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In June, 2022, 25 scientists from eight countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of occupational exposure as a firefighter. This assessment will be published in Volume 132 of the *IARC Monographs*.[1]

Occupational exposure as a firefighter was classified as "carcinogenic to humans" (Group 1) based on "sufficient" evidence for cancer in humans. The Working Group concluded that there was "sufficient" evidence in humans for mesothelioma and bladder cancer. There was "limited" evidence in humans for colon, prostate, and testicular cancers, and for melanoma and non-Hodgkin lymphoma. There was also "strong" mechanistic evidence that occupational exposure as a firefighter shows the following key characteristics of carcinogens in exposed humans: "is genotoxic", "induces epigenetic alterations", "induces oxidative stress", "induces chronic inflammation", and "modulates receptor-mediated effects". Evidence regarding cancer in experimental animal models was "inadequate" because no studies were available. The Group 1 evaluation for occupational exposure as a firefighter should be presumed to apply to all firefighters (including volunteers) and to both men and women.

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 (eg, full-time, part-time, or volunteer) that vary widely across countries and change over their career. Firefighters respond to various types of fires (eg, structure, wildland, and vehicle fires) and other events (eg, vehicle accidents, medical incidents, hazardous material releases, and building collapses). Wildland fires are increasingly encroaching on urban areas. Changes in the types of fires, building materials, personal protective equipment (PPE), and roles and responsibilities among firefighters have resulted in substantial changes in firefighter exposures over time.

Firefighters can be exposed to combustion products from fires (eg, polycyclic aromatic hydrocarbons [PAHs] and particulates), building materials (eg, asbestos), chemicals in firefighting foams (eg, perfluorinated and polyfluorinated substances [PFAS]), flame retardants, diesel exhaust, and other hazards (eg, night shift work and ultraviolet or other radiation). Uptake of fire effluents or other chemicals can occur via inhalation and dermal absorption and possibly via ingestion. Firefighters rely on PPE to reduce their exposures. Self-contained breathing apparatus is often worn during firefighting activities involving structures or vehicles, but less commonly during wildland firefighting, where firefighters can be deployed to wildfires multiple times a year and remain near the fire for several weeks. Dermal absorption of chemicals can occur even in firefighters wearing PPE due to limitations of its design, fit, maintenance, or decontamination. Furthermore, exposures can occur when firefighters are not actively fighting fires and are not wearing PPE.

Since the previous classification of firefighting (as "possibly carcinogenic to humans," Group 2B) by the *IARC Monographs* in 2007,[2] many new studies have investigated the association between occupational exposure as a firefighter and

cancer risk in humans. A total of 52 cohort and case-control studies, 12 case reports, and seven meta-analyses were considered in the present evaluation. The Working Group also did a meta-analysis that incorporated cohort studies of firefighters published up to June, 2022. More than 30 non-overlapping cohort studies following firefighters for cancer over time were considered most informative for the evaluation and were conducted in Asia, Europe, North America, and Oceania.[3, 4, 5]

On the basis of the available epidemiological evidence, the Working Group concluded that a causal association exists between occupational exposure as a firefighter and mesothelioma and bladder cancer. Seven studies examining mesothelioma incidence among firefighters were included in the meta-analysis. For these combined studies, the Working Group meta-analysis estimated a 58% higher risk (95% CI 14−120%) for mesothelioma among firefighters compared with mostly general populations. Heterogeneity in the estimate was low across the group of studies (I_2=8%). Asbestos exposure in firefighting is a plausible causal agent to support the observed associations. Confounding by sources of exposure outside of firefighting, and other biases, were considered unlikely to explain the magnitude and consistency of study results.

Positive associations for bladder cancer incidence were observed consistently in several cohort studies of firefighters compared mostly with the general population. In the Working Group's meta-analysis of ten studies, the increased risk estimate was small in magnitude (16%) but was statistically precise and had low heterogeneity (95% CI 8−26%, I_2=0). This estimate was consistent with two additional higher-quality cohort studies of cancer incidence that used a slightly expanded definition of bladder cancer, and with the results from studies of bladder cancer mortality. Further, negative confounding by smoking was deemed probable, because lower risks of lung cancer among firefighters were observed in most studies, and could have led to underestimated associations for bladder cancer in comparison with the general population. In one pooled US cohort study,[4] a positive association in exposure-response analyses with adjustment for employment duration suggested that healthy-worker survivor bias might have attenuated associations in other studies that had no such adjustment. Firefighters' exposures to known and suspected human bladder carcinogens (eg, PAHs and soot) were considered plausible causal agents to support the observed associations for bladder cancer. Credible positive associations were observed for colon, prostate, and testicular cancers, and for melanoma and non-Hodgkin lymphoma, based on estimates from the cohort studies included in the meta-analysis and consideration of the larger body of evidence. However, bias from greater medical surveillance and detection in firefighters, or confounding by physical and lifestyle characteristics could not be reasonably excluded as explanations for the positive findings. Concerns about surveillance bias were particularly salient for more commonly indolent or screened cancers such as prostate and colon, which were supported by the observation of attenuated or null associations in studies of mortality versus incidence. For some of these cancer types, high heterogeneity in the meta-analysis estimates, inconsistent positive findings from informative studies, or little evidence for firefighting exposures known to be associated with these cancer types also reduced confidence

in a causal conclusion. For these reasons, a determination of "limited" evidence was reached for these five cancer types.

The human cancer evidence for all other cancer types was "inadequate", including for lung and thyroid cancers. Lung cancer incidence and mortality rates were lower among firefighters than in the general population in most studies and in the meta-analysis; negative confounding by smoking and healthy worker hire bias were presumed to be likely. Surveillance bias was considered a probable explanation for the higher incidence rate of thyroid cancer observed in firefighters compared with the general population.

The evaluation of the mechanistic evidence was based on exposures associated with fighting structure and wildland fires, and on employment as a firefighter. Consistent and coherent evidence of genotoxic effects was observed in firefighters: an increase in the frequency of PAH-DNA adducts was found in blood; increases in urinary mutagenicity, DNA damage in blood, and micronucleus frequency in buccal cells were associated with firefighting-related exposures. Genotoxicity was also observed in relevant experimental systems: organic extracts of combustion emissions relevant to firefighting exposure increased the frequency of micronuclei in a human cell line and of mutations in bacteria. Evidence of epigenetic effects was observed in firefighters, based on changes in blood DNA methylation at loci in cancer-related genes. Epigenome-wide association studies among firefighters showed persistent changes in DNA methylation associated with proxies for cumulative exposure and DNA methylation alterations associated either with years of service or with blood PFAS concentrations. Exposure-related alterations in the expression of microRNAs associated with cancer were also observed in the blood of firefighters. Occupational exposure as a firefighter induced exposure-related oxidative DNA damage in blood and oxidative stress markers in urine. Acute and persistent inflammation was observed in firefighters. Airway and systemic inflammatory markers, such as IL-6 and IL-8, were associated with firefighting-related exposures. Moreover, declines in lung function associated with changes in inflammatory markers and exposure-associated bronchial hyperreactivity were reported in firefighters. A minority of the Working Group considered the evidence for chronic inflammation to be only suggestive; however, the majority considered the evidence consistent and coherent for this key characteristic. Consistent and coherent evidence was found that occupational exposure as a firefighter modulates receptor-mediated effects, as show by the activation of the aryl hydrocarbon receptor.

References

○ 1. International Agency for Research on Cancer. Volume 132: Occupational exposure as a firefighter. Lyon, France; June 7–14, 2022. *IARC Monogr Identif Carcinog Hazards Hum* (in press).

View in Article Google Scholar

○ 2. International Agency for Research on Cancer

Painting, firefighting, and shift work.

IARC Monogr Identif Carcinog Risks Hum. 2010; **98**: 1-804

View in Article Google Scholar

○ 3. Glass DC
○ Pircher S
○ Del Monaco A
○ Hoorn SV
○ Sim MR

Mortality and cancer incidence in a cohort of male paid Australian firefighters.

Occup Environ Med. 2016; **73**: 761-771

View in Article

○ PubMed
○ Google Scholar

○ 4. Pinkerton L
○ Bertke S
○ Yiin J
○ et al.

Mortality in a cohort of US firefighters from San Francisco, Chicago and Philadelphia: an update.

Occup Environ Med. 2020; **77**: 84-93

View in Article

○   Scopus (11)

- [PubMed](#)

- [Crossref](#)
- [Google Scholar](#)

- 5. Marjerrison N
- Jakobsen J
- Demers PA
- et al.

Comparison of cancer incidence and mortality in the Norwegian Fire Departments Cohort, 1960–2018.

Occup Environ Med. 2022; (oemed-2022-108331.)

[View in Article](#)

- [Crossref](#)
- [Google Scholar](#)