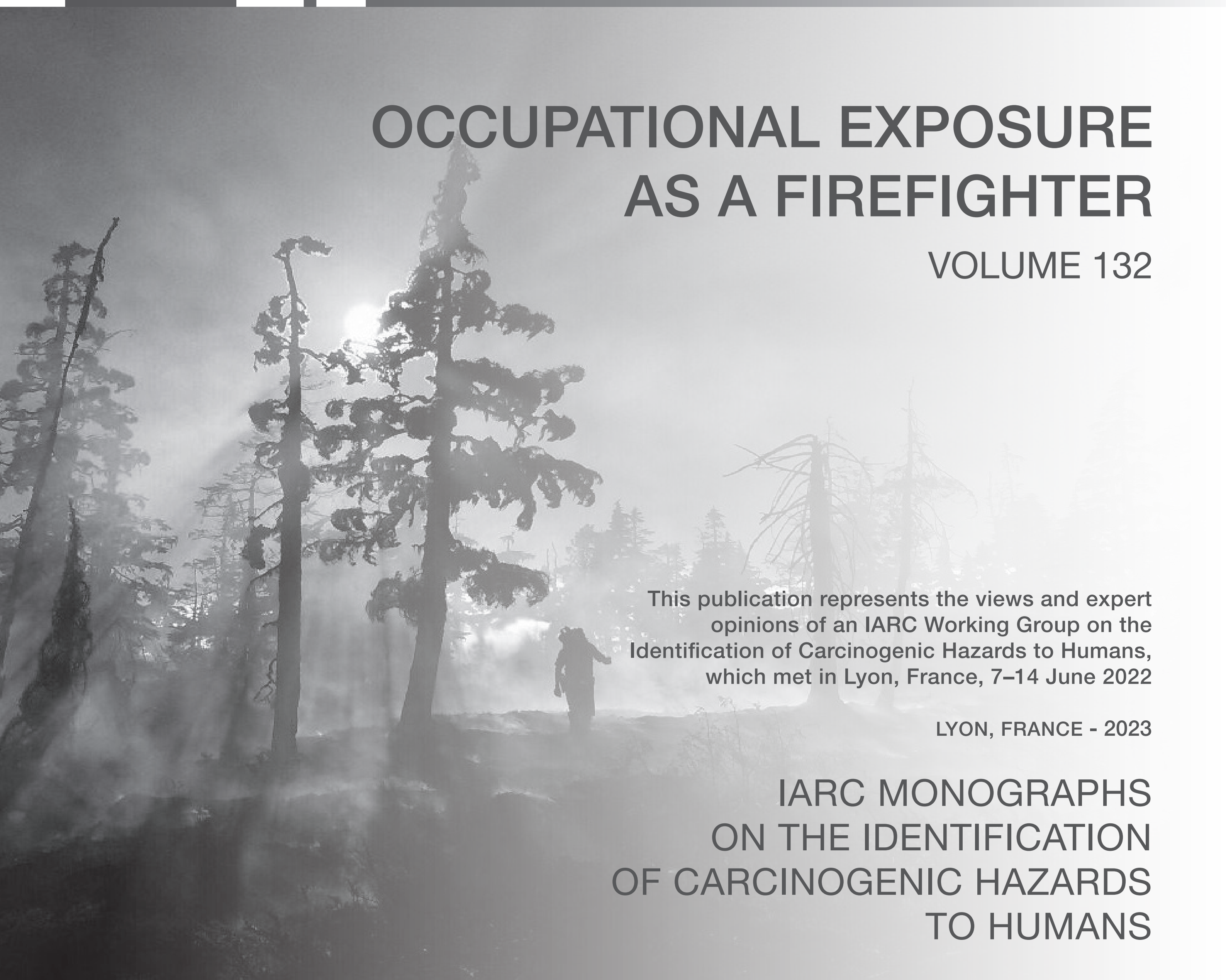
IARC MONOGRAPHS



OCCUPATIONAL EXPOSURE AS A FIREFIGHTER

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

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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 fire-fighting 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.