Report on Carcinogens Wildfire Smoke Human Cancer Hazard Evaluation Protocol

Part 3: Assessing the Evidence from Wildfire Smoke and Human Cancer

Report on Carginogens Group

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National Institute of Environmental Health Sciences
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1. Evaluating Human Cancer Studies of Exposure to Wildfire Smoke

Background and Objectives

Exposure to wildfires is a growing public health, environmental, and societal problem. Although the number of wildfires has remained generally the same or slightly decreased (Congressional Budget Office 2022), over the past 20 years the U.S. has seen an increase in both the amount of land burned and frequency of occurrence of wildfires (Iglesias et al. 2022). The consequences of wildfires are far reaching, including health effects from smoke exposure by burning of wildland vegetation.

Because exposure to wildfires poses a potential carcinogenic hazard for people living in the United States, the National Institute of Environmental Health Sciences (NIEHS) is conducting a cancer hazard evaluation of wildfire smoke (WFS) exposure for potential listing in the Report on Carcinogens (RoC), a congressionally mandated, science-based public health document. As mentioned in part 1 of the protocol, the overall cancer hazard evaluation will (1) assess and integrate the evidence from human cancer studies and mechanistic studies, and (2) apply the RoC listing criteria to the assessment to reach a listing recommendation.

Note, that initially, a single protocol on wood smoke and wildfire for human cancer studies was developed (Report on Carcinogen Wood Smoke and Wildfire Cancer Hazard Evaluation Protocol Part 1), however after the evaluation of wood smoke studies and the consideration of exposure data on sufficient similarities between wood smoke and wildfire, it was decided to conduct an independent evaluation of human cancer studies on exposure to wildfire (See section 1.5 for more information). A separate scoping and literature search was completed for animal cancer and mechanistic studies for wood smoke and wildfire (Report on Carcinogen Wood Smoke and Wildfire Cancer Hazard Evaluation Protocol Part 2); during this step, no experimental animal cancer studies of wildfire smoke were identified.

This document is the protocol for the cancer hazard evaluation of the human cancer studies of wildfire smoke exposure. The protocol for evaluating mechanistic studies of wildfire smoke is available on the RoC website.

Overall Objective and Aims

Overall Objective

To reach conclusions about the level of evidence of the carcinogenicity of wildfire smoke provided by human epidemiology studies based on the RoC listing criteria (see Section 1.6).

Key questions

- What are the study characteristics and key scientific issues to consider in the evaluation?
    - What cancer outcomes have an adequate database for review?

  - How is wildfire smoke exposure characterized in the studies and what are the most relevant exposure proxies for humans?
- How informative (e.g., risk of bias, study sensitivity) are the studies for the evaluation?
  - What are the potential confounders and effect modifiers for cancer risk for the tumor sites of interest in these studies?
  - For each study, what is the impact (magnitude, direction) of the distortion of bias on reported study results
- What is the level of evidence for carcinogenicity for each cancer outcome?
- Is there a credible association between exposure to wildfire smoke exposure and cancer across studies?
    - If so, can the relationship between each cancer outcome and wildfire smoke be explained by chance, bias, or confounding?

Protocol Contents and Evaluation Process

This document describes the (1) completed scoping and problem formulation steps used to develop the human cancer framework (Section 1.1) and (2) proposed methods used to conduct the cancer hazard evaluation, including the study evaluation (Section 1.2), and evidence integration (Section 1.3). The methods are based on applying the specific issues relevant to wildfire smoke to the procedures outlined in the RoC handbook. The roles of the researchers and the literature search terms are described in Appendices.

Figure 1-1 provides a schematic of how the protocol (Step 2) fits into the cancer hazard evaluation process. The protocol is informed by the scoping and problem formulation (i.e., developing the framework) done in Step 1, and the methods in the protocol are then used to conduct the cancer hazard evaluation and write the RoC monograph (Step 3). Note that Steps 1 and 2 are iterative.

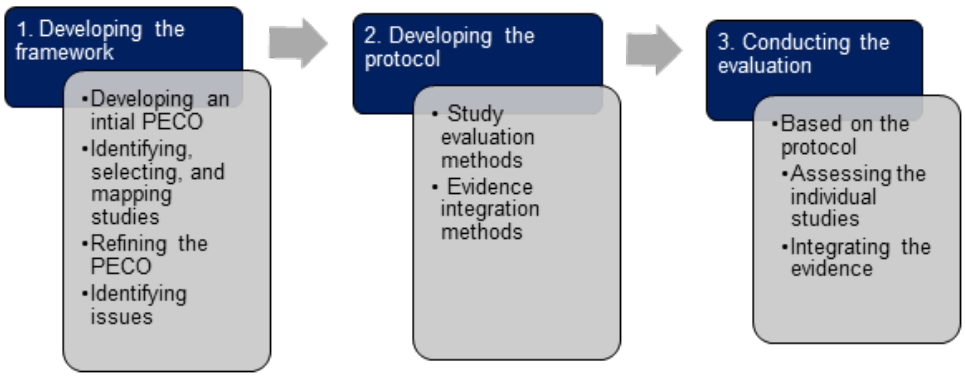

Figure 1-1. Cancer hazard evaluation process

Figure 1-1 depicts the cancer hazard evaluation process. Scoping, problem formulation, and evidence mapping lead to the development of the framework (Step 1), which includes the overall objective and aims, PECO statements (i.e., body of evidence) to address the study objective(s), and identification of hazard specific issues to be explored in the evaluation. This step has been completed and the findings are reported in Section 1.1.

This step also informed the methods, i.e., the protocol (Step 2) for conducting the cancer hazard evaluation (Step 3), the results of which will be captured in the RoC monograph. The methods focus on study evaluation (risk of bias and study sensitivity, Section 1.2) and evidence integration (Section 1.3). **PECO** = **P**opulation, **E**xposure, **C**omparison group, and **O**utcome.

1.1. Developing the Framework

Preliminary scoping and problem formulation activities informed the evaluation framework for the entire cancer hazard evaluation for wildfire smoke, which includes the evaluation of human cancer studies using the methods described in this protocol, as well as evaluation mechanistic studies in humans, animals, and cells (Report on Carcinogens Wood Smoke and Wildfire Evaluation Protocol Part 2: Animal Cancer and Mechanistic Studies, NTP 2024).

For human studies, the body of evidence is defined by the PECO (**P**opulation, **E**xposure, **C**omparison Group, **O**utcome) Statements.

Based on a review of the literature database, we further refined the initial PECO (see the Report on Carcinogens Wood Smoke and Wildfire Evaluation Protocol Part 1: Human Cancer, NTP 2022) to develop a final PECO for studies to be included in the qualitative cancer hazard evaluation for exposure to wildfire smoke. Details are discussed in Sections 1.1.1 and 1.1.2.

Table 1-1: Initial and Final PECOs for WFS Cancer Epidemiology Studies

PECO element	Initial PECO	Final PECO
Population	All populations	All populations
Exposure	Wildfire smoke	Wildfire smoke: firefighting events, wildfires
Comparison group	No or little wildfire smoke exposure	No or little wildfire smoke exposure
Outcomes	Any cancer	Cancer sites of interest[a]: all cancer combined[b], lung cancer, colorectal cancer, female breast cancer

[a]Other cancers may be evaluated if new studies are published; data for all cancers will be summarized
[b]All cancer combined is study specific, if a study reported "all cancers" or "total cancers", it will be included. This review will not post-hoc aggregate data from specific estimates to generate a "total/all" cancer estimate.

1.1.1. Identifying and Selecting the Literature

Biomedical citation databases, namely PubMed, Scopus, and Web of Science, were searched for human cancer studies and exposure to wildfire smoke by combining search terms for exposure to WFS (see Appendix B), cancer (see RoC Search String Document), and human cancer studies (see RoC Search String Document) using the procedures outlined in the RoC Handbook. Studies specific for wetland or wildland firefighters would be identified by the terms (wetland* and (fire*) OR (wildland* and fire*) or wildfire*). We may miss studies of firefighters and general population studies that report

specific analysis for wildfire studies and do not mention that in the keywords, title, and abstract and that are not part of our database of occupational case-control studies.

Search results were processed in Endnote and imported into a content management system [e.g., Health Assessment Workplace Collaborative (HAWC)] software to select relevant literature (Shapiro et al. 2018). Studies are included in HAWC based on the initial PECO.

Studies were initially included in the evaluation if they met any of the following criteria when conducting a title and abstract or subsequent full-text screening:

- Primary studies (analytical epidemiologic studies or pooled analyses of multiple studies) meeting the initial PECO statement (see Table 1-1). Other criteria or details are listed below
    - Study clearly indicates exposure to wildfire
        - Study reports a risk estimate (or information to calculate a risk estimate) for cancer at the individual level
        - Studies providing supporting information for topics relevant to the evaluation of the human epidemiologic evidence. These include, but are not limited to, qualitative reviews or letters to the editor, and information on co-exposures or potential confounders.
        - Meta-analyses, and systematic and narrative reviews.

1.1.2. Mapping the Evidence

Citations in HAWC were tagged by cancer type and type of study (primary epidemiology studies versus supporting studies). In total, 17 studies of WFS exposure and human cancer in individuals were identified. Of the identified studies, 7 were included in the review for evaluation.

Identified studies were excluded from the review because they did not provide information relevant to the objective of the review, e.g. ecological studies (e.g., population level exposure and outcome), cancer survival, not specific for wildfire exposure, case studies (see Table 1-2). We identified three studies of Australian firefighters [male paid (full and part-time), male volunteer, and female volunteer firefighters] that reported risk estimates for landscape fire incidents for all cancers (Glass et al. 2019) or specific cancers (Glass et al. 2016; Glass et al. 2017). Landscape fires are defined as bushfires and grass fires and can include prescribed or planned burns in addition to wildfires. In these three studies of Australian firefighters, the same firefighters could have also responded to non-landscape related incidents; in the volunteer firefighters, participants were more likely to respond to one type of fire, therefore those responding to landscape fires typically only attended landscape fires (personal communication with study author). Part-time paid firefighters responded to a larger proportion of landscape fires compared to full-time paid firefighters. As such, the risk estimates for the part-time paid firefighters from the 2016 Glass et al. study on male paid firefighters were included in the evaluation.

Table 1-2. Selected excluded studies

Study (Location)	Rationale	Summary of Findings
Chizhov and Pinaev 2018; Pinaev and Chizhov 2020; Pinaev et al. 2023 (Russia)	Ecological studies (primarily childhood): Correlations between number of WF and cancer rates (no individual level outcome data, no risk estimates)	Positive correlations between wildfire and cancers (primarily leukemia and embryonal) in children and leukemia/lymphomas in the entire population
Lichter et al. 2025 (USA)	Cancer survival: Association of wildfire with survival of patients who had radiotherapy for non-small cell lung cancer (NSCLC)	Small association of worse survival of those in a county with a wildfire disaster declaration during treatment compared to those who were not.
Remigio et al. 2025 (USA)	Ecological study: Association between county level WFS and county level lung cancer mortality (no individual level outcome data)	Identification of counties where WFS may be association with lung cancer mortality
Silva et al. 2026 (Brazil)	Ecological study: Association between wildfire counts and ratio of adenocarcinoma to total lung cancer within regional health department areas (no individual level outcome data)	Regions with higher adenocarcinoma to total lung cancer ratios had higher mean numbers of wildfires
VoPham et al. 2025 (USA)	Cancer survival: Association of WFS and cancer survival (i.e., mortality) among cancer patients	Positive association between WFS and cancer mortality; association between PM stronger in areas impacted by wildfires
Wolfe et al. 2012 (USA)	Case study	Single case report on a wildland firefighter diagnosed with squamous cell carcinoma
Zhang et al. 2023 (USA)	Cancer survival: Association of wildfire with survival after surgery for NSCLC.	Those with exposure to wildfires had worse survival compared to unexposed.
Zewdie et al. 2026 (USA)	Ecological study: Association between estimated census tract level cancer history prevalence and WF-$PM_{2.5}$	Positive association in the Midwest and Northeast regions.

WF = wildfire, WFS = wildfire smoke, WF-$PM_{2.5}$ = Wildfire smoke particulate matter <2.5 ug/m^3, CRC = colorectal cancer, NSCLC = non-small cell lung cancer

Several cancer types –all cancers, breast cancer, colorectal cancer (CRC), lung cancer, oral cancers (including pharynx), lymphohematopoietic cancers–had an adequate database for review, i.e., were reported in four or more studies, for evaluation (see Table 1-3). The findings for lymphohematopoietic cancers (LHC) and oral cancers were largely null across all studies. Based on this initial evidence scoping, we refined the PECO for the systematic review and evidence integration (see Table 1-1) to be specific for the other four cancers of interest (all cancers, breast, CRC, lung). As the database consists of cohort studies (no case-control studies were identified) that report on multiple cancer outcome types, all studies/cohorts will be evaluated for informativeness and the findings

for each reported cancer type will be briefly summarized. Findings for LHC, oral cancers, and other subtypes will be briefly summarized as a narrative review in the final report. Literature searches will continue to be updated during the conduct of this review; if new information becomes available, an in-depth systematic review of other types of cancer may be conducted.

Although "all cancers combined" is not typically an outcome that is assessed in cancer hazard assessment due to low specificity, we included it because WFS is a mixture of many carcinogens, which can be linked to different types of cancer. WFS mixtures, i.e., the level of specific component carcinogens vary across different populations, which could potentially result in association with different cancer types (if causal) across populations, especially if the studies are underpowered. Thus, all cancer could be an appropriate or more sensitive outcome for this complex scenario. "All cancer" in this review is study specific, e.g. if a study reported an effect estimate for "all" or "total" cancer, it will be included in the evaluation of all cancers. This review will not post-hoc aggregate data from specific estimates to generate an "all" cancer estimate. Study specific definitions of all cancers and comparisons across studies will be included in the final evaluation.

Table 1-3. Characterization of human studies on wildfire smoke

Study Location	Population	Exposure Metric	Cancers[a]								
			All[b]	Breast	CRC	Kidney	LHC	Lung	Oral[c]	Prostate/ Testis	Skin
Firefighter Populations											
Cherry et al. 2025 Canada	Wildfire fighters	Deployments, service, task, fire complexity	Rep	Rep	Rep	NR	Rep	Rep	NR	Rep	Rep
Glass et al. 2016 Australia	Male paid firefighters	Landscape firefighting incidents	Rep	NR	Rep	Rep	Rep	Rep	Rep	Rep	Rep
Glass et al. 2017 Australia	Male volunteer firefighters	Landscape firefighting incidents	Rep	NR	Rep	Rep	Rep	Rep	Rep	Rep	NR
Glass et al. 2019 Australia	Female volunteer firefighters	Landscape firefighting incidents	Rep	Rep	Rep	Rep	Rep	Rep	Rep	NR	Rep
General Population											
Gao et al. 2023; Gao et al. 2024 UK	Adults (Mortality)	WF $PM_{2.5}$	Rep	Rep	NR[d]	NR	Rep	Rep	Rep	NR[d]	Rep

Study Location	Population	Exposure Metric	Cancers[a]								
			All[b]	Breast	CRC	Kidney	LHC	Lung	Oral[c]	Prostate/ Testis	Skin
Korsiak et al. 2022 Canada	Adults	WF proximity, area burned	NR	NR	NR	NR	Rep	Rep	NR	NR	NR
Yu et al. 2022 Brazil	Death records	WF $PM_{2.5}$	Rep	Rep	Rep	Rep	Rep	Rep	Rep	Rep	Rep

Abbreviations: CRC = colorectal cancer, LHC = lymphohematopoietic cancers, PM = particulate matter, $PM_{2.5}$ = particulate matter ≤2.5 µg, Rep = reported, NR = not reported, WF = wildfire, UK = United Kingdom
[a]Select cancers and all cancers listed here were reported in multiple studies
[b]All cancer as defined/reported by the study
[c]Includes lip, oral, and pharynx
[d]Reported all digestive cancers (not CRC separately) and all male genital cancers (not prostate/testis separately)

1.2. Study Informativeness Evaluation of Individual Studies

The methods are adapted from the 2025 RoC Handbook. Details of the types of bias, questions, and general guidance can be found there. Here we include guidance and judgements specific to human cancer studies of exposure to wildfire smoke. Each primary study will be systematically evaluated for its ability to inform the cancer hazard evaluation using five domains related to bias – selection and attrition bias, exposure measurement error and exposure misclassification, outcome misclassification, confounding bias, and analysis bias – and one domain related to study sensitivity [or the ability of the study to detect a true effect (Cooper et al. 2016)] that includes elements related to study design and exposure conditions.

The evaluation of the potential for bias (i.e., risk of bias) in each domain will be captured by core questions for each domain. For each core question, a series of signaling questions will be used to address specific issues related to the core question. These questions are used to provide guidance and transparency for the domain-level judgment (options for domain-level judgements are described below). Responses to signaling questions will then captured in the rationale for the response to the core question. These questions are meant to provide guidance, not to be a checklist. When adequate study information is available, a domain-level judgment will be made for the direction and distortion of each bias. General guidance is available in the 2025 RoC Handbook, guidance and responses specific to wildfire smoke are included below in Table 1-4 to 1-11.

Response to signaling questions:

- **No/Minimal concerns**: Study design or methodologies are ideal or very close to the ideal study characteristics and potential for bias is unlikely or minor. These studies are generally considered informative for the cancer hazard evaluation.
- **Some concerns**: Study design or methodologies indicate a possible low to moderate risk of bias. These studies are generally considered informative for the cancer hazard evaluation.

- **Major concerns**: Study designs or methodologies suggest that the potential for a specific type of bias is high. However, depending on the direction and distortion of the potential bias, the study may still be informative for cancer hazard evaluation, but should be viewed with caution.
- **Critical concerns**: Study design or methodologies suggest that the bias would likely make study findings unreliable for hazard identification. This category is rare.
- **No information in the study**: The information in the study is inadequate to evaluate the level of concern.
- **Direction of bias**: ↑Away from the null or overestimate of the effect (e.g., false positive); ↓towards the null or underestimate of the effect (e.g., false negative); ↔ not known (unable to determine).

Our approach will be to evaluate the components of study quality separately for studies reporting on each cancer type using the questions, domain level ratings, and guidelines given below.

1.2.1. Selection and Attrition Bias

To date, all identified human cancer and wildfire smoke studies for evaluation are cohort studies. As such, the questions and guidance below are specific for cohort studies (see Table 1-4). If any case-control or cross-sectional studies are identified, we will follow the questions and guidance in the 2025 RoC Handbook. No other unique issues related to wildfire smoke were identified for this type of bias.

Questions and guidance

Core question: Is there a concern that selection into the study or out of the study was related to both exposure (e.g., wildfire smoke) and to cancer?

Table 1-4. Selection bias questions, guidance, and response options

Signaling question	Guidance	Response Options
Selection into the study: All study designs Are there concerns that the selection methods, such as eligibility criteria (inclusion/exclusion) or recruitment strategies for exposed and non-exposed are not adequately conducted or differ by exposure status? Is there concern that exposed or non-exposed cohort participants are not representative of the same underlying population during a similar time period? In cohort studies, is there concern that the health of a participant may have affected their selection into the study (e.g., the healthy worker hire effect or the healthy volunteer effect) or that the cohort was selected based on a cancer cluster, leading to underlying differences between exposed and unexposed individuals?	Ideally, the WFS-exposed and unexposed groups should be similar in all respects except for exposure status, and from the same underlying population. In addition, participation should not be related to both outcome and exposure status.	**No/minimal concern** Exposed and non-exposed groups were selected from the same population by similar methods and criteria. There is no evidence that selection of the participants was related to both WFS exposure and cancer. The cohort is clearly defined (e.g., includes groups of those exposed to WFS and unexposed) with no evidence that follow-up differs between the exposed and non-exposed. **Some concern** Exposed and non-exposed groups were selected by similar methods and criteria, however, there is some evidence that study selection and/or cohort attrition may be related to both exposure and outcome, but the magnitude of distortion is believed to be minor. HWE and/or HWSE could be possible. **Moderate/major concern**

Selection out of the study: Cohort study

Is there concern about attrition bias or incomplete follow-up?

- If there is a concern, is selection out of the study related to both exposure and outcome status?

Is there concern that an analysis that is conditioned on censoring is related to both exposure and outcome?

Is there concern about the timing of follow-up (e.g., follow-up time did not coincide with or pre-date the start of the measurement/estimation of exposure, especially for outcomes with shorter latencies)?

In occupational studies, is there concern regarding healthy worker survival effect (HWSE)?

If there is concern regarding selection bias, were there any analyses to address or evaluate the potential for bias?

Ideally, rigorous methods should be used to ascertain case status and should not differ by WFS exposure status.

Ideally, participants are enrolled and follow-up begins at the onset of exposure, however this approach may not be feasible for WFS exposure, which is seasonal may reoccur over many years. A cohort that enrolls participants at a specific point in time (or at a delayed later time) may be at risk for left truncation, because individuals who were exposed and diagnosed prior to enrollment are not eligible to be in the study population. A cohort where follow-up begins after onset of exposure, however, estimates WFS retrospectively, may be appropriate depending on the study design – a cohort that enrolls participant may still be subject to left truncation, however a study based on records, may be appropriate.

Wildfire firefighters are healthier than the general population, and thus are very likely subject to healthy worker hire effect if comparing to the general population and possibly certain referent groups (e.g., calculating SMR/SIRs). This form of HWE parallels HWE seen in cohorts of other occupations (e.g., military). Moreover, it is possible that healthier workers (e.g., physically capable, younger age) may be assigned to fight fires of higher intensity, more widespread, or those with longer duration compared to those deemed less able, potentially attenuating exposure-response relationships when evaluating across all firefighters,.

Although the HWSE typically biases results toward the null (Stayner et al. 2003), its magnitude can be estimated, given sufficient information on the proportions of prevalent participants or workers and the length of the follow-up period. HWSE can also be considered as a confounder; in this evaluation it is considered as a form of selection bias, though its influence can be controlled for by adjusting for employment status, job type, and

Exposed and non-exposed groups were selected in such a manner that they are unlikely to represent the exposure distribution in the underlying population and could be related to cancer outcome. No analytic methods were used to address potential selection bias. There is concern that HWE and/or HWSE is likely and not accounted for.

Critical concern

There is substantial evidence that selection or attrition of participants was clearly related to both WFS exposure and outcome.

Signaling question	Guidance	Response Options
	duration of employment, applying appropriate exposure lags, employing statistical methods (e.g., g methods), or restricting follow up time to recent hires. Ideally, studies should conduct sensitivity analysis to estimate the extent of selection bias or control for it if feasible and appropriate (similar to HWSE) and/or use analytic methods to address potential selection bias (e.g., inverse probability weighting, quantitative bias analysis, or other approaches).	

1.2.2. Exposure Measurement Error and Exposure Misclassification

One of the most important aspects of an epidemiologic study is its ability to correctly classify study participants at the individual level with respect to their exposure status. This involves several dimensions: carefully defining the exposure metric used in the study, knowing information about the exposure setting, selecting appropriate data collection tools, methods for modeling exposure data, evaluating the quality of the exposure assessment methods, determining whether individuals can be adequately separated in terms of their level of exposure, and assessing whether study participants' knowledge of the outcome may have affected their reporting of exposure.

Wildfire smoke exposure

Wildfires can consist of wildland fires, i.e. unplanned and uncontrolled fires fueled by wildland vegetation (also called landscape fires), and prescribed burns, i.e. intentionally set fires to vegetation. For the human cancer section, wildfire is used to refer to both wildland fires and prescribed burns.

Wildfires can result in several exposures, most prominently wildfire smoke, which is a complex mixture of water vapor, gases, particulate matter (PM), and other substances. Wildfire PM concentrations are often used as a proxy for total wildfire smoke exposure. Wildfire smoke particulate sizes are predominantly fine (≤2.5 μm, Wildfire $PM_{2.5}$) or ultrafine (≤0.1 μm) (Reid et al. 2005; Groß et al. 2013; Vicente et al. 2013). Wildfire PM is thought to have differences in typical composition compared to ambient PM, which indicates that it might have a different toxicity compared to more widely studied ambient PM air pollution. Studies using data from air pollution monitors and complex modeling, found that wildfire PM compared to non-wildfire PM, has higher concentrations of organic carbon, elemental carbon, and potassium (Krasovich Southworth et al. 2025). In addition to PM, carbon monoxide produced by incomplete combustion of biomass and ozone formed from smoke plumes also present as a result of wildfires. Volatile and semivolatile organic compounds, polycyclic aromatic hydrocarbons, aldehydes, nitrogen oxides, sulfur oxides, and metals have also been detected as constituents of wildfire smoke. Lastly, ash and debris can remain on surface after an active wildfire, though most if not all studies on wildfire have focused on wildfire smoke exposure.

Wildfires in the wildland-urban-interface (WUI), which are becoming more frequent, have their own unique chemistry due to the burning of a large variety of materials, beyond biomass (Radeloff et al. 2018; NAS 2022). Smoke from wildfires that also burned manmade structures have higher concentrations or copper, lead, zinc, and nickel (Krasovich Southworth et al. 2025).

In the U.S., areas burned have increased over time, with increases in the overall area burned in the West, the Great Plains, and consistently large areas burned in the South U.S. Trends of rates of burned areas are consistently increasing over time across the continental U.S.; rates of change in burned area from 1984-1993 to 1994-2003 increased by 73% and between 1994-2003 and 2004-2014 increased by another 66% (Hawbaker et al. 2017). Wildfires in burn areas near communities have increased over time, thus increasing the risk of wildfire exposure to communities and larger populations (Wilner et

al. 2025). Wildfire $PM_{2.5}$ in the U.S. has increased over time, with estimates of wildfire smoke adding up to 0.69 $\mu g/m^3$ to annual ambient $PM_{2.5}$ concentrations in the continental U.S. from 2016 to 2022, and in the west and mid-west, up to 0.97 $\mu g/m^3$ (Burke et al. 2023). Though averages of wildfire $PM_{2.5}$ over time might be relatively low, the maximum peak levels during wildfire events can be extremely high, resulting in short-term high exposures. Estimates across the U.S. vary widely over time and by location vary widely, with some areas showing increases of average wildfire smoke $PM_{2.5}$ concentrations of 5 $\mu g/m^3$ or more and estimates of the number of people in the U.S. with at least 1 day of a level above 100 $\mu g/m^3$ per year increasing up to 27-times over the last decade (Childs et al. 2022).

Wildfire smoke exposure is broken into two broad categories, occupational exposure and general population exposures. In the studies identified in section 1, three types of exposure estimation were used: 1) occupational exposure based on employment records; 2) residential proximity to wildfire; 3) modeled wildfire $PM_{2.5}$ exposure concentrations. These are further described below.

For occupational studies, the assessment of WFS exposure is usually based on employment records. The assessment is typically based on information on types and numbers of fires a firefighter attended, information on the firefighter (e.g., years of employment, type of firefighter), and potentially types of tasks a firefighter performed during an incident/deployment. The quality of occupational WFS exposure assessment is largely dependent on the employment data extraction tool used to estimate exposure and is subject to varying levels of measurement error, though this will likely be non-differential as these are all derived from employment records. Recently, there are efforts to capture real-time measures of WFS exposure from rapidly deployed monitors during wildland fires; however, thus far, this approach has typically been used to enhance characterization of exposures, rather than long-term exposure monitoring conducive to evaluating associations with chronic health outcomes.

In general population studies, WFS exposure is usually assessed using spatial estimates of proximity to wildfire events or modeled wildfire $PM_{2.5}$ exposure concentrations. Proximity measures typically categorize individuals as exposed/unexposed (e.g. proximity to a fire), or based on counts of exposure (e.g., number of fires, number of smoke days) based on locations and dates of wildfires in relation to residential locations within a buffer area; this is subject to non-differential measurement error as it does not take into account several factors that would influence exposure, including intensity of exposure or composition. While proximity is a factor, so are other factors such as meteorological factors including wind direction and speed which influences smoke plumes. Exposure estimation of wildfire $PM_{2.5}$ is typically based on complex modeling that uses satellite data, chemical transport data, ground level monitoring data, meteorological data, and fire-specific data (e.g. smoke plumes, fire locations and perimeters) to estimate wildfire $PM_{2.5}$ concentrations (Qiu et al. 2024; Orr et al. 2025). There are three main types of modeling methods used to estimate wildfire $PM_{2.5}$: 1) chemical extraction (distinguishing wildfire $PM_{2.5}$ from other source $PM_{2.5}$ based on the chemical composition measured by air samplers); 2) thresholding (setting a concentration of $PM_{2.5}$ above which $PM_{2.5}$ is assumed to be mostly from wildfires – this may be

accomplished using air quality index (AQI values), Environmental Protection Agency (EPA)-assigned wildfire days, and smoke wave days; lastly, 3) using additional wildfire data (including satellite observations to map wildfire detection and monitoring, satellite data detection using thermal anomalies, reflected radiation, and smoke plumes, and satellite data to detect fire-affected areas from land imaging) (Orr et al. 2025). These data sources are then mapped to a residential location to estimate the individual-level exposure. The utility of these models is dependent on their ability to adequately distinguish wildfire $PM_{2.5}$ from non-wildfire $PM_{2.5}$. Each method has strengths and limitations, and the validity of wildfire $PM_{2.5}$ estimation methods used for a specific model for should be evaluated (Connolly et al. 2026). Wildfire $PM_{2.5}$ modeling is typically considered more accurate for assessing WFS exposure compared to proximity measures; however, although WFS is believed to be composed primarily of $PM_{2.5}$, modeled estimates of wildfire $PM_{2.5}$ do not account for other wildfire-related exposures (Reid et al. 2005; Vicente et al. 2013). Other types of exposure estimation used for WFS in general population studies include measurements from the nearest regulatory monitor, and the presence or absence of smoke. Concerns regarding potential for bias due to exposure modeling methods will be addressed in the exposure section, rather than in the analytic section.

Regardless of exposure model precision, spatially-based exposure estimation is dependent on accurately capturing where people are located, which is subject to varying levels of error, particularly if information is only known for a single point in time (e.g. study baseline); measurement error could occur if information on residential moving is not incorporated into exposure estimation. However, because wildfire $PM_{2.5}$ concentrations tend to vary at a regional level, residential movement within the same region is not likely to introduce substantial estimation error, whereas movement into or out of the region may result in greater error. In addition, general population exposure estimates also do not account for behaviors and mitigation factors that might impact exposure levels, such as use of home filters and infiltration of WFS into residences, time inside/outside, proportion of time spent in residence, evacuation to shelters or out of the area. These factors may result in classical and/or Berkson error in exposure estimation.

Questions and guidance

Core question: Is there concern that the exposure assessment did not distinguish between exposed and non-exposed people or among exposure categories at a relevant time window of exposure?

Table 1-5. Exposure measurement/misclassification bias questions, guidance, and response options

Signaling question	Guidance	Response Options
Exposure surrogate: Is there a concern that the exposure proxy did not adequately represent the exposure of interest and the appropriate time window of exposure for the outcome of interest? If yes, was this true for all exposure metrics, or a particular metric?	Ideally, studies would have measurement of WFS or its components over the relevant time period. All available studies use either employment classifications of exposure to WFS, proximity to WFS, or estimates of $PM_{2.5}$ attributed to WFS based on modeling (e.g., satellite based/public databases). Exposure misclassification will vary based on the quality of the exposure estimation methods (see above), however, exposure misclassification of WFS is likely to be non-differential and bias towards the null. Ideally, exposure assessment in the general population would also incorporate time at geographical location, and include an evaluation of behavioral factors that may modify exposure level (e.g. in home behaviors, evacuation, etc). Ideally, occupational studies would include information on the characteristics of fire incidents (e.g., size, intensity, and frequency). Studies that only capture some of the cumulative exposure to wildfire over time, may misclassify exposure, this would likely be non-differential exposure misclassification and bias towards the null.	**No/minimal concern** The exposure assessment used in the study closely approximates the exposure of interest. Exposure groups are adequately separated. Any measurement error is non-differential and small in relation to between-individual variation compared to differences between groups. **Some concern** Study may use a proxy such employment records and collects extensive exposure information allowing for good discrimination between exposed and non-exposed, and potentially between exposure categories, and the study characterizes multiple metrics of wildfire smoke exposure. **Moderate/major concern** The exposure proxy does not capture the exposure (wildfire smoke exposure) well or the exposure assessment is not extensive enough to be confident that exposed and non-exposed, and/or exposure categories, do not overlap somewhat. Minimal additional exposure metrics are available. Nonetheless, it is evident that the exposed are, on average, more highly exposed to wildfire smoke than the 'unexposed'.
Exposure measurement: Is there concern about measurement error of the proxy or exposure of interest? Is there concern about the use of the collected data to classify exposure groups?	As of this report, no validated instruments are in use for assessing exposure to WFS. All studies use either employment classifications of exposure to WFS, proximity to WFS, or estimates of $PM_{2.5}$ levels attributed to WFS.	

Signaling question	Guidance	Response Options
If yes to either, is there concern that measurement error resulted in inadequate separation of groups with respect to exposure? Did any misclassification vary by exposure category (such as non-exposed, high and low exposure) Is there concern that the exposure classification did not capture the variability of exposure?	Studies using no WFS exposure as the referent group are likely to have better exposure contrast as opposed to low WFS.	**Critical concern** Exposure assessment is not at the individual level and/or the exposure assessment proxy does not approximate the exposure of interest and there is strong evidence that it is unable to differentiate exposed and unexposed participants. No additional exposure metrics.
Observation and differential recall bias: Is there concern that knowledge of the outcome (e.g., observation or recall bias) may be differential and potentially bias the exposure assessment (away from the null)?	As of this report, all studies of WFS are cohort studies that use records, or spatial estimates of WFS exposure and do not depend on participant recall for exposure data. If any studies identified in the future use participant derived information for exposure, there may be differential recall bias if cases remember WFS differently than controls due to prior respiratory conditions linked to WFS exposure. However, this is not a concern in studies where exposure is classified through employment records or through geographical and PM data. Differential recall bias is not a concern in cohort studies.	
Is any misclassification differential or nondifferential, and what is the predicted direction or distortion of the effect estimate (if there is adequate information)?	Non-differential exposure misclassification most likely biases towards the null and is most likely present in all studies.	

1.2.3. Outcome Misclassification

Assessment of the potential for bias (i.e., risk of bias) due to measurement error or other outcome misclassification types considers (1) how well the study outcome represents the outcome of interest, (2) the accuracy of the outcome measurement methods, and (3) the potential for observation bias. The evaluation of follow-up length is usually considered in the assessment of study sensitivity. Relevant cancer statistics are discussed below, and questions and guidance are provided in Table 1-7.

Relevant cancer statistics

Incidence and mortality rates, as well as 5-year survival, for the major cancer sites of interest in relation to wildfire smoke exposure (all cancers, breast cancer, colorectal cancer [CRC], and lung cancer) are presented in Table 1-6 for the countries in which the included studies were conducted. All studies were conducted in high-income countries (Australia, Canada, the United Kingdom, and the United States), except for one study from Brazil, an upper-middle-income country. Hereafter, Australia, Brazil, Canada, the United Kingdom, and the United States are referred to as the relevant countries.

To facilitate comparisons across studies conducted in different countries, our protocol reports global age-standardized incidence and mortality rates (ASRs) per 100,000 population from GLOBOCAN 2024 (Ervik et al. 2026; Sung et al. 2026). Age-standardized rates account for differences in population age structure and therefore differ from country-specific age adjusted rates, particularly for countries with older populations, such as the United States.

Worldwide, the 2024 ASRs for all cancers (including nonmelanoma skin cancer [NMSC]) are 194.9 per 100,000 for incidence and 87.8 per 100,000 for mortality. However, cancer incidence and mortality vary substantially by country and geographic region (Ervik et al. 2026). Among the relevant countries, incidence rates for all cancers and most cancer sites of interest were generally higher than the global ASRs, whereas mortality rates were generally similar to the global averages. Brazil was an exception, with overall cancer incidence rates more comparable to the global ASRs. Lung cancer also differed from the overall pattern: incidence and mortality rates were higher than the global averages in the United Kingdom and Canada but lower in Brazil (see Table 1-6). The most common cancers, globally and across countries, are female breast cancer, colorectal cancer, lung cancer, and prostate cancer in men.

The pattern of higher cancer incidence in high-income countries despite similar mortality rates likely reflects disparities in cancer detection, access to care, treatment, and survival. Five-year survival also varies substantially by cancer site. In the relevant countries, 5-year survival is lowest for lung cancer (approximately 18% to nearly 30%), highest for breast cancer (~90%, Girardi et al. 2026), and intermediate for colorectal cancer (~ 60% to 70%, but lower in Brazil, ~50%). Consequently, mortality may be a less informative outcome than incidence for evaluating the association between WFS and breast cancer risk, and, to a lesser extent, colorectal cancer risk, because survival after diagnosis is relatively high for these cancers. [Sources for survival for lung and CRC: Australia, Lung and CRC (AIHW 2021); Brazil, Lung (Emmerick et al. 2023), CRC (Monteiro Dos Santos et al. 2026); Canada: Lung (Statistics Canada 2025a; 2025b), CRC (Canadian

Cancer Society 2023); UK, Lung and CRC (Nuffield Trust 2026); USA, (SEER 2026, 5-year survival rates, 2016-2022)]

Table 1-6. Global age-standardized cancer incidence and mortality rates (per 100,000) for selected cancers and countries[a]

Cancer	Worldwide		Oceania		Europe		North America				South America	
			Australia		United Kingdom		Canada		United States		Brazil	
	Inc	Mort	Inc	Mort	Inc	Mort	Inc	Mort	Inc	Mort	Inc	Mor
All cancers	195	88	461	82	306	97	345	88	359	80	211	92
Breast[b]	48	13	104	12	93	14	83	12	97	12	59	14
CRC	19	8	35	8	31	11	29	9	27	8	22	10
Lung	24	16	24	15	32	20	31	21	30	16	14	12

Sources GLOBOCAN, International Agency for Cancer Research/World Health Organization, (Ervik et al. 2026) (2024 age standardized incidence and mortality rates)
Abbreviations: CRC = colorectal cancer, Inc = incidence, Mort = mortality
[a]The cells report on the global age-standardized rates (ASR) per 100,000 people for cancer mortality and incidence. The global rates account for differences in population age structure and therefore differ from country-specific age adjusted rates, particularly for countries with older populations, such as the United States.
[b]Breast cancer rates are for female breast cancer.

Female breast cancer

Female breast cancer comprises a heterogeneous group of diseases that vary by cell type of origin (e.g., ductal or lobular), molecular or biomarker subtype (e.g., hormone receptor and HER2 status), tumor grade, stage of disease progression (e.g., invasive or metastatic disease), and timing of development in relation to menopausal status. These different diseases vary in their etiology, progression, prognosis, and response to clinical treatment.

The most common type of breast cancer, accounting for approximately 80% of cases, is invasive or infiltrating ductal carcinoma, which originates in the lining of the breast ducts. Invasive lobular carcinoma arises from the cells lining the milk-producing lobules and is the second most common histologic subtype. Less common forms include inflammatory breast cancer (1–5% of cases), in which cancer cells block lymphatic vessels in the breast, and Paget disease of the breast (approximately 1% of cases), which involves the nipple and areola (NCI 2025; Stanford Medicine 2026).

Breast cancer is also classified by the expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). These molecular markers are important determinants of prognosis and guide treatment decisions, including endocrine therapy for hormone receptor-positive tumors and HER2-targeted therapies. Approximately 80% of breast cancers are hormone receptor-positive, while 10–20% overexpress HER2. Triple-negative breast cancer (TNBC), which lacks expression of ER, PR, and HER2, accounts for approximately 10–15% of breast cancers. TNBC is typically diagnosed at a later stage, tends to grow more rapidly, has a higher risk of recurrence, and is more difficult to treat than other invasive breast cancer subtypes. Both inflammatory breast cancer and TNBC are more frequently diagnosed at younger ages and occur more commonly among Black women than White women (NCI 2025; Stanford Medicine 2026).

Pre- and postmenopausal breast cancers can also be considered distinct diseases because they differ in hormone receptor and HER2 expression patterns (Erdogdu et al. 2024) and appear to have somewhat different etiologies. Risk factors (e.g., body mass index (BMI), neighborhood socioeconomic status (SES), alcohol intake, age at menarche) may differ in both magnitude and direction of association according to menopausal status and tumor subtype, including hormone receptor and HER2 status (Cotterchio et al. 2003; Jalili et al. 2025; Dauccia et al. 2026). TNBC also has distinct epidemiologic and biological characteristics (Kumar et al. 2024).

Ideally, epidemiologic studies should stratify by receptor status, especially TNBC, and menopausal status to assess any subtype specific associations.

Lung cancer

Lung cancer is broadly classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is generally slower growing and accounts for approximately 85% of all lung cancer cases. The major histologic subtypes of NSCLC include: adenocarcinoma (ADC), which accounts for approximately 40% of all lung cancers and typically arises in the peripheral (outer) regions of the lung; squamous cell carcinoma (SCC), which accounts for approximately 25–30% of cases and usually

originates in the bronchi; and large cell carcinoma (LCC), an uncommon but rapidly growing subtype that accounts for approximately 10–15% of cases (Siddique et al. 2024). In contrast, small cell lung cancer (SCLC) accounts for approximately 15% of lung cancers and is an aggressive, rapidly growing malignancy with a poor prognosis.

Tobacco smoking is the primary risk factor for all major lung cancer subtypes; however, the strength of the association varies by histology. SCLC and squamous cell carcinoma are most strongly associated with tobacco smoking, whereas adenocarcinoma is the predominant subtype among individuals who have never smoked, accounting for approximately 60–80% of lung cancers in this population (Murphy et al. 2025). Ambient air pollution has also been most consistently associated with an increased risk of adenocarcinoma (Wang et al. 2025). Therefore, if wildfire smoke (of which PM is a major component) contributes to lung cancer risk, it is biologically plausible that its strongest association would also be with adenocarcinoma compared with other lung cancer subtypes. Ideally, studies should conduct sub-analyses specific for ADC to have greater sensitivity to detect an effect.

Colorectal cancer (CRC)

CRC refers to cancers that form in tissues that line the colon and the rectum. Of the five histological subtypes– adenocarcinoma, adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma– adenocarcinoma, which originate in the glandular cells, make up 90% of CRC (Dubansky et al. 2023), thus stratifying by CRC subtypes may not be needed; ideally however, studies should stratify by age at onset to distinguish early onset CRC. CRC can also be classified by location (e.g., ascending or right colon, descending or left colon, and rectum) and grade. Some studies may report separate estimates for colon vs. rectal cancer, but in general, both colon and rectal cancers share similar risk estimates.

Cancer definition:

All studies should specify their definition for all cancer, lung, breast, and CRC. For all cancer this should include whether this includes or excludes nonmelanoma skin cancer. Ideally, specific International Classification of Disease (ICD) codes used to define cancer outcomes should be listed.

Questions and guidance

Core question: Is there a concern that the outcome measure does not reliably distinguish between the presence or absence of the cancer under study?

Table 1-7. Outcome misclassification questions, guidance, and response options

Signaling question	Guidance	Response Options
Is there concern that the method of measuring outcome did not represent the outcome of interest? If mortality data are used, do they adequately reflect incidence?	Mortality assessment will miss cases that do not result in death, which is a concern for, breast cancer which has a very high survival rate, and to a lesser degree CRC and all cancer. This would create a bias towards the null.	**No/minimal concern** Outcome methods clearly distinguish between participants diagnosed with a specific cancer type and participants not diagnosed with that cancer. Follow-up and diagnoses are conducted independent of exposure status. Cancers are histologically/cytologically verified (documented in hospital/personal medical records or cancer registry). Cancer incidence (not mortality) is used for cancers with high survival rates.
Is there concern that the disease was not accurately diagnosed? For example: Does misclassification of outcome vary across exposure groups or levels of exposure? If so, were there methods to adjust for any potential bias? Is there concern that the control group may have cancer?	Ideally, cases of cancer should be histologically confirmed and/or undergo independent pathology review (e.g., on a subset of the cases) by the study investigator. Cases should be coded according to international classification standards (e.g., ICD codes). Incidence data from population-based cancer registry sources or hospital pathology data are generally more detailed and accurate than death certificates, as their sources are medical records and cancer registry data.	**Some concern** Cancer diagnoses, or a substantial proportion of cancer diagnoses, are histologically/cytologically verified. Some diagnoses may be verified only clinically but criteria are well documented. Mortality data is used for study with higher survival. Breast cancer studies did not stratify by receptor or menopausal status.

Signaling question	Guidance	Response Options
	Self-reports (or a large percentage of them) should be medically confirmed. Most studies used hospital records, registry, or death records. Proportion of cases ascertained by method(s) other than histological confirmation, and the potential for this to be related to exposure, should be noted. Ideally studies of female breast cancers should stratify by hormone or HER2 status, especially triple negative and menopausal status and to a lesser degree studies of lung cancer should stratify by subtype. Studies that do not stratify will be biased towards the null when evaluating overall breast cancer and may miss associations specific to certain subtypes. Ideally, studies of CRC will stratify by age at onset. Studies that do not stratify will be biased towards the null and may miss associations specific to age at onset.	**Moderate/major concern** Cancer diagnosis and type are self-reported, and neither are verified by cancer registry or medical/hospital records. **Critical concern** There is strong evidence that follow-up and cancer diagnoses are likely related to exposure status or that the methods do not discriminate between diseased and non-diseased participants (unlikely in most cancer studies).
Is any misclassification differential or nondifferential, and what is the predicted direction or distortion of the effect estimate (if there is adequate information)?	Nondifferential outcome misclassification is possible, but unlikely due to medical records, and will bias results toward the null.	

1.2.4. Confounding Bias

The evaluation of confounding is a multi-step process that involves consideration of both study methods and study findings that includes (1) identification of the key confounders, (2) assessment the potential for confounding, and (3) assessment of the effect estimates.

Potential confounders

For the cancers under consideration (i.e., all cancers, breast, colorectal, lung cancers), candidates for evaluation as potential confounders are shown in Table 1-8. Factors which have been established as known risk factors (e.g., identified from authoritative sources such as IARC, RoC) for the cancers of interest are shown in Column 2. The risk factors likely to be also related to WFS exposure by population type (occupational/firefighter, general population) that are considered major potential confounders and shown in Columns 3 and 4. Key confounders are defined as those factors which are likely to be associated with exposure and strongly associated with disease, are not in the causal pathway, and are not correlated with other risk factors. WFS exposure in the general population is determined primarily by wildfire occurrence and proximity to residential location, and meteorology, and unlikely to be associated with many of the known risk factors for the cancers of interest. Known risk factors for these cancers may differ between firefighters and the general population but may not differ within firefighter populations (e.g., wildfire vs. other firefighters).

Potential confounders for the general population are presented in a directed acyclic graph (DAG) in Figure 1-2. Due to the complex relationship between potential confounders, it may not be necessary for a single study to adjust for all listed confounders, and certain confounders are likely study and population specific. Confounders, such as age and calendar year, may be accounted for in the model specification, rather than as an adjustment in the model. Factors that may be in the causal pathway between WFS exposure and cancer outcomes, such as components of WFS (e.g., PM concentrations), intermediate biomarkers of effect (inflammatory biomarkers), and diagnostic markers of cancer (e.g., PSA test for prostate cancer) are not considered potential confounders. Potential confounders are discussed below.

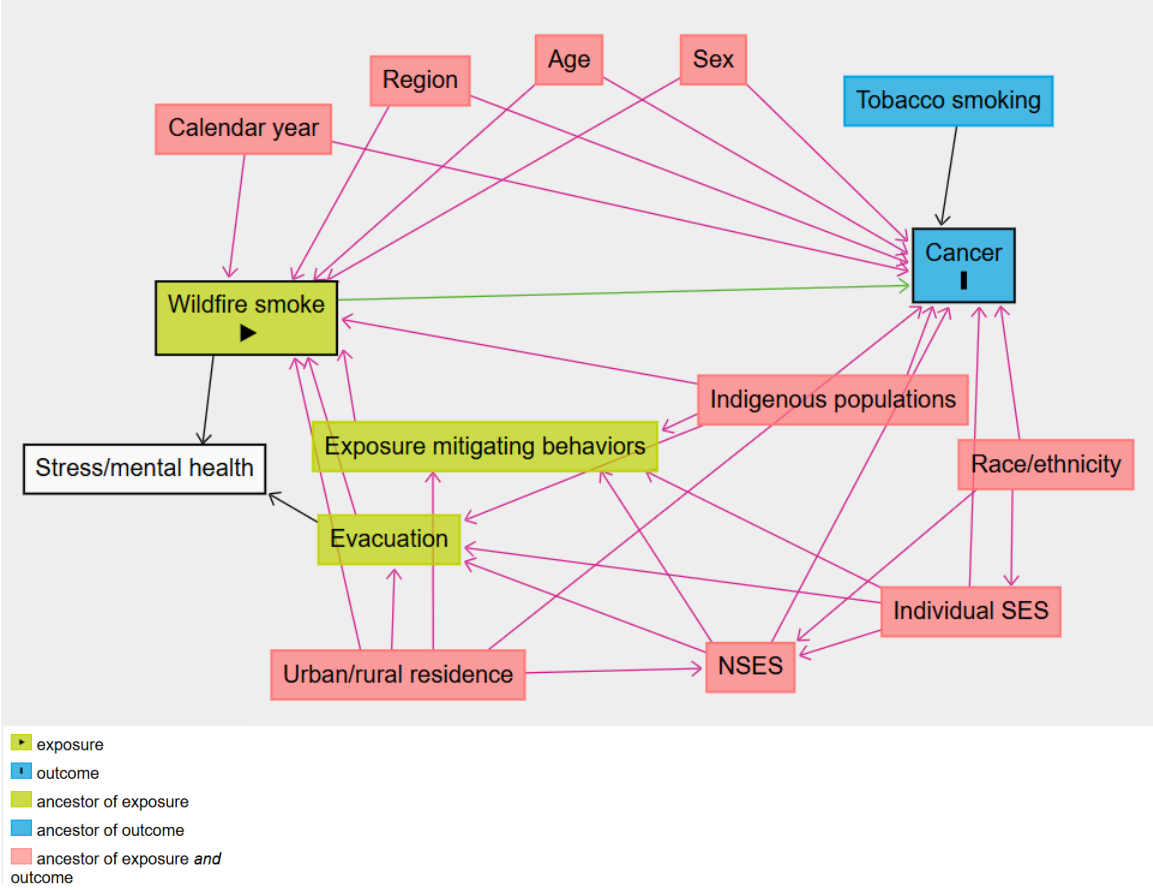

Figure 1-2. Directed acyclic graph for wildfire smoke exposure and cancer outcomes in general populations

DAG created DAGitty (Textor et al. 2016). Abbreviations: SES = socioeconomic status; NSES = neighborhood level socioeconomic status.
Figure Note: DAG is a conceptual diagram depicting wildfire smoke and cancer and potential confounders and effect modifiers. Red boxes indicate potential confounders (ancestors of exposure and outcome). Green boxes indicate ancestors of the exposure, blue boxes indicate ancestors of the outcome (risk factors); these are potential effect modifiers.

Confounders or effect modifiers across cancer types

Age, sex: Ideally, age, sex, and race/ethnicity should be evaluated as potential effect modifiers by stratified analyses in addition to being controlled for in overall analyses as potential confounders.

In general population studies, age and sex may affect personal behaviors related to evacuation or other means to decrease exposure. Age may increase one's risk to cumulative exposure to wildfires by nature of years lived, and is considered a potential confounder or effect modifier.

In firefighter populations, age and sex are considered potential confounders because they may be related to specific assignments and tasks that are associated with wildfire exposure concentrations.

Race/ethnicity: Race and ethnicity are associated with cancer mortality (Islami et al. 2026) and may also be associated with wildfire exposure (Nguyen et al. 2026). The association of race/ethnicity with wildfire exposure is likely driven primarily by associations with neighborhood socioeconomic status (NSES) as discussed below. However, wildfires are more likely to occur near indigenous populations in North America (Canada Public Health Agency 2024; Casey et al. 2024) as these populations live in isolated regions that are susceptible to wildfires. Thus, race and ethnicity should be considered as population specific potential confounders, and ideally should be investigated as potential effect modification by race/ethnicity in general population studies.

Tobacco smoking and exposure to environmental tobacco smoke (ETS): Tobacco smoking is a strong risk factor for lung cancer (~15- to 30-fold increased risk, CDC 2026), and a more modest risk factor for all cancers (~40%, Weber et al. 2021), colorectal cancer (~20% increased risk, with higher risk for rectal cancer, Tsoi et al. 2009), and female breast cancer (~15% increased risks, primarily women diagnosed with breast cancer before menopause or with ER+ breast cancer, He et al. 2022). ETS is also a modest risk factor (~10 to 30% and may vary by subtype of other factors) for lung cancer, female breast cancer, and CRC; however, the strength of the evidence for an association between ETS and the latter two cancers is weak (Taylor et al. 2001; Yang et al. 2016; Possenti et al. 2024).

General population: Despite being established cancer risk factors, tobacco smoking and ETS are unlikely to be important confounders in general population studies of WFS because there is little evidence that either factor is systematically associated with WFS exposure. Nevertheless, tobacco smoke and WFS are both complex combustion mixtures that share many chemical constituents, raising the possibility that tobacco smoking or ETS could modify the health effects of wildfire smoke. In addition, smoking-related comorbidities, particularly chronic respiratory and cardiovascular disease, may also increase susceptibility to cancers following WFS exposure. Accordingly, where individual smoking data are available, studies should consider evaluating tobacco smoking as a potential effect modifier, especially for lung cancer mortality.

Firefighter studies: Tobacco smoking patterns differ in firefighter populations from those in the general population, with firefighters generally having lower smoking prevalence (Jitnarin et al. 2015; Glass et al. 2017; Phan et al. 2022). Consequently, tobacco smoking could confound comparisons between firefighters and the general population if appropriate adjustment is not made. Tobacco smoking is less likely to be an important confounder in studies that compare firefighters with other firefighters (e.g., high- versus low-exposure groups) or in studies of volunteer firefighters, where smoking prevalence is expected to be more similar across comparison groups.

Neighborhood Socioeconomic status (NSES): For studies of WFS exposure in the general population, wildfire exposure may be associated with neighborhood level SES. In the U.S., more disadvantaged areas are prone to higher wildfire $PM_{2.5}$ (Nguyen et al. 2026). For breast cancer incidence and mortality, NSES is associated with cancer mortality and with incidence for some but not all types of breast cancer; NSES is a risk factor for TNBC and HER2 positive breast cancer. For mortality studies on breast cancer, NSES

should be considered a confounder (Jalili et al. 2026). For lung cancer, NSES is associated with both incidence and mortality. These may be driven by a number of different factors, and potentially partially driven by smoking. Ideally, studies on lung cancer incidence and mortality, adjust for NSES (Jalili et al. 2026). CRC incidence and mortality are highest in Black Americans compared to other racial groups (Carethers 2021). There is an indication that CRC mortality is related to race/ethnicity and SES driven by delays in treatment (Ali et al. 2026). Though, not all of the association by race is due to differences in SES (McCullough et al. 2026), the differences in incidence and mortality that are driven by SES, with race as a proxy, are those that are likely acting as potential confounders due to the association of NSES with wildfire.

SES does not predict WFS exposure; however, it may be associated with individual- and neighborhood-level factors regarding mitigation of harmful WFS exposure. Lower neighborhood- or area-level SES and individual SES could be associated with increased WFS exposure, particularly in low SES populations, such as outside laborers without filtration who have to work through smoke events and communities with a lack of resources or knowledge to prevent or mitigate exposure. For high SES individuals and communities, factors that might reduce individual exposure include housing and building conditions (e.g. construction, ventilation, and filtration that controls for indoor WFS infiltration).

Individual SES is associated with cancer incidence and mortality and any correlation with WFS is likely via NSES, thus adjusting for NSES should be sufficient to control for confounding by SES. If studies only adjust for individual SES, this would account for some, but not all of the confounding by NSES resulting in residual confounding by area based socioeconomic factors.

NSES is likely a key confounder and may distort the observed effect if not adequately accounted for when evaluating the association of wildfire exposure and cancer outcomes. Confounding by NSES may bias the results away from or towards the null.

Calendar year: While wildfire exposure has been increasing over time (Hawbaker et al. 2017; Wilner et al. 2025), in most areas, overall cancer incidence has been decreasing, though for some cancer types and ages groups, incidence is increasing. Given the secular trends in both the exposure and the outcome, studies in both the general and firefighter population studies that include a span of time, should adjust for calendar year or other metrics of time. Calendar year is considered a key confounder and may bias the results away from or towards the null.

Geographical Region (U.S.): Wildfire exposure is associated with region as there are certain regions that are prone to wildfires. In the U.S., there are certain regions that are known to have high rates of cancer incidence (Luo et al. 2025) due to a combination of known and unknown factors (Guo et al. 2024). In addition to differing rates, declines in cancer incidence are not universal across the U.S. Although the specific factors underlying regional variation in cancer patterns themselves may not individually be considered confounders, U.S. studies in the general and firefighter populations should account for region in their analysis or study design because both cancer patterns and WFS exposure vary geographically.

Exposure to non-wildfire PM is addressed in the exposure measurement section (1.2.2).

Rural/Urban residence: In the general population, wildfire exposure is higher in rural areas compared to urban areas. Those living in rural areas may have more difficulty in evacuating during wildfire events due to long travel distances and other factors; for example, those in agricultural settings are less likely to evacuate when there are livestock present. Rural/urban residence is also associated with cancer incidence and mortality due to limited access to care in rural areas. Studies of wildfire exposure and cancer in the general population should account for rural/urban residence, as it is considered a confounder. If an exposure assessment method considers evacuation or rural/urban location, this will account for any confounding by rural/urban residence.

Stress and mental health: Stress and mental health have both been linked to wildfires in the general population, in particular in the recovery period after large scale events. Increases in adverse mental health after wildfires include depression, anxiety, post-traumatic stress disorder (PTSD), psychological stress and distress; evacuation itself has also been associated with depression and adverse mental health outcomes (Teigen et al. 2026). Firefighters deployed to wildfires have high rates of adverse mental health conditions including PTSD, anxiety disorders, and depressive disorders (Canada Public Health Agency 2024). These may act as potential effect modifiers.

Occupational exposures in firefighter populations

Co-exposures: Several substances that might occur as co-exposures with WFS, particularly in occupational settings, are also risk factors for cancer. These include diesel exhaust from vehicles and generators used in firefighting activities, diesel and gas exposure for firefighters performing lighting tasks in prescribed burns, firefighting chemicals including fire retardants and other fire suppressants, such as aqueous film forming foam (AFFFs), and chemicals found in firefighting protective gear, including per- and polyfluoroalkyl substances (PFAS) (NIFC 2022; USDA 2026).

Other firefighting: In the study of wildland firefighters, many firefighters do not exclusively attend to wildland fires or may only work seasonally as a wildland firefighter. For firefighters who also attend to non-wildfire fires (e.g. structural fires), other firefighting activity may act as a confounder.

Key confounders for the general population and firefighter populations are outlined in Table 1-8.

Table 1-8. Potential confounders for all cancers and cancers of the lung, colorectal cancer, and female breast cancer by study population

Cancer site	Cancer risk factors	Firefighter population potential confounders	General population potential confounders
All cancers	None	*Potential effect modifiers or confounders:* Stress and mental health *Key confounders:* Age, sex Calendar year Tobacco smoking (lung cancer, if comparing to the general population) Co-exposures: e.g. non-wildfire firefighting, diesel exhaust, PFAS, AFFFs	*Potential effect modifiers or confounders:* Age, sex, individual SES, race/ethnicity, indigenous populations, tobacco smoking (lung cancer, mortality), stress and mental health *Key confounders:* NSES Calendar year Region Rural-Urban
Female breast cancer (vary by pre-post-menopausal stats and hormone/HER2) status	**Reproductive factors**: later age at first full-term pregnancy, lower parity, oral contraceptive or hormone therapy use, diethylstilbestrol breastfeeding (preventive) **Diet, lifestyle, and pharmacologic factors**: alcohol consumption, tobacco smoke, obesity (complex pattern dependent on timing), low physical activity, oral contraceptive or hormone therapy use, dioxin, diethylstilbestrol **Occupational or environmental agents**: night shift work, x and gamma radiation, ethylene oxide, polychlorinated biphenyls, dieldrin		
Colorectal cancer	**Diet and lifestyle**: Lack of physical activity, obesity, consumption of red and processed meats, low fiber diet, alcohol consumption, tobacco smoking **Occupational agents**: X-and gamma radiation, asbestos, firefighting		

Cancer site	Cancer risk factors	Firefighter population potential confounders	General population potential confounders
Lung	Demographics; Family history of cancer or lung cancer **Diet and lifestyle**: Vegetable and fruit consumption, High dose beta-carotene supplements, opium use, tobacco smoking, environment tobacco smoking **Indoor or outdoor air Pollution**: benzene, metals, coal, soot, indoor coal or biomass use, frying emissions, diesel exhaust, engine exhaust, outdoor air pollution (including PM) **Other environmental or occupational**: Arsenic, radon and ionizing radiation, dioxins, diazinon and numerous occupational		

Sources: WCRF 2018; IARC 2022

Questions and guidance

Core question: Is there a concern that either the methods are inadequate or there is inadequate information to evaluate potential confounding?

Table 1-9. Confounding questions, guidance, and response options

Signaling question	Guidance	Response Options
Is there concern about the measurement of co-exposures or lifestyle risk factors measured in the study? If no data are provided about confounders, are surrogate data on potential confounders available?	Ideally, quantitative information on lifestyle factors should be assessed by in-person interview by interviewers blinded to the status of the respondent, rather than via proxy respondents. Residual confounding is more likely when only limited qualitative information on a given risk factor (dichotomous yes/no) is available. Studies should provide, at minimum, data on the distribution of potential confounders among the exposed and unexposed in cohort studies. In some cases, data may be available on potential confounders in sub-samples, which can help provide interpretation of the prevalence of the potential confounder in the exposed and unexposed or cases and controls. In addition, data on diseases associated with wildfire smoke (e.g., respiratory diseases such as COPD) may provide indirect information about risk factors for specific cancer endpoints of concern.	**No/minimal concern** The study measured all major potential confounders (see above) and/or used appropriate statistical analyses or designs (e.g., stratification, study population restriction by confounding factor) to address them. Final statistical models should, however, only include "actual" confounders and not variables that have minimal effect on the risk estimate. **Some concern** Statistical models or designs did not address all major confounders; however, external other information was available to partially evaluate them, or the analysis controlled for surrogates of the potential confounder. **Moderate/major concern** Statistical models or designs did not address major confounders. **Critical concern** There is strong evidence that the effects of the exposure cannot be distinguished from the effects of potential confounders.
Is there concern that the design or analysis may not adequately address important confounding through	External information can be used to account for potential confounding.	

Signaling question	Guidance	Response Options
matching, stratification, multivariable analysis, or other approaches? Is there additional information available to evaluate potential confounding or conduct sensitivity analyses (indirect adjustment)? Is there concern that controlling for particular variable would result in bias (e.g., variable is in the causal pathway or other reasons)? Is there concern that not adjusting for one or more confounders is expected to differentially favor outcomes in those with higher or lower levels of exposure?	Care should be taken to assess whether models are over-controlled and controlling for factors on the causal pathway or a factor that is part of exposure, would introduce a bias.	
What is the direction and magnitude of confounding?	Positive confounding biases the estimated risk estimate away from the null and negative confounding towards the null.	

1.2.5. Analysis Bias

Currently, all studies included in the evaluation are cohort studies; none of the ecological studies met our inclusion criteria and, therefore, are not being included.

As mentioned in the exposure assessment section, a portion of the studies measured exposure to WFS via modeled PM concentrations using quantitative approaches. The potential for exposure misclassification based on these modeling approaches is being considered in the exposure misclassification section (Section 1.2.2).

Our evaluation includes consideration of multiple individual cancer outcomes in addition to all cancer sites (not specified). Given the variability of latency periods by cancer site, it is reasonable to include analytical methods that may account for a lag (see Study Sensitivity below). In addition, lag models help address potential concern for healthy worker survivor effect. Consideration of an appropriate analytical approach should be given when accounting for an exposure lag in statistical models.

Note that controlling for unnecessary variables (i.e., control that might reduce precision but does not bias the risk estimate) is addressed in this domain as an analytic issue, while analysis related to actual confounding is addressed in the confounding domain.

Correction for multiple testing (or lack of correction) for studies considering multiple cancer types is not considered a concern for bias. Correction for multiple testing adjusts the threshold for statistical inference for study findings, and thus impacts statistical inference, and is useful in exploratory, non-targeted analyses, or large scale analyses (e.g., GWAS studies) which does not apply to any of the evaluated hypothesis-driven cancer epidemiology studies. The use of correction for multiple testing does not pose a threat to the validity of an individual analytic model for an exposure (WFS) and an individual cancer outcome.

All studies should address how missing data are handled the analysis. If there is a large proportion of missing data that is not appropriately accounted for in the analysis, this can create bias towards or away from the null.

Questions and guidance

Core question: Is there a concern that the data assumptions and analysis were not adequate or that the study did not conduct relevant analyses of available data?

Table 1-10. Analysis bias questions, guidance, and response options

Signaling question	Guidance	Response options
Data assumptions		**No/minimal concern**
Is there concern about whether the data assumptions used in the statistical analysis were adequate?	For continuous exposure data, data should be appropriately transformed or reported that an assumption of linearity is appropriate. Typically, models using continuous wildfire PM concentrations will evaluate a risk estimate for a defined unit increase (e.g., $\mu g/m^3$) in wildfire PM. An appropriate and interpretable increment in unit exposure-based risk should be used. Ideally outliers should not be removed without strong justification (as that may be where the effect is strongest).	Study used appropriate models, data assumptions, analytical methods, and handled missing data appropriately. **Some concern** The study uses accepted methods or data assumptions but not the most sensitive or ideal analyses. Missing data: imputed data may raise some concerns or missing data not missing at random with complete case analysis. **Major or critical concern** Strong evidence that the study's analytical methods were so limited that the findings were substantially distorted or uninterpretable.
Statistical model and methods Is there concern about the appropriateness of the statistical model for the study design and adequacy of the conduct of the analysis? If the study data were adequate, did the study use appropriate methods to adequately evaluate exposure-response and latency, or to conduct subgroup analyses?	Ideally, a study should use the appropriate models (e.g., Cox proportional hazard regression, Poisson regression) for the study design, with appropriate approaches (e.g., evaluation of proportional hazard assumption being met). If exposure-response and exposure lag were evaluated, models and modeling techniques would be statistically appropriate. For example, should exposure be measured by quantile of WF PM exposure, is there a separate linear test for trend across quantiles to measure exposure-response.	
Is there concern about "over-controlling", i.e., controlling for variables that are not necessary?	Controlling for variables that are not related to exposure or disease will most likely cause a loss in precision of the risk estimate.	

Signaling question	Guidance	Response options
Missing data Is there concern that missing data may have biased the findings? • Is there concern that missing data for exposure, outcome, or any potential confounders is substantial? • Is there concern missing data was not handled by an analytically appropriate method (e.g., sensitivity analysis, imputation of missing data)? • Do missing data strategies consider assumptions of the data, such as if the data are missing completely at random, or missing at random?	Ideally, there should be little to no concern that missingness of data is related to both exposure and disease and missing data are missing completely at random. Missing data should be handled appropriately based on the underlying data.	
What is the direction, magnitude, and impact of this bias on the effect estimate?	It may be difficult to ascertain for most analyses whether any bias is differential or non-differential.	

1.2.6. Study Sensitivity

Study sensitivity is the ability of a study to detect a true effect or hazard (Cooper et al. 2016) and is analogous to the term "informativeness" used in the preamble to the IARC Monographs (IARC 2019; Samet et al. 2020). Studies with low risk of bias, but which lack sensitivity, may not be informative for reaching public health decisions about a potential causal relationship between exposure and outcome. Our assessment of study sensitivity includes consideration of (1) study size or the numbers of exposed and non-exposed participants, or cases and controls, (2) exposure contrast and window, and (3) latency. The overall sensitivity evaluation requires an integration of each of these factors.

Questions and guidance

Core question: Does the study have adequate sensitivity to detect an effect from exposure to wildfire smoke (if present)?

Table 1-11. Study sensitivity questions, guidance, and response options

Signaling question	Guidance	Response
Statistical power: Is there concern that the numbers of exposed cases are not adequate for detection of an effect in the exposed population or subgroups of the exposed population?	When both exposure and disease are rare, statistical power is largely determined by the number of exposed cases, and larger studies are generally considered to be more informative.	**Minor concern** The study has an adequate number of exposed participants, with substantial exposure (level, duration, or range) and with adequate duration of follow-up for latency status.
Exposure contrast and window: Is there concern that the levels, duration, or range of exposure of the population at risk in cohort and case-control studies are not sufficient or adequate for detection of an effect of exposure? - Does the exposed group include individuals with a low or unknown probability of exposure?	Dilution of risk estimates using an overly broad categorization of exposure (e.g., exposed/not exposed) can occur when there is large variation in exposure level and/or duration captured within a given exposure grouping . Metrics which adequately capture variation in exposure within a population are, therefore, ideal. Studies in wildfire fighters with higher exposure e.g., throughout a season or over several seasons, may be more sensitive than those in populations with low exposure, e.g. to a single or occasional wildfires. Further, the ability to evaluate exposure-response relationships depends on an adequate range of exposure (in intensity or duration) among the study participants, and adequate numbers of participants in each exposure category.	**Some or major concern** Study has less than ideal number of exposed participants, poor exposure contrast or metrics to determine level/range/duration of WFS exposure, or short duration for latency. **Critical concern** Study with few exposed participants, inadequate latency period and/or very minimal exposure contrast.
Latency: Is there sufficient elapsed time between when the exposure occurred and when outcome occurred to allow for a cancer induction period?	Cancer latency (i.e., tumor induction period) information specific for WFS exposure is not available. Minimal estimates for latency for specific cancer based using Weibull Model (Nadler and Zurbenko 2014); however, latency can vary widely by the carcinogen. Cancer incidence and mortality are both subject to adequate latency periods. Estimated latency periods: *(estimates vary and differ based on type of exposure)* • Lung, 10-20+ years (Berg et al. 2023);	

Signaling question	Guidance	Response
	• Breast cancer (female), ~20 years (Olsson et al. 2003), with differences by subtype • Colorectal cancer, 10-25 years (Hicks et al. 2023) However, it is possible that latency may be shorter in sensitive populations who may have underlying health conditions or diseases. If cohort studies of wildfire exposure and cancer include participants of a younger average age than the general population, they may need a longer follow-up time for cancer development. Given some WFS exposure is modeled based on PM concentrations, the use of lag and non-lag models may both be of relevance. Latency can also be inferred by duration of exposure.	

1.2.7. Judgment for Study Informativeness for Health Hazard Evaluation

Box 1-1. Study Informativeness-Level Judgement

High: no minimal concerns about most potential biases, high or moderate sensitivity.

Moderate: low, minimal, or some concerns about most potential biases.

Low: major concerns about several biases, sensitivity rating varies. Depending on the direction and distortion of the potential biases, the study may still be informative for the cancer hazard evaluation and can help explain heterogeneity of the findings.

Inadequate (very rare): critical concern about any bias, sensitivity rating varies.

How well a study can inform the cancer hazard assessment is based on consideration of both the potential (or risk) for biases (i.e., study quality) and consideration of study sensitivity for each database (Box 1-1). Serious concerns about risk of biases would result in lower study informativeness; however, a well-designed study with low study sensitivity (such as few exposed/expected cases for a specific endpoint) could be given a lower ranking. When adequate information is available, a judgment is made for the direction and distortion from the overall biases for a study or whether it has low sensitivity to detect an effect. Studies with critical concern for bias in a domain are considered to be inadequate and are usually not brought forward to the cancer evaluation. The impact of the bias on the risk estimate is considered in the cancer hazard evaluation.

For transparency, the study informativeness assessments are included in the monograph, and the findings may be briefly summarized, or evaluated in sensitivity analyses. The goal of the evaluation is to consider all the evidence and triangulate across the body of evidence, rather than exclude studies from consideration. Studies raising critical concern about bias (which is very rare) in at least one domain may be evaluated in the sensitivity analysis. The overall judgment of study informativeness is not meant to be an algorithm that sums up the ratings across domains. For databases in which the quality of the studies varies considerably, informativeness-level categories may be combined, such as “moderate or low”.

1.3. Evidence Evaluation and Integration

Level of evidence conclusions are reached by (1) interpreting the confidence in the evidence from each study, (2) integrating the evidence across studies, and (3) applying the RoC listing criteria (below) to the assessment. The most informative studies (i.e., lowest risk of bias and greatest sensitivity to detect an effect) are given the most weight in the evaluation. The identification of the potential for specific types of uncontrolled bias or confounding, the assessment of study sensitivity, and the presence of effect modification are also used to interpret the findings from studies and to help explain heterogeneity across studies.

Report on Carcinogens Listing Criteria

The listing criteria defines two categories; the evidence is considered inadequate if it does not meet the criteria for limited:

Sufficient evidence of carcinogenicity from studies in humans

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

Limited evidence of carcinogenicity from studies in humans

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded.

General information on evidence evaluation and integration are found in the 2025 RoC Handbook. Considerations specific to human cancer studies of wildfire exposure are included here.

Bias impact

We use a multi-step approach for evaluating the impact of bias on the body of literature. First, we assess the potential for bias as described in section 1.2. Next, we evaluate the impact (magnitude, direction) of bias of the individual study's effect estimate using the quantitative and/or qualitative methods, including those developed by an IARC working group, Bias Assessment in Case–Control and Cohort Studies for Hazard Identification (Berrington de González et al. 2024). Lastly, we evaluate the impact of bias across studies.

1.3.1. Evaluation of the Evidence from Individual Studies

The presence of potential bias (such as selection bias, information bias from misclassification of exposure, or outcome or confounding) in a study does not necessarily mean that the study will be excluded from the assessment. Conclusions about the evidence from each study will consider the strengths and weaknesses of the study, the direction and distortion of the biases, and the strength of the association between exposure to the substance and the cancer end point. Our assessment of individual study bias impact will focus on confounding, but other types of bias domains will be considered as needed. All studies will be evaluated by a primary and a secondary reviewer at minimum, and disagreements about evaluation of domains or studies will be discussed by

the evaluation team (See Appendix A). The evaluation team consists of individuals with expertise in environmental epidemiology, cancer epidemiology, and systematic review.

Bias impact in individual studies

Confounding

If there are concerns about confounding (e.g., potential for bias) and adequate information is available, we may conduct qualitative (e.g., negative controls) or quantitative bias assessment, such as indirect adjustments using exposure prevalence data (when available) or application of quantitative bounding analysis to calculate the lower bound for a given confounder to evaluate bias at the individual study level, consistent with guidance from the Berrington de Gonzalez et al. (2024).

Confidence in the evidence of individual studies

The level of confidence in the evidence from the individual studies (rated as "moderate to strong evidence", "some evidence", "null", or "inconclusive") will be reached by considering the strength of the association, the potential for specific biases or confounding, the expected directions of distortions as well as the impact of these potential biases or unaddressed confounding on the effect estimate, and the sensitivity of the study to detect an effect. In addition to considering the potential for biases in context with strength of the findings (magnitude of the effect and exposure response relationships), confidence in a study also considers other factors such as internal consistency.

Guidelines for evaluating the overall confidence in the evidence from each study are as follows:

Moderate to strong evidence: Elevated effect estimates associated with WFS are observed across different exposure metrics, different populations, or in different subgroup analyses, with at least one estimate having a confidence interval that does not include one. The evidence generally comes from studies with lower potential for bias. However, studies with a higher potential for bias may also contribute when the expected direction of the bias is toward the null or when the impact of the bias is not expected to explain the full magnitude of the observed excess risk. Evidence of an association may also be supported by a positive finding from a study with limited sensitivity to detect a true effect.

Some evidence: Elevated effect estimates associated with exposure to WFS are observed with moderate precision for at least one metric of exposure. Studies with higher potential for bias may contribute evidence of an association when the expected direction of the bias is toward the null, the impact of the bias is not expected to explain the full magnitude of the observed excess risk, or the findings are positive despite having limited sensitivity.

Null: Studies which are considered "null" show effect estimates ≤ 1.0.

Inconclusive: Findings vary; the overall direction of potential biases is unknown; potential confounding may explain the findings. Alternatively, studies have very low precision, and the findings may be due to chance.

1.3.2. Evaluation of Evidence Across Studies

Bias impact across studies

If there is adequate information, we may evaluate bias, such as exposure misclassification, selection bias, or outcome assessment, across studies by stratifying studies with high compared to low concern for exposure misclassification. For confounding, studies would be stratified based on whether confounding was accounted for in the design, analysis, or by exclusion of participants at risk of confounding.

1.3.3. Evidence Integration Across Human Cancer Studies

Application of the RoC listing criteria (see Section 1.3) to the body of studies meeting final PECO criteria involves evaluating (1) whether there is credible evidence for an association between exposure to the substance and cancer, and (2) whether such an observed association can be explained by chance, bias, or confounding. Level of evidence conclusions are based on an in-depth and cohesive integration of the body of evidence that systematically evaluates consistency and the key issues – impact of biases, sensitivity, exposure metrics, and effect modification across the studies (Arroyave et al. 2021). We plan to use triangulation methods that integrate findings from different approaches with potentially different sources of biases to evaluate the evidence. For example, consistent results from studies with different sources of biases can help strengthen the confidence of the conclusions (Lawlor et al. 2016). Finally, additional overall considerations — strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure (Hill 1965) — are used to help guide the evaluation of these questions. However, it should be noted that that these are not criteria; except for temporality, no single element is required to demonstrate causality (Rothman and Greenland 2005).

As mentioned in Section 1.1, four types of cancers had an adequate database for conducting a systematic review – all cancers, female breast, colorectal, and lung cancers. The approach to reaching level of evidence conclusions for each cancer type is as follows:

- Integrate the overall confidence of evidence judgements for the individual studies (see Section 1.3.1) to evaluate the strength of the findings and consistency for that cancer.
- Systematically evaluate key issues identified to – overall study informativeness, specific biases and key confounders, exposure metrics, effect modification – using triangulation methods (when appropriate) across studies.
- Consider and evaluate the consistency of cancer outcome definitions across studies.
- Consider other causality considerations (e.g., Hill guidelines) such as temporality and strength of the association (e.g., magnitude and exposure/duration response)
- Apply the RoC listing criteria.

Finally, for each cancer, the confidence of carcinogenic hazard may be contextualized further based on the evidence.

In addition to evaluating the impact of biases on individual studies, we will evaluate the impact of bias across studies (see Section 1.3.2).

Given the size of the database for review, we are not considering a meta-analysis at this time. Within each population type (firefighters/occupational exposure, general population), there are three studies each. This will be revisited if additional studies are identified during the review process that facilitate the conduct of a meta-analysis.

1.4. Reporting and Data Extraction

Detailed information on data extraction and reporting are found in the 2025 RoC Handbook.

1.4.1. Data Extraction

Briefly, data will be extracted from individual studies into a standardized data entry (such as Table Builder, Shapiro et al. 2018). The database contains fields that are specific for the various types of extracted information (such as study population characteristics, exposure and outcome assessment, analytical methods, and results). The instructions for data extraction (questions and considerations) describe the specific type of information that should be summarized or entered into each field. The fields from the database are used to populate tables for the monograph. Quality assurance of data extraction and database entry are accomplished by: (1) review of the data entry by an independent reviewer and (2) resolution of any discrepancies by mutual discussion with reference to the original data source.

1.4.2. Reporting

We plan to include the following elements in our monograph:

- An overview of study characteristics (e.g., population characteristics, exposure assessment methods, outcomes) included in the review, even if not included in the evidence integration for bias, quality, or other reasons.
- A discussion of biases and limitations for each bias domain across studies, in addition to the rationale for the risk-of-bias at the study level.
- A scientific narrative of the interpretation of study findings including a discussion of the confidence in the evidence of each study, heterogeneity across studies (not limited to potential for biases) and the rationale for the conclusion (e.g., consideration of dose-response relationships, consistency, ruling out chance, bias and confounding).
- Findings from studies – reported in summary tables or graphs. We may use heatmaps and forest plots to visualize evidence across studies.
- Preliminary level of evidence conclusions for breast, colorectal, lung cancers, and all cancers.

1.5. Protocol Addendum –Similarity Comparison of Components of WS and WFS

In Part 2 of the Wood smoke and Wildfire protocol, on animal cancer and mechanism evaluation, we presented a plan to statistically evaluate the similarity in the chemical compositions between wood smoke and wildfire smoke (Protocol Part 2, Section 4). The goal of this analysis was to determine if the composition of the two types of smoke were similar enough that hazard conclusions of one (wood smoke) could reasonably be applied to the other (wildfire smoke).

After literature searches and data extraction to identify studies that include information on the chemical composition of both WS and WFS, we determined that the data were inadequate to conduct this quantitative analysis. The reported chemicals, study methods, and exposure conditions varied too widely between studies to conduct a meaningful statistical comparison. As such, we instead will conduct a qualitative assessment with the goal of comparing the presence of components between WS and WFS, which will be part of the evidence integration.

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Appendix A. Roles and responsibilities

A.1. Human Cancer Evaluation Team:

Evaluation teams are composed of federal staff and contractor staff. Procedures are in place to avoid actual or perceived conflicts of interest. Members of the evaluation team have experience or training in conducting literature searches and/or evaluating occupational and environmental epidemiology studies. Researchers have epidemiological expertise and play a role in all parts of the assessment, including assess study informativeness, evidence evaluation and integration, writing, and critical review.

Responsibilities	Member	Affiliation
Project leader (overall) and researcher	Ruth M. Lunn, DrPH	NIEHS
Human cancer project lead and researcher	Sabah Quraishi, PhD	NIEHS
Contract project management and researcher	Whitney Arroyave, PhD	Inotiv
Researcher	Suril Mehta, DrPH	NIEHS
Supporting staff		
Develop search strategy, conduct literature searches, and manage literature	Rachael Kalsch, MLIS	Inotiv
Literature management, document preparation, visualization	Tracy Saunders, BS	Inotiv

A.2. Technical Advisors and Reviewers

Expertise or Role	Member	Affiliation
Protocol reviewer (human cancer assessment)	Abee Boyles, PhD	NIEHS
	Jennifer Ish, PhD	NIEHS
	Bonnie Joubert, PhD	NIEHS

Appendix B. Citation Database Search Terms

Pubmed:

(((wetland*) and (fire*)) OR ((wildland*) and (fire*)) OR (wildfire*) OR ("wildfire"[MeSH Terms]) OR (forest AND fire*) OR (landscape AND fire*))

WOS:

TS=(Fire* AND wetland*)

OR TS=(Fire* AND wildland*)

OR TS=(Wildfire*)

OR TS=(forest AND fire*)

OR TS=(landscape AND fire*)

Scopus:

TITLE-ABS-KEY (fire* AND wetland*) OR TITLE-ABS-KEY (fire* AND wildland*)

OR TITLE-ABS-KEY(wildfire*)

OR TITLE-ABS-KEY(forest AND fire*)

OR TITLE-ABS-KEY(landscape AND fire*)