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Wildfire Smoke Toxicology and Health

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Abstract:	With wildfires increasing in activity in the Western United States and around the world, there is an immediate need to understand the toxic effects of the smoke. This chapter will provide a background of toxicology and apply principle concepts such as dose, duration and frequency to help define the potential effects of smoke exposure. Characteristics that influence toxicity will be discussed, which include particle size, source and temperature and the mixture of chemical constituents. An overview of the routes of exposure, mechanisms of action, toxicokinetics and the role of the immune system will all be covered. The importance and mutual benefits of in vitro, ex vivo and in vivo studies will be discussed. Finally, the chapter concludes by outlining knowledge gaps and research needs.

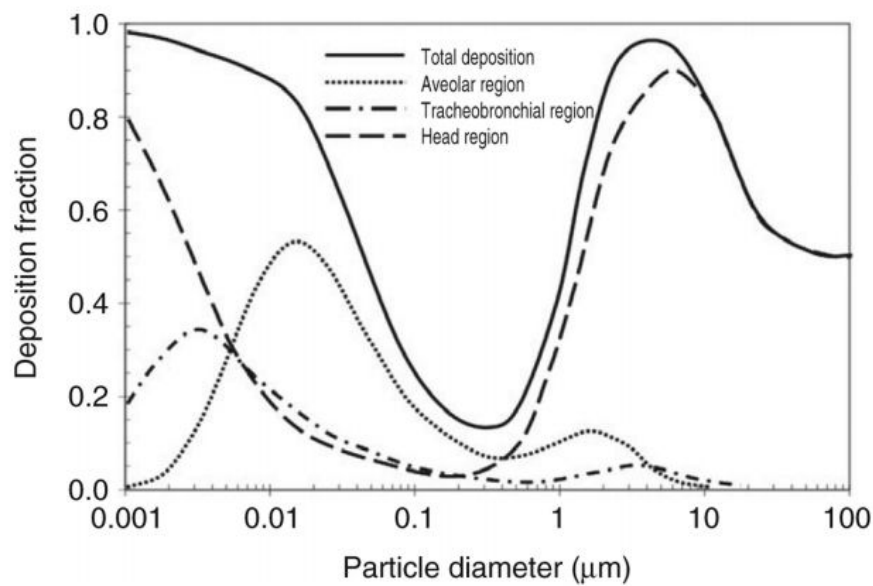


Figure 1. Probability of pulmonary deposition by size fraction.

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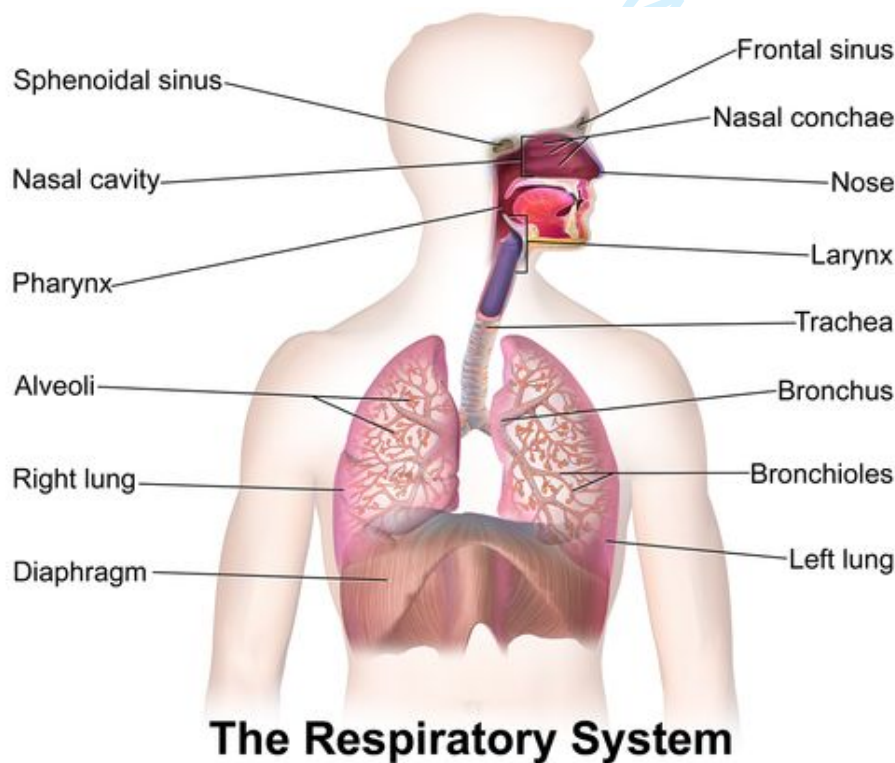


Figure 2. The Respiratory System.

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Chapter 11. Wildfire Smoke Toxicology and Health

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Introduction to the basic elements of toxicology

To understand how complex chemical mixtures like wildfire smoke impact human health, or to compare and contrast the impacts of similar agents (e.g., wildfire smoke vs urban air pollution), some toxicology fundamentals should first be introduced. The cornerstone concept of toxicology is 'the dose makes the poison', a phrase which is credited to Philippus Theophrastus Aureolus Bombastus von Hohenheim better known as Paracelsus (Grandjean, 2016). This concept posits that any chemical agent whether snake venom, a pharmaceutical drug, or table salt, at some threshold amount can become deleterious for one's health. In addition to dose, this chapter will also introduce two additional fundamental concepts in toxicology; *duration* and *frequency*, which ultimately contribute to the *dose*. Note that the introduction and fundamentals of toxicology sections of this chapter are meant to establish a foundation of knowledge for those new to this field.

This chapter will explore wildfire smoke toxicity through occupational and public health lenses. Certain characteristics are particularly important to recognize including particle size, source and the mixture of chemical constituents. This chapter will also briefly highlight some human factors that can contribute to wildfire smoke toxicity such as age, genetics, and comorbidities. Route of exposure and mechanism of action are key concepts in toxicology that help explain how wildfire smoke enters the body and what it can potentially affect once inside. Accordingly, defense mechanisms, toxicokinetics, and the role of the immune system will be covered. Model systems are important to all toxicology research and thus we will outline the state of science in terms of

in vitro, *ex vivo* and *in vivo* studies. Finally, the chapter will conclude with a discussion of future research needs, challenges and opportunities.

Fundamental concepts of toxicology: Dose, Duration, and Frequency

Dose

In the medical literature, dose is defined as the amount of a therapeutic drug that is administered at a given time, and a toxic dose is the sum of a chemical that will “produce a harmful or untoward effect (Tsatsakis et al., 2018).” Thus, the ability to measure the amount of a chemical entering the body is critical in determining the dose of that chemical. An *exposure*, by contrast, is just one of many substances an individual comes into contact with as they move through the world. The concentration of such substances in the environment can be measured. In the occupational setting this could take the form of an industrial hygienist placing an air monitor near a specific workstation. Because the dose is how much of this exposure enters into the body, we cannot simply assume that the external concentration is equal to the amount that is deposited in the lungs or other target tissues, and this is the clear distinction between dose and exposure. Instead, toxic principles such as absorption, distribution, metabolism, and excretion (ADME) must be applied and this adds to the difficulty of attributing dose from a measured exposure. For most occupational and public health studies, an exposure rather than a dose will be discussed.

Another complicating factor to understanding dosage of a substance, like wildfire smoke, is recognizing and appreciating the complexity of mixtures. Wildfire smoke is comprised of a mixture of particulate matter (PM) and toxic gasses, which can vary by temperature, fuel type and distance from source, among other factors (Black, Tesfaigzi, Bassein, & Miller, 2017). Given that there can be thousands of individual chemical constituents in smoke from wildfires, and that this mixture is dynamic throughout the life of a fire and variable among fires, each of

these factors requires reconsideration of the questions “What is the dose?” and “Dose of what?” Of all the wildfire smoke constituents, PM is often cited as the most abundant, considering weight by volume, and is also one of the US Environmental Protection Agency's (US EPA's) six criteria air pollutants for ambient air quality (O. US EPA, 2014). Thus, PM is often used as the primary proxy measurement of exposure. Having a standardized method of measurement can be helpful in both research and in policy making. However, appreciation of the many other chemical constituents and their potential health effects is important. The health effects of PM will be briefly discussed in the section on “size fractions” within this chapter as well as Chapters 10, 12, and 13. Other important constituents of wildfire smoke include carbon monoxide (CO), nitrogen oxides (NO_x), and polycyclic aromatic hydrocarbons (PAHs), just to name a few. CO, at elevated levels, forms carboxyhemoglobin (COHb) which can increase incidence of adverse health outcomes, such as chest pain among those with preexisting comorbidities like heart disease (Anderson, Andelman, Strauch, Fortuin, & Knelson, 1973). From research using a canine model, we know that NO_x binds to hemoglobin resulting in the production of methemoglobin which can impact enzyme function and cause vascular membrane injury (Brizio-Molteni et al., 1984). Among those with asthma, NO_x exposure can lead to bronchoconstriction (Zelikoff, Chen, Cohen, & Schlesinger, 2002). PAHs have been found to adsorb onto PM particles resulting in immunosuppressive and cancerous effects in animals and potentially in humans (Bauer et al., 2022; K. M. Navarro, Cisneros, Noth, Balmes, & Hammond, 2017).

In the scientific literature, exposure to wildfire-related air pollutants is commonly measured by local environmental air monitors. These could include a government monitoring station, a temporary monitor installed proximally to an active wildfire, or personal air monitors. The latter is somewhat less common due to a number of factors including cost, access, transport burden and timely distribution. Discussion of passive versus active samplers and parsing out the merits of real-time or cumulative exposure monitoring are outside this chapter's scope. These methods

all have advantages and disadvantages that need to be weighed based on specific exposure circumstances. Most notably, *all* of these methods are limited as a proxy for dose.

Compared to environmental monitoring, the appropriate use of biomarkers may be able to more accurately measure internal dose (Adetona et al., 2017). Distinguishing between biomarkers of exposure and biomarkers of effect is important. Biological monitoring methods for wildfire smoke exposure include chemicals exhaled in breath (e.g., CO), urinary markers (e.g., levoglucosan, methoxyphenols or PAHs) as well as blood markers (e.g., carboxyhemoglobin) (Bergauff et al., 2010; Gill & Britz-McKibbin, 2020; Migliaccio et al., 2009; Schmidt, Borrás, Nguyen, Kenyon, & Davis, 2021). The use of such biomarkers is not always straightforward as variability may be introduced by diet, age, lifestyle, or other habits (e.g., smoking). Very few studies published to date adequately consider such factors and thus the utility of the biomarker data is somewhat limited. Nevertheless, future studies can improve upon the collection of these factors and enhance the accuracy of biomarkers as a proxy for internal dose.

Duration

Duration is the amount of time an individual is exposed to a given substance. In the literature on chemical agent exposure (e.g., acid) you might see duration described as 'contact time'. With regard to wildfire smoke, duration could be quantified differently depending on the situation. In the community setting, a town could be exposed to elevated wildfire smoke PM for multiple hours or days. Occupationally, wildland firefighters spend a certain number of hours on the fireline each year, and these hours add up over their career. Duration is not a mutually exclusive term from dose, but rather a contributing factor. In other words, the longer an individual is in contact with an exposure, the larger the likely dose will become. Another aspect of duration is to consider the time between repeated exposures. Among those exposed to wildfire smoke

annually, little is currently known about the ability of lungs or other tissues to return to baseline after a “washout period”; however, this should be explored.

Duration of exposure is a particularly interesting concept to consider when we think about unique toxicologic profiles of ambient PM versus wildfire PM. Background or regional ambient PM in North American and European cities is often a relatively consistent, exposure that combines with more variable localized PM, both of which are typically chronic exposures for the residential populations of large, urban areas, that have been a main focus of air pollution epidemiology research. By contrast, epidemiological studies investigating wildfire smoke exposure are generally investigating high dose acute exposures that may occur once annually or repeatedly and sporadically during a specific time of year to sparse, rural, and migratory populations, as well as larger, more dense populations in metropolitan areas. Notably, the fire season is growing in length (Jia Coco Liu et al., 2016). Given that the health effects of PM exposure are variable based on a number of factors including duration (Kampa & Castanas, 2008), the ultimate challenge will be understanding how these high dose acute and/or episodic events differ in toxicity.

Frequency

Like duration, frequency is not mutually exclusive from dose, but rather an important contributing factor. Frequency, or the repetitive nature of exposure, is an inherent feature that differentiates occupational and community exposure. Wildland firefighters are, by design, at greater risk for exposure due to the proximity to a fire to conduct suppression activities. While communities are impacted by smoke only by chance, wildland firefighters work purposefully near active fires for up to 14 consecutive days on what is termed a “roll”, working up to 16 consecutive hours each shift (K. Navarro, 2020). While the time that each firefighter spends on the fireline is largely dependent on their duties (Reinhardt & Broyles, 2019), the frequency of

exposure for this occupational group as a whole is starkly different than individuals who live in nearby communities. This does not discount the potential health risks of living in a community, especially as the fire season lengthens and the number of episodes increases. Moreover, we should also focus our attention on the communities that find themselves in a cyclical pattern of exposure – fire season in the summer and fall, temperature inversions in the winter in combination with residential wood burning, and prescribed burning events in the spring. This exposure paradigm would be distinctly different from a wildland firefighter's experience, and also unique relative to communities that only have a few smoke events throughout a year. Remarkably, communities can adapt, sometimes called becoming “smoke ready”, to wildfires in ways that build resilience and that should be addressed in exposure assessment. For example, buildings can be designated as clean air spaces, stand-alone air filtration devices can be distributed, and community members can wear appropriate protective equipment such as N95 masks. Depending on the circumstances, firefighters and other outdoor workers may not have the same opportunities to mitigate smoke exposures.

Characteristics that impact toxicity

Here we will discuss some of the characteristics that can vary with any biomass combustion-generated air pollution event, including wildfire smoke events. While not exhaustive, this section will discuss factors that help to explain some common toxicological responses in both humans and animals.

Size Fractions

Wildfires can generate particles ranging from ultrafine up to ash or debris that may be several centimeters in size. Most large wildfire smoke particles including ash will precipitate within close proximity of the active fire and pose no inhalation risk to downwind communities. In contrast, smaller more transient particles can travel long distances, even reaching other continents.

Particulate pollution can be categorized many different ways, with these systems being mostly arbitrary but having some basis in characteristics of suspension or deposition in the human respiratory tract. The historical timeline of air quality standards in various countries demonstrates how, over time, research can inform regulation. In 1971, the US Environmental Protection Agency (EPA) regulated PM based on total suspended particles, whereas today they regulate based on aerodynamic diameter of 10 and 2.5 micrometers (PM_{10} and $PM_{2.5}$) (O. US EPA, 2016). These two size fractions are notable because they are the approximate cutoffs for deposition in upper respiratory tract and lower respiratory tract or alveolar spaces (Figure 1), respectively. Australia has developed similar cutoffs, developed in 1998 with the National Environment Protection Measure for Ambient Air Quality (the 'Air NEPM'), which were recently updated to include $PM_{2.5}$ in addition to PM_{10} ((NEPC)). The European Union has two overarching air quality policies, the Thematic Strategy on Air Pollution and the National Emission Ceiling Directive, which were created in the early 2000's to set concentration standards for ambient air quality. These policies include standards for $PM_{2.5}$ and PM_{10} that are similar to US EPA standards ("Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe," 2008).

Sources and Fuels

With biomass combustion, "what is burning?" is an important question. Regarding wildfires, this could include some or all of the following: grass, brush, plant material on the forest floor (i.e., needles, duff, foliage), and trees, as well as manufactured materials (i.e., vehicles, structures). The ratio of these fuels can vary within a given ecosystem. Globally fire suppression policies in certain regions have added to the availability of fuel (Curt, Borgniet, & Bouillon, 2013; Westerling et al.). As fires encroach on communities and communities encroach on the wilderness, building materials and other manmade products at this wildland-urban interface

have also become a fuel. Wildfires in California, US, during the 2018 and 2020 wildfire seasons were particularly notable for their overlap into the wildland-urban interface according to the US Forest Service ("Most California Fires Occur in Area of Wildland-urban Interface with Less Fuel and More People,"). Reducing smoke exposure risks from building materials and protecting homes that are bush fire prone is also a major goal in Australia ("Planning for Bush Fire Protection,").

Investigation of the toxicology profiles of different fuels is critical to help guide smoke mitigation and intervention activities. Researchers from the US EPA conducted a trial of five different woodland fuels representing different US geographical regions. The study found that toxicity, which was measured by quantifying the number of neutrophils infiltrating a mouse lung following exposure, differed by fuel source and that mutagenicity, measured using the Ames Mutation assay, also varied by fuel source (Kim et al., 2018).

Temperature

Wildfire smoke is sometimes discussed as a static monolith of distinct chemicals. In reality it is an extremely complicated and dynamic array of organic and inorganic compounds resulting from the unique combustion chemistry occurring under a set of specific conditions (Stephen S. Leonard et al., 2007). If the conditions or chemistry surrounding a fire event changes, then the resulting constituents of wildfire smoke will be different. Temperature is one of the most important conditions that contributes to combustion of wildland vegetation. Incomplete combustion of wildland vegetation occurs at temperatures between 300 and 500°C and results in more organic carbon particles than is the case with more complete combustion (Kocbach Bølling et al., 2009). This slow, low temperature burning of solid material is known as 'smoldering', which is in contrast to the more homogeneous combustion of gasses at higher temperatures known as 'flaming' (Santoso, Christensen, Yang, & Rein, 2019). Temperatures

conductive to flaming are approximately 640°C, with the most favorable conditions for complete combustion being around 900°C (Seltenrich, 2018). Under flaming, oxygen-starved conditions, smoke products contain more elemental carbon aggregates; at higher temperatures with more oxygen, complete combustion produces mostly inorganic ash particles including alkali salts, chlorides and carbonates (Kocbach Bølling et al., 2009).

Several studies have attempted to address how smoke toxicity is influenced by flaming versus smoldering conditions. In a study that burned eucalyptus, peat and oak, researchers found that temperature overall had a dramatic effect on the smoke product for all sources (Hargrove et al., 2019). Smoldering conditions resulted in 10 times greater PM compared to flaming whereas flaming conditions resulted in CO₂ and NO₂ levels that were 1000 times higher compared to smoldering. In a separate study that evaluated oak, peat, pine needles, and pine wood, the researchers also demonstrated that smoldering conditions produce more PM, while flaming conditions produce more gases (Kim et al., 2018). In the studies cited above, the groups exposed mice under variable conditions and found that toxicity metrics differed with both burn temperature and fuel type (Hargrove et al., 2019; Kim et al., 2019; Kim et al., 2018).

Aging and Distance

Wildfires in the US primarily affect forests on the West coast, and data suggests the downwind areas most impacted by this smoke are the Rocky Mountain states (McClure & Jaffe, 2018).

Intuitively, one could assume that as the smoke plume rises from a fire and is transported tens to thousands of miles away, that the PM concentration of the plume would decrease as dispersion and dilution occurs and thus, the toxic potential of the wildfire smoke would presumably be diminished. This conclusion is accurate, but incomplete. Indeed, dilution of particles increases with distance (Radke, Hegg, Hobbs, & Penner, 1995). These changes to

particles that occur with transport are referred to as 'smoke aging'. However, photochemical processes with the aid of ultraviolet radiation from the sun along with chemical mixing in the atmosphere can also alter the chemical makeup of the smoke (Wong et al., 2019). Interim findings from the PyroTRACH project in Greece suggest that aged smoke particles may actually be more toxic than fresh smoke particles (Gray, Magazine, Research, & Magazine).

One product that is primarily generated by smoldering fires is brown carbon airborne particles, also called "tar balls," (Chakrabarty et al., 2010) which become particularly abundant in aged wildfire smoke (Giroto et al., 2018). Identification of brown carbon particles may be important for distinguishing it from black carbon which is a signature of urban PM (Martenies et al., 2021). Brown carbon is a water-soluble organic component of wildfire smoke and Pardo et al. found that it increased the inflammatory and oxidative stress response in mice, was toxic to bronchial epithelial cells, and also induced an apoptotic pathway (Pardo et al., 2020).

Mixtures

Wildfire smoke exposures do not occur in isolation from other sources of contamination.

Accordingly, researchers must appreciate and attempt to account for potential interactions – whether they are additive, synergistic, agonistic, or antagonistic – between wildfire smoke and other possible air pollution exposures. As mentioned previously in this chapter, defining wildfire smoke alone can be problematic given the dynamic nature of wildfire smoke production.

Though perhaps an immense task, the addition of other PM sources, is the reality of ambient air exposures.

Studying co-exposures is particularly important for those who work primarily outside, including wildland firefighters, agriculture, construction, landscape, utility, and facility maintenance workers (K. Navarro, 2020). Some of these co-exposures could include silica, farm-related

pesticides, traffic-related air pollution (TRAP) or diesel exhaust. There have been many studies that observed the effects of ambient air on health in both humans and animals, and some have likely overlapped with wildfire season. However, very few have been intentionally designed to consider the health effects associated with mixtures involving wildfire smoke among occupational workers. Reinhardt et al. found that a wildland firefighter's exposure to smoke and silica is more dependent on the task they perform than on the amount of time on the fireline (Reinhardt & Broyles, 2019).

Human factors

A comprehensive discussion of human health effects and factors that may increase risk for wildfire smoke effects can be found elsewhere in this book (Chapters 10, 12, 13), but it is important within the context of toxicology to point out these factors. In addition to the dose, duration or frequency of exposure are the human factors that can influence toxicity. Factors that could make an individual more vulnerable, sensitive or susceptible to smoke exposure include such pre-existing variables as disease, lifestyle, ethnicity and age. Genetic and epigenetic factors may also play a role, but are outside the scope of this review (Black et al., 2017; Prunicki et al., 2020; Reid et al., 2016a; Schuller & Montrose, 2020). Future studies could also focus on the vulnerability of communities which might include an assessment of adaptive capacity and resilience.

Routes of exposure

Humans are exposed to all the constituents of wildfire smoke through dermal absorption, inhalation, and ingestion. While the major route of exposure is inhalation through the pulmonary system, there are increasingly studied and notable extrapulmonary effects including neurological, reproductive, and cardiovascular health effects of wildfire smoke exposure (Brook

et al., 2010; Fu, Guo, Cheung, & Yung, 2019; Klepac, Locatelli, Korošec, Künzli, & Kušec, 2018). The mechanisms of these effects, as well as the mechanisms of transport, are areas of on-going research. This section will briefly discuss all routes of exposure as well as tissue-specific mechanisms (barriers, cells, soluble factors) of toxicity.

Respiratory exposure route

The most common and significant route of exposure to wildfire smoke is via the respiratory system. This system includes the nasal passage, trachea, bronchi, and alveolar spaces, as well as a wide variety of cell types (Figure 1).

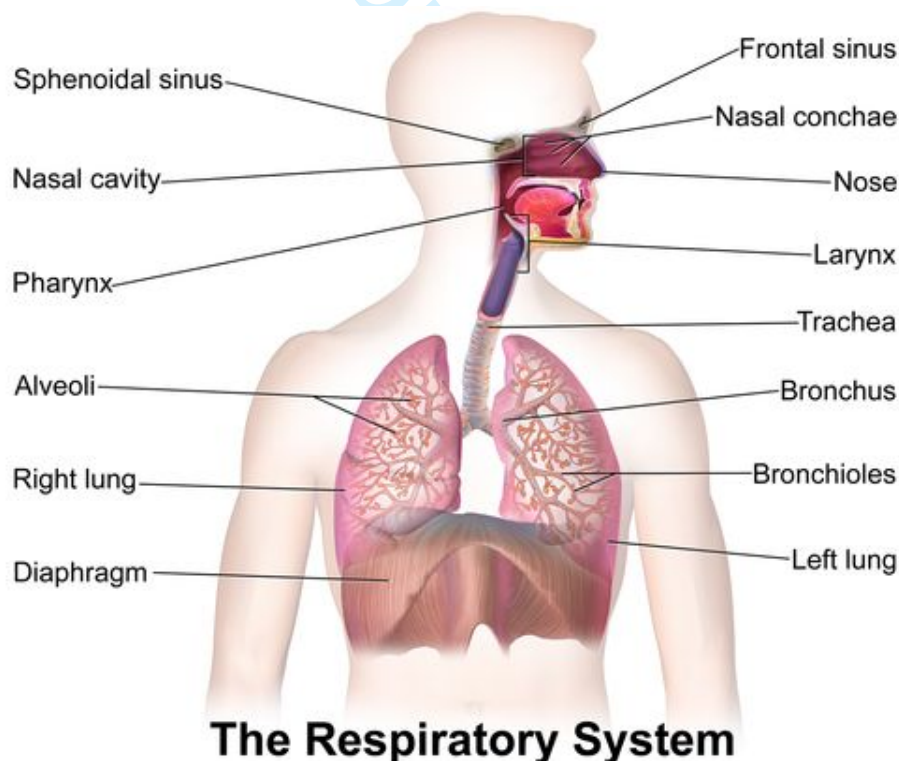


Figure 1. The Respiratory System.

https://commons.wikimedia.org/wiki/File:Blausen_0770_RespiratorySystem_02.png

The trachea divides into two main bronchi, which then subdivide into secondary bronchi, tertiary bronchi, and ultimately bronchopulmonary segments, lung sections separated by connective

tissue. These tertiary bronchi further divide into 4th, 5th, and 6th order segmental bronchi eventually culminating in terminal bronchioles which give rise to multiple alveolar ducts and 5-6 alveolar sacs with each duct (Bucher & Reid, 1961).

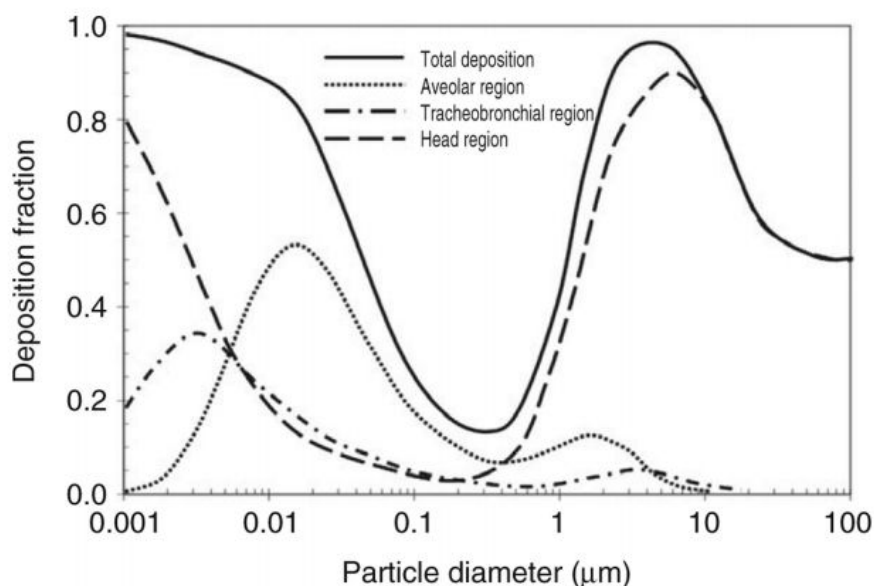


Figure 2. Probability of pulmonary deposition by size fraction.

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The science behind particle deposition in the respiratory system is complex and includes “inertial impaction, gravitational sedimentation, and Brownian diffusion, and to a lesser extent turbulent flows, interception, and electrostatic precipitation (Darquenne, 2012).” Particles larger than PM_{10} will be deposited and cleared by the anatomy and physiology of nostrils (Figure 2). The coarse fraction, particles less than 10 but greater than 2.5 micrometers, can evade impaction in the nasal conchae, but will be deposited in the upper respiratory where they are removed via mucociliary clearance (Bustamante-Marin & Ostrowski, 2017). The fine fraction, or $PM_{2.5}$, are at least 30 times smaller than the diameter of a human hair and bypass both the nasal conchae as well as the mucociliary escalator allowing for deposition in the lower airways

and alveolar space. The last line of defense for fine ($PM_{2.5}$) and PM with an aerodynamic diameter less than 0.1 micrometers (ultrafine), is endocytosis by epithelial cells, or phagocytosis by two types of specialized innate immune cells, macrophages and polymorphonuclear neutrophils (Reynolds, 1985). Some particles avoid phagocytosis and remain in the alveolar space causing inflammation, while others may diffuse through the lung-blood barrier and gain access to other tissues via the body's circulatory system (Schraufnagel, 2020).

The US EPA and its global counterparts categorize $PM_{2.5}$ as an atmospheric contaminant when determining pollution levels, and thus most respiratory studies focus on this size fraction. While many studies revolve around atmospheric $PM_{2.5}$ exposures and subsequent health effects (Brook et al., 2010; Brunekreef & Holgate, 2002; Pope III, 2002; Shah et al., 2013), most of these involve chronic exposures (i.e. living in urban areas with elevated pollution) and the subsequent effects on at-risk groups such as those with cardiovascular disease, asthma, or COPD (Carey et al., 2013; Faustini et al., 2013; Karakatsani et al., 2012; Kelly & Fussell, 2011). These studies have illustrated the health complications for these groups including increased morbidity and mortality with exacerbations of pathologies. While many air quality indices (including the EPA's AQI) are mainly calculated using $PM_{2.5}$ levels ("Air Quality Index (AQI) Basics"), there are two major reasons for independently assessing particle exposures from wildfire smoke and then comparing to the body of urban PM literature: duration of exposures and chemical content. Wildfire smoke exposures are usually higher in particle concentration and relatively shorter in duration compared to ambient PM exposures, suggesting the potential for distinct health effects.

Dermal exposure route

The skin is the largest organ of the body and is key to protecting from environmental insults including microbial pathogens, airborne particulates or chemicals, and helps with regulation of

body temperature. Based on the extensive surface area the skin is subject to significant environmental exposures and has potential for subsequent adverse effects. While the field of wood smoke research is increasing in the number of both human and animal studies, none to date have specifically addressed the effects of smoke-derived PM_{2.5} on the dermal system (Schwartz, Bølling, & Carlsten, 2020).

Ingestion exposure route

There are no direct studies to date assessing the contribution of ingested particles from wildfire smoke. However, gastrointestinal exposures via the mucociliary escalator can occur (W. Lee et al., 2020). Additional occupational-related exposures are possible through the ingestion route. For example, wildland firefighters could plausibly ingest smoke PM while eating given the lack of hygiene supplies in the field (K. M. Navarro et al., 2021).

Target organs and effects

This section will describe the areas of the body that are impacted by wildfire smoke and what toxic effects have been demonstrated or observed. Ambient PM effects will also be discussed where wildfire smoke data is lacking.

Respiratory effects

The effects of ambient PM in the respiratory system have been examined. For example, research has shown increased asthma morbidity associated with increased exposures to certain air pollutants including ambient PM_{2.5} (O. R. D. Us Epa, 2018). The lung is a major interface with the environment and requires a high level of immune regulation to limit reactivity. Exposure to a variety of environmental agents, both manmade and natural, can result in an increased susceptibility to infectious disease (Ciencewicki & Jaspers, 2007; de Perio, Kobayashi, & Wortham, 2020; Huang et al., 2016). Inhaled diesel exhaust, cigarette smoke, and mining PM

have been linked with an increased susceptibility to respiratory infections in both humans and animal models (Antonini et al., 2000; Arredouani et al., 2004; Castranova et al., 2001; Martin et al., 2006; McDonald, Harrod, Seagrave, Seilkop, & Mauderly, 2004; Ross & Murray, 2004; Zelikoff et al., 2002). In developing countries, chronic exposures to residential wood smoke (i.e. home heating, cooking) have correlated with increased incidence of respiratory infections (Akunne, Louis, Sanon, & Sauerborn, 2006; Bautista, Correa, Baumgartner, Breyse, & Matanoski, 2009; Bruce, Perez-Padilla, & Albalak, 2000; Kilabuko, Matsuki, & Nakai, 2007; V. Mishra, 2003; V. K. Mishra & Retherford, 1997; Smith, Samet, Romieu, & Bruce, 2000). In addition, population studies have found increased acute respiratory illnesses (ARI) in children in homes where biomass burning (i.e., wood) is the primary method of cooking (Akunne et al., 2006; Bautista et al., 2009).

Mechanistic evaluation of PM-induced susceptibility to respiratory infection has focused on prominent cell types including the alveolar macrophage and alveolar epithelial cells (Migliaccio et al., 2013; Sada-Ovalle et al., 2018; Sun et al., 2021). While wood smoke induced pulmonary inflammation has produced mixed results (Swiston et al., 2008), there are ambient PM studies that demonstrate the adverse effects of PM on the ability of macrophages to phagocytize and clear apoptotic cells and particles, a process referred to as efferocytosis (Boada-Romero, Martinez, Heckmann, & Green, 2020). A significant portion of research on the respiratory effects of smoke has focused on the alveolar macrophage (Migliaccio et al., 2013; Sada-Ovalle et al., 2018). Macrophages are key players in both innate and adaptive immune responses and with the recognition of multiple functional subsets (i.e., M1 and M2) macrophages are considered to be plastic in that they can alter their phenotype based on the current environment (Bain et al., 2016; Gordon, 2003). Trained immunity in macrophages is described as long-term functional changes resulting in exposures to particular stimulations (Netea et al., 2020). While unknown, there is a strong potential that wood smoke exposures could induce trained immunity, thus

affecting local macrophage populations and skewing subsequent responses. Most studies assessing potential roles of epithelial cells in air pollution effects focus on cellular damage and are *in vitro* with very few utilizing wood smoke particles (Tzong-Shyuan Lee et al., 2008; Zeglinski et al., 2019).

Dermal effects

Despite the lack of wildfire smoke-specific studies, there have been a number of studies assessing the dermal effects of exposure to ambient PM_{2.5} (Dijkhoff et al., 2020; Magnani et al., 2016; Vierkötter et al., 2010). These include skin aging (Vierkötter et al., 2010), skin damage (Magnani et al., 2016), and effects on cholesterol metabolism (Liao, Nie, & Sun, 2020), with the induction of oxidative stress considered a contributor to some or all effects (Jin et al., 2018; Piao et al., 2018). Due to the significant barrier and the size of particles (air quality studies historically have focused on PM_{2.5}), there are generally two main potential routes of penetration – hair follicles/pores, and across the stratum corneum – and studies are concentrated on the effects to the epidermal layer (Jin et al., 2018). In addition, the chemistry of ambient PM_{2.5} is such that there are a number of constituents that have been shown to interact with the aryl hydrocarbon receptor (AhR), a transcription factor expressed throughout the body including skin cells, which can affect genes involving metabolism, inflammation, and oxidative stress (Napolitano & Patrino, 2018; Peng, Tsuji, Zhang, Chen, & Furue, 2019).

Extrapulmonary effects

The effects of wildfire smoke on cardiovascular health outcomes have been examined, and despite the amount of quality data, the results remain mixed (Black et al., 2017; Cascio, 2018; Chen, Samet, Bromberg, & Tong, 2021; Hanigan, Johnston, & Morgan, 2008; Henderson, Brauer, Macnab, & Kennedy, 2011; Tze-San Lee, Falter, Meyer, Mott, & Gwynn, 2009; K. M. Navarro et al., 2019; Rappold et al., 2011; Reid et al., 2016b; Schranz, Castillo, & Vilke, 2010;

Stowell et al., 2019). Clinical and toxicological studies have highlighted plausible mechanisms such as systemic inflammation, oxidative stress, extracellular vesicle release of microRNAs and nervous system imbalance (Chen et al., 2021). Given the proximity of the heart to the lungs and transfer of blood as a vehicle, direct exposure to smoke PM via translocation is also a plausible exposure route (Cascio, 2018), which has been demonstrated in a mouse model (Furuyama, Kanno, Kobayashi, & Hirano, 2009). As noted in the dermal effects section, cholesterol metabolism can also be affected by exposures to air pollution, and this could indirectly impact cardiovascular health (Carson et al., 2020).

In addition to cardiovascular effects, wood smoke PM that traverses the lungs into circulation and may interact with other organs which will be essential to characterize moving forward. For example, Milton et al. 2020 and Schuller et al. 2020 reviewed the literature on plausibility of wildfire smoke PM effects on the brain and nervous system, leveraging research on urban PM and brain effects given the paucity of wildfire smoke PM literature (Milton & White, 2020; Schuller & Montrose, 2020). This is a growing area of research that is supported by epidemiological data but is in need of more mechanistic laboratory studies. Epidemiologic literature on potential links between exposure to wildfire and other adverse health impacts are examined in chapters 12 and 13, however we underscore the need for additional mechanistic and toxicologic research to elucidate further the pathophysiologic pathways. Research to date has precluded determining dose-effects of wildfire smoke exposures due to such factors as limited information on duration, frequency, characteristics that impact toxicity, and variability of individuals.

Model systems of wildfire smoke toxicology

Wildfire smoke collection and exposure

Understanding the toxicological effects of wildfire smoke exposure is dependent on the ability to collect ambient smoke or to create wood smoke PM in a laboratory setting. Collection of non-smoke ambient PM can be done using a versatile aerosol concentration enrichment system (VACES) (Ferguson, Migliaccio, & Ward, 2013), a high volume cascade impactor (Demokritou, Kavouras, Ferguson, & Koutrakis, 2002), or similar collection devices. PM collection during wildfire season may capture some smoke particles; however, depending on the location this sampling may be diluted or mixed with other sources. Ambient collection of fresh smoke alone is difficult due to the hazardous nature of wildfires. Thus, the majority of studies in the following section are conducted with experimental wood smoke exposure models (Kim et al., 2018). While useful in understanding the toxicology of the specific type of fuel, these experimental approaches are limited in that they are missing the mosaic of fuels in a naturally-occurring fire, as well as conditions such as high temperature, low humidity, wind and variable topography.

In vitro models

In vitro experimentation has many benefits in that it is relatively inexpensive, quick, and can give specific insight into disease mechanisms. These experiments are often used as a screening tool to look for initial toxicological effects before moving into an *ex vivo* or *in vivo* model.

Furthermore, these systems can later facilitate pinpointing of a specific mechanism or pathway.

To measure the effects of air pollution *in vitro*, PM particles or extracts are resuspended in liquid and added to cell culture medium. Alternatively, the air liquid interface allows particles to be

directly applied to the cells (Wang et al., 2019). There are limitations to liquid suspensions in that particles are more likely to aggregate, which has an effect on particle distribution to the cell. Aerosol exposures are much less likely to aggregate. Additionally, in the case of lab-created particulates, exposure can occur immediately after or simultaneously with combustion. This temporal aspect is important when considering the stability or volatility of certain chemical constituents. To date, there are still relatively few studies that have used *in vitro* methodologies to investigate the effect of wildfire smoke exposure on human health (Black et al., 2017; Dong, Hinwood, Callan, Zosky, & Stock, 2017). There are even fewer studies that measure outcomes from whole smoke exposure (including gaseous products), instead focusing on exposure outcomes from isolated smoke PM.

Two recent review papers published on the health effects and toxicity of smoke exposure addressed *in vitro* exposure studies through 2017 (Black et al., 2017; Dong et al., 2017). Black et al. focused on studies that came out of ambient smoke collected from the 2008 Northern California wildfires (Black et al., 2017). Authors highlighted distinct differences to non-smoke pollutant exposures, but concluded that more information is needed on the chemical composition of smoke in order to further elucidate mechanisms (Black et al., 2017). A review by Dong et al. covered *in vitro* exposures of smoke from bushfires, prescribed burns, and experimental smoke. Taken together, these reviews suggest smaller particles are more toxic than larger particles, however they also highlight the need for standardization of protocols for more effective comparisons (Dong et al., 2017).

A 2020 study by Ithantola et al. introduced both PM and the gaseous phase of smoke by using a combustion methodology for exposure to wood smoke PM and gases combined (complete combustion emissions) as well as to a HEPA-filtered combustion aerosol (without PM) (Ithantola et al., 2020). Authors exposed both macrophages and epithelial cells at the air-liquid interface

to these three separate smoke constituents. With enhanced deposition of PM, cytotoxicity (measured by lactate dehydrogenase release) was increased in exposed macrophages. The only comparison that demonstrated a difference between exposure methods was an increase in interleukin (IL)-8 with HEPA-filtered combustion in comparison to complete combustion exposures. This work represents the rare study that looks at the effects of gaseous compounds alone, and thus more work needs to be done to understand which components of smoke are leading to observed effects.

Although studies on collected ambient smoke PM are lacking, studies have investigated the toxicological effects of experimental wood smoke PM. *In vitro* experiments with smoke particles have demonstrated functional changes in cells such as a blocked autophagy pathway or decreased macrophage functions consistent with COPD (Migliaccio et al., 2013; Roscioli et al., 2018; Sada-Ovalle et al., 2018), decreased lymphocyte activation consistent with bacterial sensitivity (Migliaccio et al., 2013), DNA damage (Corsini et al., 2013; Danielsen et al., 2011; S. S. Leonard et al., 2000), and epigenetic changes linked to asthma, lung cancer and other diseases that have been associated with PM exposure (Heßelbach et al., 2017). Deering-Rice et al. compared the combustion of different types of wood to diesel exhaust particles (DEP), and identified a transient receptor potential (TRP) channel (TRPV3), a marker for pneumotoxicity, as activated by wildfire smoke (Deering-Rice et al., 2018). The results from this study were dependent on the specific wood type burned, introducing the need for a comparison to different PM sources, as well as a need to elucidate fuel-specific effects. Filling this gap is particularly important given that wildfires are moving closer to the wildland-urban interface, adding building materials to the list of potential fuels burned.

A small number of studies have attempted to address this mosaic of smoke PM by collecting ambient PM during a wildfire event and exposing these particles *in vitro*. Jalava et al.¹³⁷

collected long-range transport PM from wildfires outside of Helsinki and exposed a macrophage cell line to a range of PM size fractions (see section on aging and distance) (Jalava et al., 2006). Exposure to all size fractions demonstrated significant increases in NO production, and cytotoxicity as measured by the (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay. Fractionate particles produced differential cytokine responses, with exposure to larger particles (PM_{10-2.5}) yielding a more robust response when compared to smaller particles. Environmental particle collection by Young et al. also demonstrated increased cytokine release with exposure to settled ash collected from a wildfire in Sonoma County, California, USA (Young et al., 2021). Although significant, ash is importantly a non-respirable size fraction. These bioassays demonstrated increases in COX-2, IL-8 and CYP1a1 as well as an increased activation of the aryl hydrocarbon receptor (AhR).

In vivo models

In order to better understand the dynamic health impacts attributed to wildfire smoke exposure, the application of *in vivo* models must be considered. While epidemiologic studies have motivated efforts to further explore the effects of wildfire smoke inhalation on body systems, these studies are often unable to account for important confounding variables (i.e., medical history, tobacco smoke exposure). For this reason, use of inhalation exposure paradigms is key when combining with existing biological model organisms and/or molecular manipulations. This is especially promising in the context of comparative systems biology where researchers hope to better characterize the phenotype of humans exposed to wildfire smoke by assessing the pathologic changes that animal models undergo following simulated subsection to wildfire smoke.

While literature detailing the study of wildfire smoke-induced health impacts *in vivo* is not extensive, the correlation between increased inhalation of ambient PM and respiratory morbidity and mortality is well-established (Walter et al., 2021; Zhang et al., 2021). Research is growing in the *in vivo* arena, concurrent with climate-change induced increase in frequency and duration of wildfire events (Ford et al., 2018). These novel data are suggestive of extra-pulmonary risks that require more thorough exploration (Oudin, Segersson, Adolfsson, & Forsberg, 2018). To accomplish this, three major experimental exposure routes have been identified for laboratory animal models: intranasal/intratracheal instillation, nose-only inhalation, and whole-body exposure. Each of these methods has associated drawbacks which should be considered when developing a research strategy. In consideration of direct instillation via micropipette, this type of exposure may not reflect ambient inhalation events, especially when considering that animals are often sedated to perform the exposure. This technique is also associated with additional cost of training (e.g., using a pilot cohort of animals and dye) as well as the use of the anesthetic agent. While widely used in many experimental settings, this technique may be best reserved for studies seeking to mimic high-level occupational exposure events or for laboratory environments which are not capable of conducting in-house biomass combustion for particle generation. By conducting a nose-only exposure paradigm, animals are subjected to increased handling and confinement which can induce aberrant stress responses (Thomson, Williams, Yauk, & Vincent, 2009). On the other hand, a whole-body exposure strategy allows for deposition of particulate matter in the fur of the animal and may result in undesired oral consumption in addition to nasal inhalation. These inhalation exposure techniques are better suited for simulation of ambient PM exposure, and can even be optimized to reduce inhalation mortality for long-term study duration using kerosene to minimize carbon monoxide concentration (Zhu et al., 2012).

Another study design parameter to consider is the species of the animal model used. Many labs employ commonly used laboratory rat or mouse strains due to the pre-existence of housing facilities, low cost of implementation, and short life-span for chronic studies. One major advantage of using smaller rodents for these studies is that these organisms are obligate nasal breathers. However, there are certainly anatomic differences between small rodents and associated human counterparts (Rydell-Törmänen & Johnson, 2019). Other research groups have more recently studied wildfire smoke exposure in higher order mammals such as rhesus macaques (Black et al., 2017) and canines (Calderón-Garcidueñas et al., 2003). While these animals share more similarity to human respiratory anatomy, challenges such as cost, husbandry, lifespan and ethical considerations complicate their widespread usage.

Ethical considerations surround the sacrifice of a life to gain information that will ultimately influence future health directives. For this reason, mindfulness of the “Three Rs” (reduction, replacement, and refinement) is important, as is their implementation in the design of any animal experiment (Fenwick, Griffin, & Gauthier, 2009). Consideration of the benefits of sharing tissue with collaborators or banking tissue for future use is also worthwhile. Further, accounting for the drawbacks that each type of simulated laboratory exposure has in regards to mimicking human experience is critical. In summary, considerable evidence warrants future studies using *in vivo* models, so long as the study design and exposure paradigm pros and cons are well-considered in planning each experiment.

Future research needs

Several areas with respect to wildfire toxicology and health require increased research. First, a greater understanding of the various chemical constituents in wildfire smoke is needed. Several studies have characterized the distinct components of collected ambient wildfire smoke (O'Dell et al., 2020; Selimovic, Yokelson, McMeeking, & Coefield, 2019; Sillanpää et al., 2005). These

studies have recognized that the gaseous phase of smoke is a significant component. However, to our knowledge, only one study has isolated this gas phase to examine gas-specific toxicology (Ihantola et al., 2020). Just as ambient gases (NO_x, CO, etc.) have been associated with adverse health effects, this type of exposure through wildfire smoke could have detrimental effects and needs to be further investigated. Second, epidemiologic studies have typically used administrative data (i.e. emergency department visits and hospitalizations) to examine the relationship of acute wildfire exposures with respiratory and cardiovascular diagnoses (Alman et al., 2016; Cascio, 2018; Haikerwal et al., 2016; Hutchinson et al., 2018; Jia C. Liu, Pereira, Uhl, Bravo, & Bell, 2015). However research is limited for physiological systems beyond the respiratory and cardiovascular pathways (Chapters 12, 13), delayed health impacts from acute exposures (Orr, A. L. Migliaccio, Buford, Ballou, & Migliaccio, 2020), long-term morbidity (Schuller & Montrose, 2020; Sosedova et al., 2020), and assessment of effects from chronic, cumulative and mixtures of exposures. This research is expensive, complex and time-consuming; but these studies are necessary to protect both public and occupational health. Lastly, there is a need for establishing a more refined PM exposure classification system. Evolving multidisciplinary research topics often lack a common language. More than just identifying consistent terminology, establishing a PM exposure classification system could help researchers design animal studies that are human-relevant and human studies that are more applicable to realistic wildfire exposures. Classifications will need to include exposure duration, frequency (i.e. episodic, annual) as well as higher resolved exposure levels to allow for continuity and comparison among studies. A shift from assigning the same exposure level to an entire population or a period of time to more temporally and spatially-specific, and variable community and individual-level exposures will also be necessary in future epidemiologic studies.

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