CYP	cytochrome P450

DCF	dichlorofluorescein
DPhP	diphenyl phosphate
EBC	exhaled breath condensate
ECHA	European Chemicals Agency
ECP	eosinophil cationic protein
EdU	5-ethynyl-2′-deoxyuridine
EH-TBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate
ELISA	enzyme-linked immunosorbent assay
EOM	extractable organic material
EWAS	epigenome-wide association study
FDNY	Fire Department of the City of New York
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
$FEV_{1,\%Predicted}$	predicted forced expiratory volume in 1 second
Fpg	formamidopyrimidine DNA glycosylase
FTIR	Fourier transform infrared spectroscopy
FVC	forced vital capacity
GC-FID	gas chromatography-flame ionization detection
GC-HRMS	gas chromatography-high-resolution mass spectrometry
GC-MS	gas chromatography-mass spectrometry
GC-NPD	gas chromatography-nitrogen–phosphorus detection
GGT	gamma glutamyl transpeptidase
GM-CSF	granulocyte/macrophage colony-stimulating factor
GR	glutathione reductase
GSH	glutathione
GSH-Px	glutathione peroxidase
GSSG	oxidized glutathione
HBCDD	hexabromocyclododecane
HBr	hydrogen bromide
HBV	hepatitis B virus
HCl	hydrogen chloride
HCN	hydrogen cyanide
HCV	hepatitis C virus
HFPO-DA	hexafluoropropylene oxide-dimer acid
HIV	human immunodeficiency virus
HpCDD	1,2,3,4,6,7,8-heptachlorodibenzo-*para*-dioxin
HPIC	high-performance liquid chromatography
HPLC-MS/MS	high-performance liquid chromatography coupled with tandem mass spectrometry
HPLC-UV-DAD	high-performance liquid chromatography coupled with ultraviolet or diode-array detection
HPLC-UV-FL	high-performance liquid chromatography with ultraviolet or fluorescence detection
HR	hazard ratio
HRGC-HRMS	high-resolution gas chromatography-high-resolution mass spectrometry
HxCDF	hexachlorodibenzofuran
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology

ICP-MS	inductively coupled plasma-mass spectrometry
IDLH	immediately dangerous to life or health
IDR	incidence density ratio
Ig	immunoglobulin
IL	interleukin
IL-1RA	interleukin-1 receptor antagonist
indel	small insertions and deletions
8-iso-$PGF_{2\alpha}$	8-iso-prostaglandin F2α
KEGG	Kyoto Encyclopedia of Genes and Genomes
LC-MGUS	light-chain monoclonal gammopathy of undetermined significance
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LOD	limit of detection
LOOH	lipid hydroperoxides
LOQ	limit of quantification
LPA	lysophosphatidic acid
MCP-1	monocyte chemoattractant protein 1
MDA	malondialdehyde
meta-RR	meta-rate ratio
meta-SIR	meta-standardized incidence ratio
meta-SMR	meta-standardized mortality ratio
MGUS	monoclonal gammopathy of undetermined significance
MIP-1α	macrophage inflammatory protein 1 alpha
MN	micronucleus, micronuclei
MOR	mortality odds ratio
MPO	myeloperoxidase
MRR	mortality rate ratio
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B-cells
NFPA	National Fire Protection Association
NHL	non-Hodgkin lymphoma
NIOSH	National Institute for Occupational Safety and Health
NK	natural killer
NOCCA	Nordic Occupational Cancer
NO_x	nitrogen oxides
3-NT	3-nitrotyrosine
OEL	occupational exposure limit
3-OH-BaP	3-hydroxybenzo[*a*]pyrene
8-OHdG	8-hydroxy-2′-deoxyguanosine
8-OHG	8-hydroxyguanosine
8-OHGua	8-hydroxyguanine
1-OHP	1-hydroxypyrene
OPFR	organophosphate flame retardant
OR	odds ratio
OSHA	Occupational Safety and Health Administration
Ox-GS	oxidized guanine species
8-oxodG	8-oxo-7,8-dihydro-2′-deoxyguanosine

PAH	polycyclic aromatic hydrocarbon
PAH-CALUX	polycyclic aromatic hydrocarbon-chemical activated luciferase gene expression
p-Akt	protein kinase B
PBDD/Fs	polybrominated dibenzo-*para*-dioxins and dibenzofurans
PBDE	polybrominated diphenyl ether
PBDF	polybrominated dibenzofurans
PBL	peripheral blood lymphocytes
PBMCs	peripheral blood mononuclear cells
PC	protein carbonyls
PCA	principal component analysis
PCB	polychlorinated biphenyl
PCDD/Fs	polychlorinated dibenzo-*para*-dioxins and dibenzofurans
PCDF	polychlorinated dibenzofurans
PCG-1α	plasma peroxisome proliferator-activated receptor γ coactivator-1α
PeCDF	2,3,4,7,8-pentachlorodibenzofuran
PFAS	per- and polyfluoroalkyl substances
PFBS	perfluorobutanesulfonic acid
PFDA	perfluorodecanoic acid
PFDoA	perfluorododecanoic acid
PFHxS	perfluorohexanesulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
n-PFOS	linear perfluorooctanesulfonic acid
PFOS	perfluorooctanesulfonic acid
PM	particulate matter
PM_{10}	particulate matter with a diameter of 10 μm or less
$PM_{2.5}$	particulate matter with a diameter of 2.5 μm or less
PMN	polymorphonuclear neutrophils
PMR	proportionate mortality ratio
PPE	personal protective equipment
PTH	parathyroid hormone
PVC	polyvinyl chloride
PXDFs	mixed halogenated dibenzofurans
QTOF-MS/MS	quadrupole time-of-flight tandem mass spectrometry
RAGE	receptor for advanced glycation end-products
RAL	relative adduct labelling
RIR	relative incidence ratio [equivalent to rate ratio]
ROS	reactive oxygen species
RR	rate ratio
S9	9000 × *g* supernatant
SCBA	self-contained breathing apparatus
SCC	squamous cell carcinoma
SCE	sister-chromatid exchange
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SIRE	summary of incidence risk estimate
SMR	standardized mortality ratio

SMBOR	standardized morbidity odds ratio
SMOR	standardized mortality odds ratio
SMRE	summary of mortality risk estimate
SNP	single nucleotide polymorphism
SOD	superoxide dismutase
SP-A	surfactant-associated protein A
SRR	standardized rate ratio
STEL	short-term exposure limit
sVOC	semi-volatile organic compound
T3	triiodothyronine
T4	thyroxine
TBBA	2,3,4,5-tetrabromobenzoic acid
TBBPA	tetrabromobisphenol A
TDCPP	tris(1,3-dichloro-2-propyl) phosphate
TEAC	trolox equivalent antioxidant capacity
TGFβ	transforming growth factor beta
Th	T-helper
TNFα	tumour necrosis factor alpha
TRAP	total radical-trapping antioxidant potential
Treg	T-regulatory
TSH	thyroid-stimulating hormone
UA	uric acid
UPLC-MS/MS	ultra-performance liquid chromatography-tandem mass spectrometry
US EPA	United States Environmental Protection Agency
UV	ultraviolet
VEGF	vascular endothelial growth factor
VOC	volatile organic compound
WTC	World Trade Center
WUI	wildland–urban interface
XRE	xenobiotic response element

ANNEX 1. SUPPLEMENTARY MATERIAL FOR SECTION 1, EXPOSURE CHARACTERIZATION

These supplementary online-only tables are available from: https://publications.iarc.fr/615.

Please report any errors to imo@iarc.who.int.

Table S1.2	Number of firefighters, by employment status, in 57 countries
Table S1.11	Biomonitoring methods for chemical and physical agents excluding fire smoke components
Table S1.12	Levels of carbon monoxide, polycyclic aromatic hydrocarbons, particulate matter, and volatile and semi-volatile organic compounds measured at structure fires
Table S1.13	Levels of carbon monoxide, polycyclic aromatic hydrocarbons, particulate matter, and volatile and semi-volatile organic compounds measured at wildland fires
Table S1.14	Levels of carbon monoxide, polycyclic aromatic hydrocarbons, particulate matter, and volatile and semi-volatile organic compounds measured at vehicle fires
Table S1.15	Levels of carbon monoxide, polycyclic aromatic hydrocarbons, particulate matter, and volatile and semi-volatile organic compounds measured at other fire types
Table S1.22	Measures of compounds other than fire smoke and polycyclic aromatic hydrocarbons in the firefighting setting
Table S1.25	Biomarkers of exposure other than fire smoke and polycyclic aromatic hydrocarbons

The following tables were produced in draft form by the Working Group and were subsequently fact-checked but not edited:

ANNEX 2. SUPPLEMENTARY MATERIAL FOR SECTION 2, CANCER IN HUMANS

These supplementary online-only tables are available from: https://publications.iarc.fr/615.

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Table S2.2	Cohort and case–control studies only reporting having ever worked as a fire fighter and cancers of the lung and respiratory system, including mesothelioma
Table S2.4	Cohort and case–control studies only reporting having ever worked as a fire fighter and cancers of the urogenital system
Table S2.6	Cohort and case–control studies only reporting having ever worked as a fire fighter and cancers of lymphatic and haematopoietic tissues
Table S2.8	Cohort and case–control studies only reporting having ever worked as a fire fighter and cancers of the skin, thyroid, and brain
Table S2.10	Cohort and case–control studies only reporting ever having worked as a fire fighter and cancers of the colon and rectum, oesophagus, stomach, and other sites
Table S2.11	Cohort studies reporting occupational characteristics of firefighters and cancer of all sites combined
Table S2.12	Cohort and case–control studies only reporting having ever worked as a fire fighter and cancer of all sites combined

SUMMARY OF FINAL EVALUATIONS

Summary of final evaluations for Volume 132

Agent	Evidence stream			Overall evaluation
	Cancer in humans	Cancer in experimental animals	Mechanistic evidence	
Occupational exposure as a firefighter	*Sufficient*	*Inadequate*	*Strong*	Group 1

IARC MONOGRAPHS

This volume of the *IARC Monographs* provides an evaluation of the carcinogenicity of occupational exposure as a firefighter.

Occupational exposure as a firefighter is complex and includes a variety of hazards resulting from fires and non-fire events. Firefighters can have diverse roles, responsibilities, and employment (e.g. full-time, part-time, volunteer) that vary widely across countries and change over their careers. Firefighters respond to various types of fire (e.g. structure, wildland, and vehicle fires) and other events (e.g. vehicle accidents, medical incidents, hazardous material releases, and building collapses). Wildland fires are increasingly encroaching on urban areas. Changes in types of fire, building materials, and personal protective equipment have resulted in significant changes in firefighter exposures over time.

Firefighters may be exposed to combustion products from fires (e.g. polycyclic aromatic hydrocarbons, particulate matter), building materials (e.g. asbestos), chemicals in firefighting foams (e.g. per- and polyfluorinated substances), flame retardants, diesel exhaust, as well as other hazards (e.g. night shift work and ultraviolet or other radiation).

An *IARC Monographs* Working Group reviewed evidence from cancer studies and mechanistic studies in humans to assess the carcinogenic hazard to humans of occupational exposure as a firefighter and concluded that:

- Occupational exposure as a firefighter is *carcinogenic to humans (Group 1)*.

IARC MONOGRAPHS ANNIVERSARY 2021