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Respiratory Health Effects of Exposure to Ambient Particulate Matter and Bioaerosols

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Abstract

Researchers have been studying the respiratory health effects of ambient air pollution for more than 70 years. While air pollution as a whole can include gaseous, solid, and liquid constituents, this article focuses only on the solid and liquid fractions, termed particulate matter (PM). Although PM may contain anthropogenic, geogenic, and/or biogenic fractions, in this article, particles that originate from microbial, fungal, animal, or plant sources are distinguished from PM as bioaerosols. Many advances have been made toward understanding which particle and exposure characteristics most influence deposition and clearance processes in the respiratory tract. These characteristics include particle size, shape, charge, and composition as well as the exposure concentration and dose rate. Exposure to particles has been directly associated with the exacerbation and, under certain circumstances, onset of respiratory disease. The circumstances of exposure leading to disease are dependent on stressors such as human activity level and changing particle composition in the environment. Historically, researchers assumed that bioaerosols were too large to be inhaled into the deep lung, and thus, not applicable for study in conjunction with $PM_{2.5}$ (the 2.5-μm and below size fraction that can reach the deep lung); however, this concept is beginning to be challenged. While there is extensive research on the health effects of PM and bioaerosols independent of each other, only limited work has been performed on their coexposure. Studying these two particle types as dual stressors to the respiratory system may aid in more thoroughly understanding the etiology of respiratory injury and disease. © 2020 American Physiological Society. *Compr Physiol* 10:1–20, 2020.

Introduction

Of all the body's various organ systems, the lung has the greatest exposure to the environment. Although the skin would appear to be the organ system most exposed to the vast array of air constituents (gases, liquids, and particles), the lung possesses a surface area nearly 25 times larger than the skin. The average adult human takes 12 to 14 breaths/minute with an average tidal volume of 500 mL/breath, and a total intake of approximately 10,000 L of air/day. Atmospheric air is composed of nitrogen, oxygen, and hydrogen gases—all

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essential for life and normal body function. However, chemical aerosols are also entering the respiratory tract with each breath. Even in relatively clean environments, it is estimated there are 2000 to 3000 particles (both aqueous and solid) per milliliter of air. Although the respiratory system has many inherent defenses, the proportion of particles that reaches the lung has the potential to exacerbate or cause new respiratory disease. Particles that are filtered out and deposited in the upper respiratory tract before reaching the lung are defined as *inhalable*, while particles reaching the lung are defined as *respirable*.

Understanding the etiology of respiratory disease has changed dramatically in the past millennia dating back to the ancient Greeks who described respiratory disease as a wasting of the body. Virtually all respiratory diseases, which today are known to comprise a vast array of etiologies, were termed “phthisis” or “consumption.” It was not until the early to mid-20th century, with the development of new medical procedures and the implementation of chest radiography, that these diseases were recognized as distinct conditions with different causative agents. The pathological effects of airborne particulate matter (PM), which includes, but is not limited to, household pollutants, wood smoke, bioaerosols, and diesel exhaust, were implicated and studied in detail due to much greater incidences of respiratory diseases noted among occupations involving dusty trades (e.g., coal and granite mining and founding) compared to other occupations. In more recent times, especially in the second half of the 20th century, nonoccupational exposure to airborne particles, and their relationship to respiratory and cardiovascular disease, emerged as major research topics. Significant attention was placed on pollution-associated respiratory diseases following the occurrence of several historic pollution events such as the Donora death fog in 1948 and the London fog in 1952 that led to thousands of deaths (39). These incidents and others led to the development of the first Clean Air Act in 1970 (2). They also led researchers to conduct experimental studies in animals to identify specific causative agents and begin to understand dose-response patterns. Further work in the Harvard six cities studies in 1993 (39) demonstrated that peak PM-driven air pollution events were associated with increased deaths from lung cancer and cardiopulmonary disease. These studies not only contributed to our current understanding of the underlying mechanisms that contribute to the unique pathogenesis of pollutant-related diseases, but served as the bases for the National Ambient Air Quality Standards (NAAQS) for PM (142, 143).

Although the interactions between ambient particles and the respiratory system have been investigated for several decades, the mechanisms driving the resulting toxic responses and diseases are not completely understood. This is due in part to the fact that PM composition varies greatly with the source (e.g., anthropogenic, geogenic, and atmospheric), as well as environmental (e.g., proximity to a body of water and rural vs. urban vegetation patterns) and meteorological (e.g., rain and wind) conditions. Temporal changes in weather, such as wind patterns and meteorological inversions, can greatly influence the composition and quantity of aerosolized PM. Higher temperature, humidity, and carbon dioxide levels can change vegetation growth patterns and seasonal bioaerosol emissions to increase pollen production, spore numbers, and microbial spread (110). The rupture of pollen particles and sporulation of fungi occur naturally under wet weather conditions, but certain pollen-generating plants, such as grasses, also fragment (i.e., pollinate) with the wind (135). These examples emphasize that there could be an increase in inhalable bioaerosols due to a variety

of meteorological conditions. Additional bioaerosols lead to greater amounts of particle-associated air pollution overall. Understanding how this mosaic of particles comingles in the air and subsequently interacts with the body is vital to defining how it will affect the health of the respiratory tract (Figure 1).

The purpose of this article is to examine the current concepts of how the respiratory system responds to ambient particles, with a specific emphasis on PM, bioaerosols, and coexposures between the two. This article provides an introduction to the basic mechanisms for particle toxicity, specifically addressing those mechanisms by which particles are inhaled, deposited, cleared, and observed to interact with the respiratory system and other organ systems. The role particles play in causing physiological and pathological changes in the lung, including inflammation, remodeling, lung function changes, and exacerbation of existing pulmonary conditions, is also discussed. Each section discusses PM and bioaerosols separately, and gives the need to understand the complete effects of ambient air pollution; current knowledge and data gaps are also addressed relative to their coexposure.

What are Particulate Matter and Bioaerosols?

Particulate matter

Ambient particles are complex mixtures derived from a variety of anthropogenic and natural sources. PM can be divided into three size categories based on aerodynamic diameter (d_a). As airborne particles have irregular shapes, their movement in the air is expressed in terms of the diameter of an idealized spherical particle; thus, the d_a of an irregular particle is defined as the diameter of a spherical particle with a density of 1000 kg/m^3 and the same settling velocity as the irregular particle of interest. The three PM size categories are coarse (d_a >2.5 μm, but <10 μm), fine (d_a =0.1–2.5 μm), and ultrafine (d_a <0.1 μm). PM_{10} and $PM_{2.5}$ refer to particle size fractions of d_a ≤10 μm and d_a ≤2.5 μm, respectively.

The chemical composition of PM is largely dependent on the original source of the particle. Combustion particles contain a mixture of carbon, metals, and polyaromatics, while particles formed by sea mist are typically pure salts (7). Each size fraction of ambient PM can, in general, be categorized by physicochemical characteristics. Coarse particles are typically composed of natural materials (i.e., minerals, silicates, and ash) derived from weathering, disturbance of earth soils, or volcanic activity, whereas fine particles usually originate from anthropogenic sources (i.e., combustion processes and industrial emissions) and are composed of elemental and organic carbon, sulfate, nitrate, minerals, and metals (83). Ultrafine or nanoscale particles arise from many different sources; they exist naturally in the environment (e.g., in forest fires and volcanoes) and are produced as by-products of industrial or combustion processes (e.g., in engines, power plants, and incinerators).

From its original source, PM often subsequently aggregates in the air to form larger sized particles (30, 142, 143). Humid environments in particular are conducive to agglomeration due to the liquid bridge formed between particles when they are covered in an aqueous film (57). Agglomerates of individually respirable particles may act like larger sized particles due to changes in size and aerodynamic properties (30). In a laboratory setting, agglomeration is, in part, dependent on particle characteristics and dispersion media (49). Therefore,

researchers who collect specific size fractions of PM for use in exposure studies should pay particular attention to this limitation when extracting particles from filters for generating inhalation atmospheres or aspiration/instillation media.

The variability of PM by size, source, and agglomeration potential makes it important for researchers to conduct a chemical composition analysis every time a new ambient particle is used in a study. This compositional analysis helps when comparing findings between studies and aids in the identification of specific PM component that may contribute to adverse responses.

Bioaerosols

Under the broadest definition of PM, bioaerosols, as solid aerosolized particles, should be included as a subcategory of PM. However, for the purpose of this article, bioaerosols are separated from PM, and defined as particles that originate from microbial, fungal, animal, or plant sources. Douwes et al. (44) and Despres et al. (36) define bioaerosols as “live or dead airborne microorganisms” and/or constituents thereof (e.g., bacteria, fungal spores, pollens, and plant fibers). Bioaerosols are most commonly found in the coarse fraction (d_a >2.5 μm, but <10 μm) or larger (Figure 2) and are generally considered to be not respirable (107). However certain fungal spores undergoing sporulation, pollen fragments, and bacteria have been observed with d_a =0.1 to 2.5 μm (110). Pollen and fungal spores, both common bioaerosols, have been implicated in the exacerbation of asthma, a respiratory disease that originates lower in the respiratory tract where intact pollen and spores would not normally be able to reach (153). Researchers have used high volume air samplers and passive samplers to collect particles within the respirable size fraction. Chemical analyses of these particles identified fragments of pollen and fungal spores within the respirable size range (132, 135).

A recent review on bioaerosols from intensive animalbased farming operations found that the main inhalable bioaerosol generated is endotoxin, a lipopolysaccharide (LPS) found in the outer membrane of Gram-negative bacteria, followed by bacteria and fungi (43). Occupationally based sources of bioaerosols are typically related to agriculture and livestock operations, as well as compost and recycling facilities (44, 104). Increased demands for agriculture, compost, and recycling facilities have led to concerns that bioaerosols will become a more prevalent component of air pollution in the future (104).

Within the agricultural industry, ambient bioaerosols arise from a wide variety of sources. Vegetable, fruit, and nut operations have different bioaerosol profiles than animal-based facilities such as feedlots, dairies, and poultry/swine farms. These differences are driven by the types of dusts generated, type(s) of pesticide(s) applied, and specific procedures used in harvesting and processing (107). Many of the bioparticles generated from harvesting and processing of crops are of a larger size than those generated from animal-based facilities (43). Even within the animal-based operations, the composition and size of bioaerosols are greatly variable (89). Another prevalent occupational source of bioaerosol exposures is industrial composting. Covering a span of 54 years, Pearson et al. reviewed compost-related aerosols and found fungi and fungal spores, bacteria, endotoxin, and Beta (1 → 3) glucans (polysaccharides found in the cell walls of bacteria and fungi) as the major constituents

(104). Their research suggested that while occupational exposures were manageable with the proper personal protective equipment, bioaerosol drift to surrounding, unprotected communities was significant, and thus, potentially hazardous. Nygard et al. suggested that certain bioaerosols can remain suspended in the air for prolonged periods of time over distances greater than 10 km (98).

Irrespective of occupational exposures, the changing climate has increased the number of bioaerosols in the environment. As both allergens and potentially toxic particles, researchers should, especially in this day in age, identify, quantify, and examine the bioaerosols collected when sampling ambient air.

The majority of epidemiological studies on the respiratory effects of ambient particles also focuses on either PM or bioaerosols, but not both. In today's environment, it seems unlikely, other than in very specific occupational settings, that human exposure would be limited to just one or the other. Lung function and pathological changes are observed in populations when PM or bioaerosols are measured individually, but the correlative data are lacking when it comes to the measurement of coexposures. For example, a population living in an agricultural community would not only be exposed to agricultural dusts, but also pollens, diesel fumes from tractors, and aerosolized endotoxin from livestock. Correlative analyses need to be done in which all types of airborne particulates, not just PM or bioaerosols, are measured.

Regulation

Ambient particulate pollution in the United States is regulated by mass, not particle number, surface area, or composition. Thus, there is no specific standard for bioaerosols. PM is regulated by annual and daily standards of PM_{10} and $PM_{2.5}$ (US EPA's NAAQS). In 2012, the annual $PM_{2.5}$ standard was reduced from 15 to 12 $\mu g/m^3$ as part of the US EPA's mandatory 5-year review process. However, research by Nygard et al. (98) and Pearson et al. (104) concluded that bioaerosols may pose an occupational health risk that is not addressed under the current NAAQS or occupational health safety standards.

Over 100 studies from at least 35 different cities have examined the acute effects of ambient PM, with findings showing increased hospital admissions and deaths from cardiopulmonary disease such as asthma, chronic obstructive pulmonary disease (COPD), arrhythmia, myocardial infarction, and heart attack (38, 108, 120). These effects appear to best correlate with $PM_{2.5}$, showing increased mortality of 0.5% to 1.5% for every incremental concentration increase of 5 to 6$\mu g/m^3$ (108). Regardless of the standards set, the World Health Organization estimates that PM-associated pollution contributes to 4.2 million deaths annually worldwide (2). This fact and the mechanisms of toxicity described below perhaps argue for a more comprehensive standard based not only on mass, but chemical composition as well.

Mechanisms of Particle Toxicity

Deposition

While the respiratory system is primarily responsible for gas exchange, other functions include humidification or conditioning of the air, olfaction, vocalization, metabolism, and immune defense from the outside environment. Each of these functions and protective features begin with the anatomical structure of the respiratory system. Airborne coarse particles filtered out and deposited in the upper respiratory tract (nose and nasopharynx) are defined as *inhalable*, while particles reaching the lower respiratory tract (conducting airways and alveoli) are defined as *respirable*. The main entry for both inhalable and respirable particles into the respiratory tract is the nasal cavity. In the nasal cavity, the conchae, also referred to as nasal turbinates, create turbulent airflow causing impaction of larger particles on nasal surfaces. These turbinates also warm and humidify the air as an additional protective mechanism for the more sensitive distal regions of the respiratory tract. Of course, oral (mouth) breathing bypasses the protective features of the nose and allows particles that would normally deposit in the nasal cavity to enter into portions of the lower respiratory tract. As air passes down to the tracheobronchial tree, particles impact at airway bifurcations and deposit on the mucosal lining or continue into the terminal gas exchange regions, the alveoli. In a study by Pinkerton et al. (105), particle retention progressively decreased with each new generation of respiratory bronchiole (generation 1, vs. generation 2, vs. generation 3). As demonstrated in Figure 3, larger diameter particles (i.e., >10-μm diameter) will preferentially deposit in the upper respiratory tract, whereas smaller particles (i.e., <0.1-μm diameter) act by diffusion and will deposit in the nasopharyngeal (via turbulent airflow) or tracheobronchial and alveolar regions of the lungs.

The five most influential mechanisms of particle deposition in the airways are sedimentation, impaction, diffusion, interception, and electrostatic precipitation (Figure 4). Deposition by sedimentation and impaction is a function of the inertial aerodynamic particle size characteristics, whereas diffusion is a function of the diffusional properties of the aerosol and is dictated by Brownian motion. Interception occurs when one edge of a particle touches the surface of the respiratory tract before the rest of the particle, dictating its impaction. This mechanism in particular is dependent on the shape of the particle. For example, long fibrous particles are more likely to impact at one edge before the whole particle impacts. Fiber length has little effect on deposition or their ability to reach the lower airways and alveoli up to a length of about 100 μm. However, the deposition of fibers in the alveoli is inversely related to length, i.e., deposition increases as fiber length decreases (50, 91, 137). Alveolar deposition of longer fibers is also found to be directly proportional to the relative degree of injury in the lung (106), such as with asbestos.

Airway deposition by electrostatic precipitation is usually negligible because suspended particles in air are generally at equilibrium charge distribution. However, nanoparticles have been shown to react differently in the lung based on charge. Kim et al. (69) showed a correlation between particle zeta potential, a measure of the electrical charge of particles are that are suspended in liquid, and measures of acute inflammation in the lung.

The physiological characteristics of the individual breathing airborne particles will also influence deposition. These characteristics include the volume of air inhaled, as determined by respiratory rate and tidal volume, and the dimensions of the respiratory tract. In a study by Kim et al., a cohort of men and women with various tidal volumes were asked to inhale an aerosol containing 1-, 3-, or 5-μm particles for 10 to 20 breaths in a relaxed position through a mouthpiece producing a continuous aerosol flow. Particle concentration in the aerosol was continuously measured, and a total deposition fraction (TDF) anywhere along the respiratory tract was calculated [TDF = (number of particles inhaled—number of particles exhaled)/(number of particles inhaled)]. With smaller particles, d_a =1 μm, neither tidal volume nor flow rate had an effect on TDF; however, with larger particles, d_a =5 μm, deposition was largely affected by tidal volume such that larger tidal volumes led to greater deposition (68). In this same study, Kim et al. also showed a greater TDF in women versus men, but only when inhaling the two larger particle sizes (3 or 5 μm); there was no statistically significant sex difference when inhaling the 1-μm particles. This was explained by smaller airways—and lung anatomy overall—in female subjects. These data emphasize the need to take sex differences into account when studying how particles may deposit in, and subsequently impact the function of, the lung.

Particle clearance

Particle toxicity in the respiratory tract can be reduced or completely prevented if clearance mechanisms function properly. The mechanisms by which inhaled solid particles are cleared from the respiratory region of the lungs of healthy adults are depicted in Figure 5. Particle clearance mechanisms include but are not limited to:

1. sneezing, coughing, nose blowing, and transport of mucus to the nasopharyngeal region where it is swallowed into the gastrointestinal (GI) tract;
2. direct mucociliary transport of particles up the tracheobronchial tree and subsequent passage to the GI tract;
3. macrophage uptake and transport up the bronchiolar airways or across the alveolar epithelium and clearance through the pulmonary circulation or interstitial lymphatics; and
4. physicochemical actions, including dissolution, leaching, and physical breakdown of particles either by intracellular or extracellular processes.

Studies on particle clearance have generally shown that smaller particles are cleared from the lungs at a faster rate than larger particles (99). Within the nano or ultrafine size range, these results can vary. In a recent study by Buckley et al.(16), the clearance rate of various-sized (10–75 nm) iridium nanoparticles were compared and found to be independent of size within this range (16). However, in another study by Han et al. (54), smaller (~10 nm) nanoparticles were shown to clear from the lungs much faster than larger (~100 nm) nanoparticles. These latter authors suggested that smaller nanoparticles clear faster due to their ability to translocate to other organs in the body.

Swallowed PM in the GI tract is considered relatively inert due to the presence of highly potent digestive enzymes in comparison to the respiratory system to dissolve and/or

eliminate these particles via excretion. Despite these differences, some more recent studies suggest that PM may alter the GI epithelium and lead to dysbiosis, an imbalance of the gut microbiome (93). This pathology was shown via increased reactive oxygen species (ROS) and the release of inflamma-tory cytokines that led to apoptosis of colon cells (94). It should be noted, however, that these studies were done *in vitro* on epithelial cells and *in vivo* in a murine model and were stated to have limited translatability to human GI disease.

Translocation of PM to other organ systems, such as the cardiovascular and nervous systems, has also been investigated as a potential route for clearance. Particle clearance by crossing at the alveolar air-liquid interface has been shown to be size dependent, with ultrafine particles crossing more efficiently than larger ones (1, 74). Once in systemic circulation, particles can either deposit within the vasculature or continue to specific organs. Extensive research has been done on how PM negatively affects the cardiovascular system during systemic clearance. Particles translocated and deposited in the vasculature can induce production of ROS, inflammation, endothelial dysfunction, and platelet aggregation (15). Research on extrapulmonary PM transport demonstrated that fluorescently labeled, ultrafine (20 nm) gold-colloid particles instilled in the trachea of mice were detected within 15 min in the liver, kidney, heart, and spleen. The particles were observed as free within the extracellular space, and phagocytosed within macrophages (46).

To reach the brain via systemic circulation, particles generally must cross the blood-brain barrier. However, researchers have also delineated a pathway via the olfactory sensory neurons which have direct axonal connections to the olfactory bulb of the brain (90). A study by Hopkins et al. exposed mice to iron-soot combustion particles for 6 h a day, 5 days a week for 5 weeks. Staining with Prussian blue showed clear deposition of iron particles deep within the olfactory bulb. Although researchers recognized that this transport could have occurred via systemic circulation, they gave compelling arguments as to why they believed this is not the case, including the lack of systemic inflammation (60). Several other studies have validated this pathway with the intention of drug delivery to the brain via inhaled nanoparticles (100, 119, 124).

Particle toxicity

Whether a particle is toxic or relatively inert depends on the particle size, chemical composition, density, and electrostatic properties, all of which dictate the specific patterns of particle deposition, retention, and clearance from the lung. Not all particles cause adverse health effects. For example, “nuisance” or “inert” dusts are defined by the US Bureau of Mines as dusts that contain less than 1% quartz and cause very little/no toxic responses or remodeling of the lung unless extremely high exposures are experienced for short periods or over prolonged periods of time (25). Rat studies with inert dusts have shown that there are specific doses at which macrophage clearance capabilities are exceeded and accumulation occurs, leading to a condition termed “particle overload” (25). This condition has been less established in humans, as the dust tends to be internalized into the lung interstitial tissue more gradually throughout exposure rather than accumulating in the alveolar space and then being rapidly internalized, as has been shown in rats (96).

The chemical complexity of ambient PM makes it difficult to unambiguously delineate which component is the causative agent for exposure-related maladies. Since PM composition can be highly distinct between different sources, it is probable that an array of different agents and/or their metabolites lead to the cellular, structural, and functional changes observed in the lungs. Instead of one clear mechanism of toxicity, PM, irrespective of its chemical composition, has been widely accepted as capable of activating multiple different molecular pathways to produce a range of adverse responses at sufficient doses. Figure 6, for example, demonstrates several mechanisms by which PM can lead to the generation of ROS and subsequent oxidative stress.

Reactive oxygen species

Biochemical homeostasis requires the maintenance of a careful balance between anti- and pro-oxidant mechanisms, as oxidant disruptions can translate into cytotoxic responses. Oxidative stress is an imbalance or disequilibrium of the redox state of a cell. Cellular antioxidants, i.e., glutathione (GSH) and glutathione disulfide (GSSG), are primary regulators of the redox balance. Some researchers suggest that the extent and rate by which GSH/GSSG levels are changed can determine whether stress responses are protective or injurious in nature (155).

ROS can be produced as a result of the intrinsic properties of PM or through extrinsic interactions between PM and cells in the body. Transition metals in PM can lead to production of ROS by catalyzing the production of hydroxyl radicals from hydrogen peroxide via Fenton-like reactions (150). Stable free radical intermediates present on reactive particle surfaces and redox active groups (e.g., quinones) can also be intrinsic sources of particle ROS (70, 72, 78, 127).

In a normal immune response, engulfed exogenous material (e.g., PM or a bacterial pathogen) is degraded by phagocytic cells such as macrophages and neutrophils through the generation of respiratory bursts, metabolic events in which cells create large quantities of highly reactive oxidants. Phagocytic respiratory bursts are one of several endogenous sources of ROS (34). To perform this action, cells must rapidly process glucose to create adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide phosphate (NADPH). This latter metabolic step occurs in the mitochondria via ATP reduction in the pentose phosphate pathway (73). Neutrophils, which have less mitochondria than macrophages, use the NADPH oxidase isoform 2 (NOX2) enzyme complex to catalyze the production of superoxide anions from NADPH and molecular oxygen, and the myeloperoxidase enzyme to catalyze the formation of hypochlorous acid (HOCl), the most reactive ROS (11). Alveolar macrophages also generate ROS using NOX2-based metabolism but lack the myeloperoxidase present in neutrophils that is necessary for HOCl generation (83). Instead, macrophages generate nitrogen-based radicals through NO (nitric oxide) synthase and its interaction with ROS. Nonphagocytic cells such as endothelial cells use ROS-generating complexes similar to those of phagocytic cells for both innate defense (nonspecific, immediate immune defense) and intracellular signaling (13). Although the main role of these processes is protective, overstimulation by PM can create damaging levels of ROS (34).

Mitochondria are the major source of ROS formed through normal mechanisms of cellular respiration. Thus, the homeostatic balance of ROS is most apparent in the normal biochemical processes of mitochondria. Mitochondrial ROS are usually generated in the respiratory chain during ATP synthesis due to leakage of electrons from the mitochondrial electron transport chains (64). As major producers of ROS, mitochondria also serve as major targets for oxidative damage. While basal levels of ROS in the cell are controlled by cellular and mitochondrial antioxidants, perturbations can lead to mitochondrial oxidative stress and subsequent interruptions of the energy supply, imbalances of calcium, and releases of lethal proteins that culminate in cell death via apoptosis or necrosis (34).

Particle exposures and ROS

A recent study by Hou et al. (61) showed that acute exposure to PM can lead to mitochondrial damage. When damaged, mitochondria can intensify the oxidative stress response, shifting the previously mentioned homeostatic balance from protective to harmful (84).

While it has been well understood that the generation of ROS plays an important role in the pathogenesis of surface reactive particles such as quartz and asbestos, it was only recently appreciated that particle size is also an important factor in the role of ROS-mediated cytotoxic responses (5, 45, 52, 92). Nanoparticles lacking surface chemical reactivity are still capable of inducing ROS through biological interactions that directly or indirectly target mitochondrial function. For example, even though polystyrene nanoparticles do not spontaneously produce ROS, exposure in murine macrophages resulted in ROS-induced mitochondrial damage that eventually led to apoptosis (80, 154). This demonstrates the need to understand the mechanisms by which ROS is produced, biochemical processes are disrupted, and cellular damage is induced with exposure to nanoparticles.

Studies have suggested that PM, endotoxin, and the subsequent ROS produced via mitochondria can prompt activation or modulation of inflammasomes (9). Inflammasomes are a subset of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that assemble as multiple-protein complexes aggregated in the cytosol of a cell. PM has been shown to be able to activate inflammasomes through a variety of signaling pathways (9). After activation, inflammasomes can trigger an adverse inflammatory response by activating pro-inflammatory caspase-1, an enzyme that recruits a variety of cytokines [e.g., interleukin (IL)-1beta and IL-18] to trigger an adverse inflammatory response, and/or pyroptosis, a form of cell death (59). This parallel between particle- and inflammasome-induced inflammation has been observed with nanoparticles (111, 156), silica (41), and diesel exhaust particles (141). A recent study by Oya et al. (102) coexposed human airway macrophages and bronchial epithelial cells to *Aspergillus fumigatus* (a common fungus in soil and decaying organic matter) and silica fragments and measured expression of pro-IL-1beta (the IL-1beta precursor) at the messenger ribonucleic acid (mRNA) and protein levels. The induction of pro-IL-1beta was shown to be caspase-1-(inflammasome) dependent (102). The coexposure showed a more marked response than exposure to either silica or *A. fumigatus* alone. Their study emphasizes the importance of the inflammasome in particle-induced inflammation and additionally, again, demonstrates how bioaerosols and PM can enhance a response when

coadministered. Inflammasome-related pathways could play an important role in the various mechanisms of toxicity that are dependent on particle composition. If the inflammasome is activated by PM, bioaerosols, or a combination of the two, inflammasome pathways could be an important target for mediating the adverse effects to the respiratory system.

In vitro assays have also been performed in an attempt to identify more specific components of PM that lead to toxic effects. Velali et al. (147) used the MTT [3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide] and lactate dehydrogenase release bioassays on human lung fibroblasts to examine cytotoxic responses to the water-soluble organic fraction of PM from several urban combustion sources including residential heating installations and vehicular exhaust. The most severe cytotoxic response demonstrated by both bioassays was seen in response to the organic fraction from vehicular emissions (147).

Samake et al. (118) measured the role of bioaerosols on the oxidative potential (OP, the ability to catalyze or carry out the formation of ROS) of PM (118). To measure this, a dithiothreitol (DTT) assay was adapted to compare redox-active species in bioaerosols (bacterial cells and fungal spores) alone, and when combined with ambient PM. Redox-active species were measured by continuous monitoring of excess DTT depletion, a protocol established by Charrier and Anastasio (24). Airborne bioaerosols were collected from indoor and outdoor urban and natural environments directly onto culture media. Collected bacterial species included *Staphylococcus epidermidis,* various *Micrococcus* species, and *Pseudomonas fluorescens,* while fungal spores included *Stachybotrys char-tarum,* various *Penicillium* species, *Aspergillus brasiliensis*, and *A. fumigatus*. Each collected bioaerosol had a cultured model bioaerosol for standardization. Highly toxic model particulates (copper and 1,4-naphthoquinone) were used as positive controls for PM. The OPs of fungal spores versus those of bacterial cells statistically differed by species and bioaerosol concentration. At the highest concentration of fungal spores (10^5 spores/mL; an occupationally relevant concentration in composting facilities), the OP was 10 times higher than that of any of the bacterial cells. When the fungal spores were coadministered (at four different concentrations ranging from 10^2 to 10^5 spores/mL) with model particulates, the effects appeared additive because the resulting OPs were similar to the sum of the individual OPs (i.e., model PM OP + fungal OP). Conversely, the coadministration of bacterial cells with model PM had a seemingly protective effect, as the combined OP (i.e., model PM *and* bacterial OP) was significantly lower than the sum of the individual OPs (i.e., model PM OP + bacterial OP). OPs resulting from the combination of bacterial cells or fungal spores and ambient PM did not change when microorganisms were inactivated by gamma-rays, suggesting that the redox reaction is not dependent on the viability of the microorganism (118).

As of 2012, on a global basis, the total aerosol mass of sporulated or fragmented bioaerosols accounted for ≤25% of the total ambient PM mass (36). Findings by Samake et al. (118) suggest that this minimal presence, when mixed with ambient PM, bioaerosols (viable or inactivated by gamma rays), exhibits an increased ability to induce oxidative stress. These results, from a very intentional coexposure, demonstrate the additive harm of these two stressors regardless of bioaerosol viability. Although important, this study is still limited in the combinations used, as fungal spores and bacterial species represent only a fraction of

ambient bioaerosols. It does, however, present a good model of *in vitro* coexposure and a simple measure of toxicity.

Particle exposures and polycyclic aromatic hydrocarbons

An additional study by Velali et al. (147) found that particles from fireplace wood smoke exhibited the highest concentration of polycyclic aromatic hydrocarbons (PAHs). PAHs in PM activate the aryl hydrocarbon receptor (AhR) which, via various signaling pathways, has been shown to promote and enhance T-helper cell type17 (Th-17) immune responses. These responses are important in maintaining mucosal barriers like those found in the respiratory tract (22). Researchers have attempted to elucidate the mechanism of AhR activation even further by separating wood-smoke particles into individual chemical components. Deering-Rice et al. (35) used *in vitro* and *in vivo* experiments to test their hypothesis that wood-smoke particles activate transient receptor potential (TRP) channels expressed in human bronchial epithelial cells. These channels are present on vagal nerve termini situated in bronchial epithelial cells and are activated by many stimuli. The AhR has been shown to be involved in TRP activation leading to adverse respiratory responses (115). Deering-Rice et al. (35) first demonstrated that 2,3- and 3,4-xylenol, potent TRP agonists and components of wood smoke, were the most prevalent specifically in *pine*wood. *In vitro* experiments showed that human lung epithelial cells expressing transient receptor potential subfamily V, member 3 (TRPV3) cation channels produced ROS when treated with either TRPV3-specific chemical agonists or pure pinewood smoke. This response was replicated *in vivo* when mice treated with resuspended pinewood smoke particles via oropharyngeal aspiration exhibited airway hyperresponsiveness (AHR) in classic methacholine challenge tests (35). Although the studies by Velali et al. (147) and Deering-Rice et al. (35) used particles collected from wood-burning stoves and created in the laboratory, respectively, both studies have implications on how wildfire PM could affect human health through the AhR/TRP pathway.

Inflammation, Lung Remodeling, and Pulmonary Function

When particles are not cleared from the lung and reach sufficient retained doses, several physiological and anatomical changes can be observed that may collectively lead to respiratory disease. Studies of concentrated ambient particles (CAPs) showed pulmonary and extrapulmonary effects including: (i) upregulation of inflammatory and blood pressure regulation markers (62); (ii) oxidative stress in the lungs (80); and (iii) systemic effects suggesting an increased risk of arthrosclerosis (3), all of which may contribute to respiratory and cardiovascular morbidity and mortality associated with PM (56).

Inflammation

It is generally accepted in the literature that exposure to ambient particles leads to an inflammatory response in the lung (22, 151). The debate occurs when elucidating the mechanism by which this inflammatory response occurs, or when defining which response is most prevalent. The inflammatory response, as with many other responses to particles, seems to be dependent on the characteristics of the particle (51). In a study by Zhang et al. (158), a statistically significant difference in inflammatory response was observed between mice exposed to chemically distinct fine PM extracts from California versus China. The

greater inflammatory response, observed after exposure to the California extract, was Th-17 mediated, as indicated by the Th-17-associated cytokines observed, and neutrophilic. The authors suggested that this difference could be attributed to greater copper and oxidized organic content in the California PM but do not put forth an alternative mechanism for the inflammation of lesser magnitude observed with the China PM. A study by Hargrove et al. (55) showed neutrophilic and eosinophilic responses to urban and rural coarse PM exposures, respectively. The mechanisms for different inflammatory responses were not addressed, but again, the authors attributed the difference in response to unique chemical compositions with urban PM having higher levels of metals and ionic compounds. These studies are again an example of response variability based on the chemical composition of PM. Though chemical composition information should be considered in toxico-logical examinations, researchers should also examine the mechanisms driving the toxicity of the chemicals in their PM samples. This is an area in which biologists may need to create more interdisciplinary studies with chemists and atmospheric scientists to understand the role that a unique chemical makeup could play in toxicity or inflammation.

The macrophage is the first line of defense when a particle enters the lung, and thus many researchers have attempted to elucidate the inflammatory mechanism of PM through *in vitro* experiments on alveolar macrophages. Renwick et al. (112) proposed that immune function is compromised due to particle-induced impairment of macrophage phagocytosis. A human cell line of macrophages treated with ultrafine diesel emission particles demonstrated reduced phagocytosis compared to phosphate-buffered saline (PBS)-exposed controls regardless of which of the four phagocytosis-stimulating receptors was activated. Overall, these results demonstrated a dampening of the innate immune response (82). In a similar study, alveolar macrophages were collected from healthy individuals exposed to chronic household air pollutants (particles <4 μm from wood-burning stoves) and compared to an unexposed cell line of macrophages (116, 117). The phagocytic ability and cytokine response of the pollutant-exposed alveolar macrophages were significantly reduced, and an inverse relationship was observed between macrophage particle load and ability to invoke an antibacterial response. This study, if taken a step further, could have also exposed the macrophages to bacteria and observed how a PM and bioaerosol coexposure affected phagocytic and antibacterial responses.

In vitro studies on cultured human lung epithelial cells were done to evaluate the relative inflammatory potential of soil-derived mineral dusts from different geographical locations and particle size fractions [fine vs. ultrafine (148, 149)]. These studies showed that not all soil dusts are equally cytotoxic or inflammatory. To elucidate the physicochemical characteristics of soil-derived particles that may induce inflammatory cytokine release or cell death, Veranth et al. (149) compared the responses of heat-treated, solvent-leached, and untreated particles in bronchial epithelial cells. The water-soluble fraction (supernatant) and the remaining resuspended particles were also separated and compared as distinct exposures. Results suggested that cell interactions with the resuspended (water-insoluble) particles induced both the release of IL-6, a pro-inflammatory cytokine, and cytotoxic responses. These particle-cell interactions were only partially affected by organic and aqueous surface chemicals and minimally influenced by LPS (utilized as a positive control: bacterial endotoxin). These results suggest that within soil-derived dusts, the inflammatory response

is independent of the organic component of the particles (149). The organic component was not characterized in this experiment, and thus the presence of bioaerosols was not defined. However, by purposely inactivating any live components through heat and solvent inactivation, this study suggests that PM is more responsible for the inflammatory response than any potentially present bioaerosol.

In contrast to the study above, many researchers have tested and observed bioaerosols invoking a strong inflammatory response in the lung. Alveolar macrophages isolated from rat bronchoalveolar lavage fluid (BALF) demonstrated an increase in inflammatory markers when treated *ex vivo* with fungal spores [*Aspergillus* (*A.*) *fumigatus*, *A. niger*, *A. candidus, Cladosporium cladosporioides*, or *Eurotium Amstelodami*] versus a saline control (125). Specifically, Northern Blot analysis indicated that total cellular ribonucleic acid (RNA) for macrophage inflammatory proteins, *MIP-2* and *KC*, peaked when macrophages were treated with spores for anywhere between 1 and 3 h. Macrophages treated for longer than 4 h did not show a significant response. Chang et al. (23) reported results of quantitative polymerase chain reaction (qPCR) experiments, which showed that expression of mRNA, for the inflammatory markers *IL-6*, epidermal growth factor (stimulates cell growth and differentiation), and transforming growth factor beta 1 (stimulates cell growth and differentiation), was overexpressed in human lung epithelial cells exposed to bioaerosols collected from a composting plant versus a control vehicle (23). In a separate study, researchers determined that among the major components of bioaerosols collected from 22 biofuel plants, the concentrations of (1→3)-β-D-glucan, endotoxin, fungal spores, and mesophilic actinomycetes were the most closely associated to their total inflammatory potential (TIP) when compared to other bioaerosols such as *A. fumigatus* (138). TIP was defined in the study as, “all inflammatory effects measured in a granulocyte assay.” This assay quantified the production of ROS from granulocyte (i.e., neutrophil, basophil, and eosinophil)-like cells via a chemiluminometric assay and was recommended by authors as a tool for indirectly measuring unknown bioaerosol exposure doses in occupational settings. These two studies, although measuring inflammation through different methodologies, suggest that within bioaerosols, like PM, there are distinct responses due to the biochemical composition of the particle.

Unlike the *in vitro* exposures to *A. fumigatus* described in the study immediately above, chronic *in vivo inhalation* exposures in BALB/c mice (95) produced a statistically significant immune response, specifically an increase in the atopic (allergy-related) cytokine, IL-13, when compared to the filtered air control. A recent review of experimental animal studies on exposure to bioaerosols found inflammatory increases in all exposures but noted that the literature is lacking and inconsistent (157). In recent years, house dust mite (HDM) has replaced ovalbumin (OVA) as an allergen in model atopic responses (21). Dust mites are also categorized as bioaerosols (44), and thus HDM atopy studies that also expose subjects to PM should be considered among those examining coexposures. BALB/c mice intranasally exposed to HDM allergen during sensitization and challenge experiments performed over the course of 2 weeks showed an influx of immune cells to the airway subepithelium and an increase of Th2-associated cytokine expression as measured by qPCR and an enzyme-linked immunosorbent assay (22). Th2-associated cytokines such as IL-5, IL-4, and IL-13 have been associated with atopic asthma exacerbations in human populations (42) making HDM a

good model allergen for the disease. Multiple studies have shown increases in the inflammatory response when animals are coexposed to HDM and PM of various sizes and sources (22, 85, 158). These studies focus on HDM as a model allergen, but interpreted as coexposures, their results demonstrate the need for further *in vivo* experiments with various bioaerosols and PM combined.

Remodeling

Lung remodeling is collectively defined as anatomical changes to the airways and parenchyma including, but not limited to, fibrosis, thickened alveolar septa, and hypertrophy of airway smooth muscle. In an effort to isolate a regional mechanism of remodeling, researchers utilized tracheal explants as a model system for controlling the administered PM dose to a particular region of the lungs (29, 33). Their findings suggested that particles (anthropogenic PM, mineral dusts, and diesel exhaust PM) administered to the airway lead to expression of mediators promoting fibrosis and smooth muscle hyperplasia. The expression occurred without exogenous inflammatory cells and suggested that PM may directly cause injury to epithelial cells and airway remodeling thereby (29, 33).

Chronic exposure to ambient PM in occupational settings has been confirmed to cause lung remodeling. Pinkerton et al. (105) and Schenker et al. (123) evaluated the lungs of deceased young males who died of nonrespiratory causes in California's Central Valley. Each of the subjects had been exposed to a wide variety of ambient conditions consisting primarily of mineral and carbonaceous dusts. Findings from Pinkerton et al. (105) and Schenker et al. (123) suggested that prolonged exposure to ambient and/or occupational PM could result in significant changes, such as wall thickening in the respiratory bronchioles, bronchiole-alveolar duct junctions, and/or centriacinar regions of the lungs, which result in terminal and first-generation respiratory bronchiole remodeling. Pinkerton et al. (105) attributed the wall thickening to an accumulation of dust-laden macrophages, increased collagen deposition, and smooth-muscle cell hypertrophy.

Similar to the findings of Pinkerton et al. (105) and Schenker et al. (123), Churg (28) and Brook et al. (14) reported that subjects living in areas of high PM exposure (mean of 15 $\mu g/m^3$ for $PM_{2.5}$ over 20 years) in Canada demonstrated increased particle deposition in respiratory bronchioles and at airway bifurcations that correlated with airway thickening. In different studies, Churg and Pinkerton showed correlations among high ambient PM exposure, particle deposition, and airway remodeling in the lungs and indicated that, due to their prevalence in lung tissue digests and in comparison to larger particles, fine and ultrafine particle fractions were likely contributing to the observed health effects (26, 105). These results are corroborated by studies with individuals exposed to chronic, nonoccupational, ambient PM. Ambient ultrafine particles retained in the walls of airway bronchioles resulted in fibrogenic small airway remodeling and chronic airflow obstruction, which is detrimental to normal lung function (27). These results suggest harmful effects from long-term exposures to ambient particulate air pollution. However, it is important to keep in mind that many confounders, such as genetics, lifestyle, smoking, occupational exposures, and other ambient pollutants, may also contribute to these functional changes (26–29, 105, 129, 130).

The majority of studies discussed in regard to lung remodeling are due to PM exposures. One study by Chang et al. (23) measured changes in gene expression of matrix metallopeptidase (MMP)-9, known to be important in structural changes of bronchial epithelial cells, in a cell line of lung mucoepidermoid cells when exposed to ambient bioaerosols collected from a composting plant (23). Researchers showed an increase in MMP-9 mRNA expression in bioaerosol-treated cells when compared to nontreated cells. To determine if bioaerosols alone can influence airway remodeling, *in vivo* studies to observe histopathological changes should be performed.

Lung function

In addition to the morphological changes and inflammatory responses described above, PM is known to affect lung function in healthy and susceptible populations. The principle physiological functions of the lung are gas exchange and respiration. Changes in respiration are broadly termed as changes in lung function, and are most easily measured through a series of standardized pulmonary function tests. While these tests are measuring physiological changes in inspiration and expiration, from the results, researchers can deduce anatomical changes in the lung, as well as how gas exchange may be affected.

In a study conducted by Zwozdziak et al. (159) in healthy school children, exposure to ultrafine PM and $PM_{2.5}$ produced decreased lung function as measured by forced expiratory volume (FEV_1; the maximum amount of air a person can expel in one second), forced vital capacity (FVC; the maximum amount of air a person can expel after full inhalation), peak expiratory flow (PEF; the maximum speed of expiration), and mean expiratory flow at 25%, 50%, and 75% of vital capacity (VC) (MEF_{25}, MEF_{50}, and MEF_{75}). Ambient air samples were used as surrogates for personal exposures, and showed that ultrafine PM accounted for approximately 70% of the $PM_{2.5}$ measured. With this percentage measurement, Zwozdziak et al. (159) suggested that the ultrafine fraction could be the driver for the observed physiological changes. A larger observational study (63) on healthy adults exposed to average daily $PM_{2.5}$ concentrations below the European Union standard of 40 $\mu g/m^3$, but above the WHO standard of 35.2 $\mu g/m^3$ (63), also found a negative correlation between short-term $PM_{2.5}$ exposure and lung function. Specifically affected parameters included FVC, PEF, and FEV_1. These results were similar to those from an equally large cohort study (113) conducted by Rice et al. to compare lung function in healthy adults after short-term exposure to moderate or good air quality [51–100 or 0–50, respectively, on the Air Quality Index (AQI)]. Measurements of FEV_1 and FVC were significantly different in subjects exposed to moderate versus good air quality—both considered “safe” for healthy populations by the US EPA (144)]—with worse lung function occurring upon exposure to the former versus the latter. The presence of significant respiratory effects in healthy individuals after exposure to “safe” levels of $PM_{2.5}$ suggests that the current US EPA standards may need to be reevaluated (113).

In an animal-based study by Zhang et al. (158), changes in lung function were only observed in the presence of an allergenic bioaerosol. In this study, BALB/C mice were intranasally instilled with $PM_{2.5}$ and/or HDM. No significant differences were observed in AHR (measured as the concentration of methacholine required to double airway resistance) of

PBS-treated controls and their PM-treated counterparts. A significant difference in AHR was only observed when the mice were coexposed with PM and HDM and compared to controls. A similar study done by Saunders et al. (122) was able to detect significant differences in the AHR of animals exposed via intratracheal instillation to ambient PM without the presence of an allergen or bioaerosol and compared to PBS-treated controls. The discontinuity in these two *in vivo* mouse studies, in addition to the fact that the body of human epidemiological literature describing functional respiratory effects of short-term exposure to $PM_{2.5}$ consists primarily of studies performed in susceptible populations such as asthmatic or elderly individuals, calls for further investigation into whether PM alone, without coexposure with bioaerosols, has an effect on lung function in healthy human populations.

Documentation of lung function changes following occupational bioaerosol exposures, specifically, is variable. To isolate effects of bioaerosols from PM in occupational exposures, compost facility workers are commonly studied. In one long-term cohort study, the FVCs of 218 workers at six different compost facilities were measured over the course of 5 years. During the observational period, FVC declined significantly in exposed versus unexposed control subjects (17). A follow-up study conducted by the same researchers, on different compost workers, found that after up to 13 years of work in the industry, there were no significant changes in lung function between the exposed and control groups despite evidence of increased cough and phlegm in the former versus the latter (145). The authors did not explain the different results between these two cohort studies. Though the clearly observed lung function decrements and other respiratory morbidities show that occupational compost bioaerosol exposures have adverse impacts on the lungs, the lack of continuity between the two cohort studies demonstrates the need for more epidemiological studies with occupational and ambient bioaerosol exposures.

Discontinuity is also seen in the epidemiological literature on functional pulmonary effects of inhaled wood dust (6, 8). Badirdast et al. attributed this lack of consistency to an inability to differentiate the effect of bioaerosols from the effects of airborne PM dust. *In vivo* studies isolating bioaerosols from collected ambient PM are, as noted in the article by Zamfir et al. (157), lacking as a whole, but particularly when measuring effects on lung function.

Disease Exacerbation and Onset

According to the World Health Organization, 4.2 million deaths each year can be attributed to ambient air pollution. Mortality due to air pollution is classically measured with an integrated exposure-response model (19). This model estimates the burden of disease caused by long-term exposure to $PM_{2.5}$ by measuring the magnitude of relative risk. A more recent model, the Global Exposure Mortality Model, (designed by the same group) also measures the burden of disease, but does not make assumptions about equal toxicity between sources/types of PM per total inhaled dose (18). Both of these models show correlations between increased levels of $PM_{2.5}$ and increased risk of respiratory-related mortality. Figure 7 is adapted from Burnett et al. (18), showing increased hazard risk with increasing concentrations of ambient PM (18). Lower respiratory infection, lung cancer, and COPD, three out of the five PM-related diseases in their risk assessment, originate in the respiratory

system. Aside from lung cancer, these diseases, in addition to asthma and valley fever, are covered in the section below.

Asthma

There is extensive evidence that bioaerosols such as HDM and pollen can lead to atopic asthma. This understanding is through the mechanism that bioaerosol allergens stimulate an atopic, immunoglobulin (Ig)E response. IgE antibodies are produced in overreaction to a stimulus (e.g., an allergen) to mediate the subsequent allergic response. In 1992, the National Health and Nutrition Examination Survey (NHANES) cohort study connected asthma to specific allergens. The two of eight total allergens that most significantly increased the risk of asthma were *Alternaria,* an ascomycete fungi, and HDM—both of which are bioaerosols (47). When the NHANES study was reassessed, white oak and cat dander were added to the list of significant, positive associations to asthma (4). Additional cohort studies have correlated the risk and exacerbation of asthma with seasonal changes in bioaerosols (12, 71, 131, 134). One study measuring occupational exposure to bioaerosols demonstrated that increases in endotoxin are negatively correlated with lung function of workers on a pig farm (58). Another epidemiological study observed that exposure to HDM-specific endotoxin is positively correlated with asthma prevalence in adults (20). Studies on children are mixed; some state that early life exposure to endotoxin is actually protective against the development of asthma (126). The difference in results based on age suggests a need to understand the mechanism by which early exposure to allergens could be protective and why this occurs during development and not later in life.

As previously mentioned, *in vivo* models of asthma have moved from exposure to OVA to HDM exposure. HDM is a ubiquitous and, as clearly stated by the NHANES study, relevant allergen. It is a bioaerosol that increases the risk of asthma in human populations (47) and can, in organisms that do not get asthma naturally, instigate many signs of the disease.

Atopic animal models of asthma created via HDM exposure suggest that respiratory sequelae can be exacerbated with the addition of PM at sufficient doses (22, 85, 158). In addition to the studies described earlier, a separate study by Lambert et al. (75) preexposed Brown Norway rats to residual oil fly ash (a surrogate for ambient PM) and saw an enhanced allergic reaction to HDM as measured by increased expression of inflammatory cytokines in BALF and lung tissue. This study differs from the others by showing not exacerbation, but predisposition to disease. In several of these studies, bioaerosol (HDM) and PM exposures occur sequentially and not always simultaneously. In the study by Zhang et al. (158), mice are exposed to both HDM and PM concurrently in the sensitization period, but not in the challenge. In the study by Lambert et al. (75), mice were preexposed to PM, followed with an HDM exposure 1 week later. In the ambient environment, it seems more likely that these exposures would not be isolated. To truly replicate the coexposures that occur in the environment, studies need to expose animal models to PM and HDM at the same time.

Numerous researchers have shown that living in close proximity to major highways is strongly associated with a higher risk of asthma in children when measured by hospitalizations and emergency room visits (48, 67, 101). Studies have also been done to measure the respiratory health of those living in close proximity to PM created by air traffic.

Results show an increase in asthma signs, such as wheezing and coughing, in adult subjects working at or living close to airports (103, 140). Because occupational exposures to airport traffic are more commonly observed than residential exposures, the studies measuring the effects of air traffic pollutants are conducted in adults; thus, similar data in children are lacking.

PM alone has been defined as an exacerbator of asthma rather than an instigator of new disease. McConnell et al. (86, 88) have conducted multiple cross-sectional studies to examine new onset of asthma in children. In these studies, the onset was determined by new occurrences of physician-diagnosed asthma over a set period of time (3–5 years). Participant populations were specifically selected to cover a range of ozone (O_3), nitrogen dioxide (NO_2), and PM levels. In their 2010 study, McConnell et al. reported a correlation between new onset asthma and traffic-related pollutant levels at schools. This significant distinction between pollutant levels at school versus home environments was attributed to children spending the majority of high-traffic hours in the former versus the latter (88). This study did not find significant differences between the individual pollutants (O_3, NO_2, and PM). However, a previous study by the same group illustrated a significant correlation between onset of childhood asthma and high levels (mean concentration of 25.1 ppb over 24 h) of O_3 when they included exercise as an additional contributing factor. This was based on the assumption that children who play team sports spend more time outdoors, and more time under respiratory exertion. As a result, researchers found that children who played three or more team sports had a significantly higher risk of developing asthma under high levels (mean concentration of 25.1 ppb over 24 h) of O_3 pollution (86). This study and others demonstrate the importance of considering not just coexposures, but multiple stressors (i.e., exercise frequency) when studying new onset disease. To make comparisons between studies possible, especially those involving human subjects, researchers must report as much as possible about the multiple stressors that could be contributing to disease and/or confounding results.

Chronic obstructive pulmonary disease

The majority of epidemiological studies that relate COPD and PM measure acute PM exposure and subsequent exacerbation. Li et al. (79) conducted a meta-analysis of 59 studies and correlated spikes in single pollutants [10 $\mu g/m^3$ increase for $PM_{2.5}$, PM_{10}, NO_2, sulfur dioxide (SO_2), or O_3 and 100 $\mu g/m^3$ increase for carbon monoxide (CO)] with exacerbations in existing COPD. Many epidemiological researchers use cross-sectional studies to draw a correlation between exposure to PM and prevalence of respiratory disease within a set period of time and geographical area. A study by DeVries et al. (37) evaluated emergency room visits and hospitalizations for COPD through a cross-sectional analysis of 7-day averages of SO_2, NO_2, and PM. Findings from this study found a significant ($p < 0.0001$) negative association between COPD exacerbation and short-term $PM_{2.5}$ exposure (37). These acute exposure studies are coupled with a collection of studies that observe an association between COPD prevalence and chronic exposure to indoor biomass burning (121, 128). A recent article by Robertson et al. (114) summarized inconsistent results relating bioaerosol exposure from composting facilities to COPD exacerbation.

Although the positive correlation between COPD and PM is accepted, the mechanism is still not defined. A recent study by Bayram et al. (10) looked at the underlying mechanism of how diesel exhaust particles may exacerbate the nonatopic COPD. Primary epithelial cells were cultured from smokers and nonsmokers and treated with diesel exhaust particles. Exposure to diesel particles induced apoptosis in both bronchial epithelial cells and alveolar epithelial cells, suggesting that the particles modify cell viability (10). Another study by Lee et al. (77) demonstrates an increase in DNA methylation in COPD patients exposed to PM. Gene markers of methylation have been used to determine the smoking/nonsmoking status of COPD patients (133). If this is occurring in patients exposed to PM as well, with more research, these changes could be utilized as biomarkers of a disease state.

Viral infection

Cross-sectional studies have shown that short-term increases in ambient PM lead to increased hospitalizations for respiratory infections (40, 81). A study by Hajat et al. (53) looked at correlations among SO_2, coarse PM, and upper respiratory disease, and found a greater positive correlation between disease and coarse PM versus SO_2 (53). One study in Italy correlated spikes in coarse PM to incidence of respiratory syncytial virus (RSV) in infants (146). In addition to these correlative studies, researchers have shown that exposure to PM can make the body and lung more susceptible to contracting certain diseases. For example, Noah et al. (97) exposed healthy adults to diesel exhaust particles [0 (filtered air) or 100 μg/m^3 for 2 h] followed by a dose of live attenuated influenza virus (LAIV) and found that subjects exposed to diesel versus filtered air had increased eosinophilia and increased quantity of virus in nasal lavage fluid. A similar study by Rebuli et al. (109) exposed healthy adults to wood-smoke (type of wood not specified) particles [0 (filtered air) or 500 μg/cm^3 for 2 h] followed by an inoculation with a vaccine dose of LAIV. Results did not show a significant increase in viral replication between PM- and control-exposed individuals. However, they did show a significant sex difference in inflammation-related gene expression (109) and highlighted a need for further research into the sex-specific responses to both PM and LAIV.

One experimental *in vivo* study exposed Balb/c mice to *Burkholderia pseudomallei,* a bacterial bioaerosol and the causative agent of melioidosis in humans, to study infection susceptibility. Mice were exposed to a variety of bacterial size fractions, and results showed that smaller bacterial particles (1 μm) had a greater, infection-induced pathological effect, measured in alveolitis and bronchiolitis, than larger sized bacterial particles (136). To examine the infection susceptibility shown in human epidemiological studies to be related to ambient PM levels, Kaan et al. (65) coexposed cells to PM and viral pathogens. Macrophages exposed to RSV significantly ($p > 0.05$) decreased their ability to phagocytose. Though this response was not exacerbated by coexposure to PM, significantly increased levels of inflammatory cytokines (IL-6, $p < 0.001$; IL-8, $p < 0.003$) were observed upon exposure to PM or RSV versus the PBS control (65). *In vivo* experiments in BALB/C mice treated with RSV and ultrafine carbon black as a PM surrogate (40 μg of carbon black or saline via intratracheal instillation on day 3 of infection) suggested that exposure to ultrafine PM enhances the expected response to RSV (AHR and increased BALF protein), demonstrating a significant difference between co- and RSV-exposed groups (76). These

model studies on respiratory infections observe both susceptibility to and exacerbation of disease with coexposures.

Valley fever

Valley fever, an infectious disease of the respiratory tract, is caused by inhalation of spores of the fungal species *Coccidioides immitis and Coccidioides posadasii*. Thus, the etiology of this disease is directly connected to a bioaerosol. The spores live dormant in the soil of arid regions and are only aerosolized if disturbed. In a model analysis by Tong et al. (139), researchers found that there has been an increase in dust storms (primarily identified by high levels of ambient coarse and fine PM concentrations) over the past decade. Researchers found that this increase correlated most strongly with increases in Valley fever outbreaks in the Southwestern United States (139). This study, along with others, has shown outbreaks of Valley fever to follow large fluctuations in precipitation or temperature (152). Coates and Fox (32) hypothesize that with more variable temperatures and precipitation levels, we will continue to see more frequent and more abundant outbreaks of Valley fever (32).

This disease is a unique example that has a known bioaerosol-specific etiology. Dust particulates, or coarse PM, are host to the causative fungal spores, but do not cause, or, as far as is known, exacerbate the disease. Valley fever is an example of a disease that will increase with the changing environment and should be taken into consideration when monitoring and regulating levels of coarse PM.

Due to the variability in results in these studies, it is still controversial to state that PM could lead to the onset of new disease. However, in the few studies that do show new disease onset, multiple stressors are present. As described throughout this article, PM and bioaerosols affect the lung in unique ways, necessitating that they be considered as individual stressors. Thus, coexposure by these two could be a multiple-stressor situation in itself. More epidemiological and model research on this topic could lead to insights into the predisposition and/or onset of respiratory disease. In a rapidly changing climate environment, this research could also be used to set new standards based not only on the amount of particulate pollution but the composition as well.

Conclusion

This article concludes that (i) respiratory effects worsen with coexposure to PM and bioaerosols; (ii) there is a data gap in coexposure studies; and (iii) particulate pollution should be studied through specific ambient environments.

The current understanding of ambient particulate pollution is that depending on the source, and thus the size and chemical makeup, at certain doses, it can elicit harmful effects to the lung. This rather broad statement has been further defined by researchers attempting to tease out the specific causative agent or the specific mechanism by which the lung is harmed. Each different source, diesel, wood smoke, agriculture, etc., has been found to affect the lung in a different fashion. On a cellular level, particulate exposure creates ROS, which can lead to oxidative stress and cellular death. On a slightly larger scale, exposure can lead to inflammation, remodeling of the airway anatomy, and changes to lung function. Taken

collectively, these physiological and anatomical changes can predis-pose, exacerbate, or lead to the onset of disease.

In vitro and *in vivo* experiments have established in multiple cell and animal types that exposure to PM or bioaerosols can lead to detrimental effects. There are a very limited number of *intentional* studies on the coexposures of PM and bioaerosols. For example, the authors believe that researchers could be learning a lot more about coexposure through the current models of asthma. Many researchers use HDM (a bioaerosol) as a model allergen, expose atopic subjects to PM, and see an exacerbation on symptoms without recognizing the significance of this experiment as a coexposure. In the intentionally coexposed study by Samake et al. (118), there is an additive effect demonstrating a higher level of oxidative stress and thus a higher likelihood for injury and disease when PM and bioaerosols are both present. These experiments need to be replicated with other PM and bioaerosol types in various models to ensure replicability and accuracy.

Researchers who have attempted to compare the relative toxicity of PM and bioaerosol exposure by source (car traffic, air traffic, agriculture, composting, wood-smoke, etc.) have come to different conclusions as to which source is most harmful to the respiratory system (31, 87, 88). Contrasting conclusions are understandable due to the multitude of variables that can contribute to respiratory disease. Also, to group agriculture or wood-smoke into broad categories can be highly problematic. Deering et al. (35) showed that burning different types of woods creates unique aerosolized particles that lead to a range of toxic responses. In a similar fashion, the toxicity of PM and bioaerosols generated from agriculture can be different, depending on the time of year, the crop grown, the pesticides used, and even the weather (107, 110, 118).

These differences lead us to believe that ambient particulate-related research should be situational and focused on the ambient particles present on a case-by-case basis. When collected, ambient particles should be thoroughly characterized for both bioaerosol and PM content to understand the environment from which they were collected. This is not to say that mechanistic studies should not be done. For example, this article and others (9) show that the inflammasome is activated by a wide range of pollutants, and is thus a likely common driver of the mechanisms leading to toxicity, regardless of the particle source. This type of situational experiment will easily lend itself to coexposure studies, as ambient particles, especially in today’s environment, are likely to contain both PM and bioaerosols. A recognition of this and an intentional examination of both particle types and how they interact in the environment and within the respiratory system are essential to understand how they can affect individuals and populations as a whole.

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List of Abbreviations

AhR	aryl hydrocarbon receptor
AHR	airway hyperresponsiveness
AQI	air quality index
ATP	adenosine triphosphate
BALF	bronchoalveolar lavage fluid
CAPs	concentrated ambient particles
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
d_a	aerodynamic diameter, the diameter of a spherical particle with a density of 1000 kg/m^3 and the same settling velocity as the particle of interest
DTT	dithiothreitol
FEV_1	forced expiratory volume, the maximum amount of air a person can expel, in 1 s
FVC	forced vital capacity, the maximum amount of air a person can expel after a full inhalation
GI	gastrointestinal
GSH	glutathione
GSSG	glutathione disulfide
HDM	house dust mite
HOCl	hypochlorous acid
IL	interleukin
LAIV	live attenuated influenza virus
MEF_{25}	mean expiratory flow at 25% of vital capacity (VC)
MEF_{50}	mean expiratory flow at 50% of VC
MEF_{75}	mean expiratory flow at 75% of VC mRNA messenger ribonucleic acid
MTT	3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide
NAAQS	National Ambient Air Quality Standards NADPH nicotinamide adenine dinucleotide phosphate

NHANES	National Health and Nutrition Examination Survey
NO_2	nitrogen dioxide
NOX2	NADPH oxidase isoform 2
O_3	ozone
OP	oxidative potential
OVA	ovalbumin
PAH	polycyclic aromatic hydrocarbon
PBS	phosphate-buffered saline
PEF	peak expiratory flow, the maximum speed of expiration
PM	particulate matter
$PM_{2.5}$	PM with an aerodynamic diameter (d_a)≤2 μm
PM_{10}	PM with a d_a ≤10 μm
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
ROS	reactive oxygen species, e.g., peroxides, superoxide, hydroxyl radical, and singlet oxygen
RSV	respiratory syncytial virus
SO_2	sulfur dioxide
TDF	total deposition fraction
TIP	total inflammatory potential
TRP	transient receptor potential
TRPV3	transient receptor potential subfamily V, member 3
VC	vital capacity, the greatest volume of air that can be expelled from the lungs after taking the deepest possible breath

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Didactic Synopsis

Major Teaching Points

- Particulate matter (PM) includes all solid and liquid pollutants. Examples are environmental, anthropogenic, and combustion-based particles.
- Bioaerosols are particles originating from microbial, fungal, animal, and plant sources.
- When combined with other stressors (such as bioaerosols), chronic exposure to PM could lead to new onset lung disease.
- Respirable bioaerosol fragments can be found in $PM_{2.5}$ and PM_{10}.
- Bioaerosol dispersion is dependent on the environment (i.e., the location, weather, and climate).
- Coexposure of PM and bioaerosols is associated with increased inflammation, lung injury, and disease exacerbation.
- New research on coexposure to PM and bioaerosols in human populations and cellular and animal models is needed.

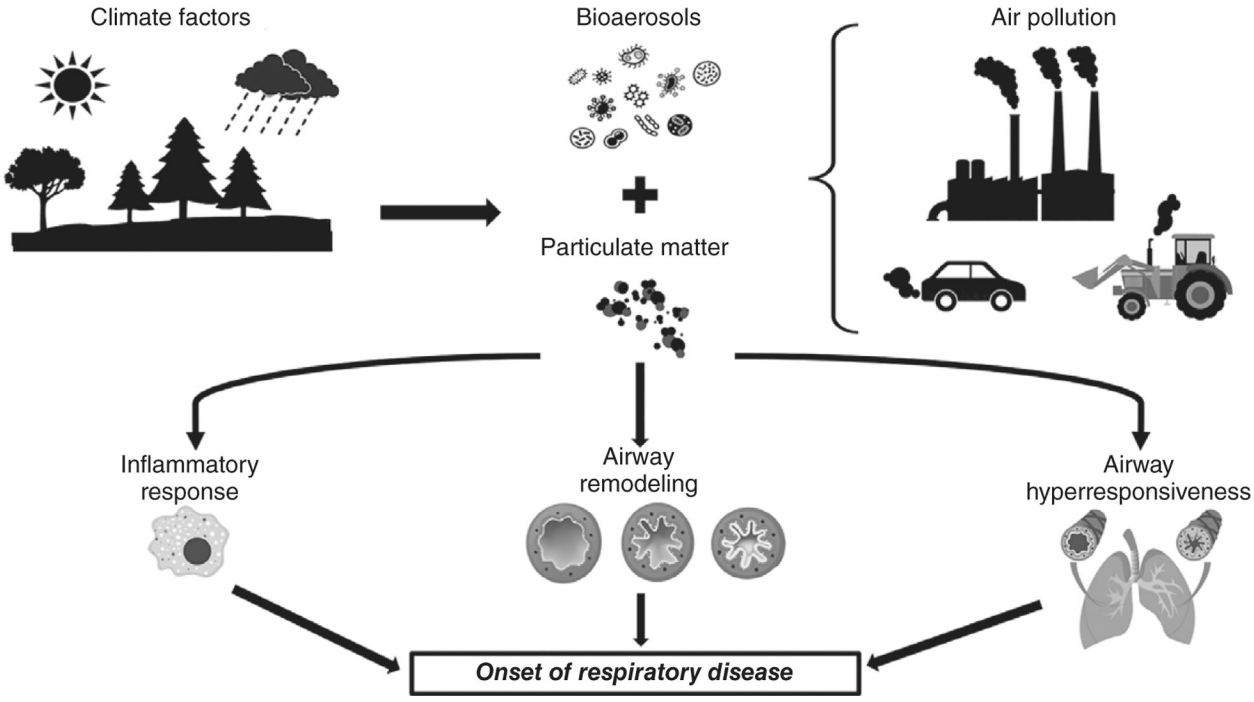

Figure 1.

Simplified schematic of the combined effects of climate, bioaerosols, and particulate matter acting as multiple stressors in the onset of respiratory disease.

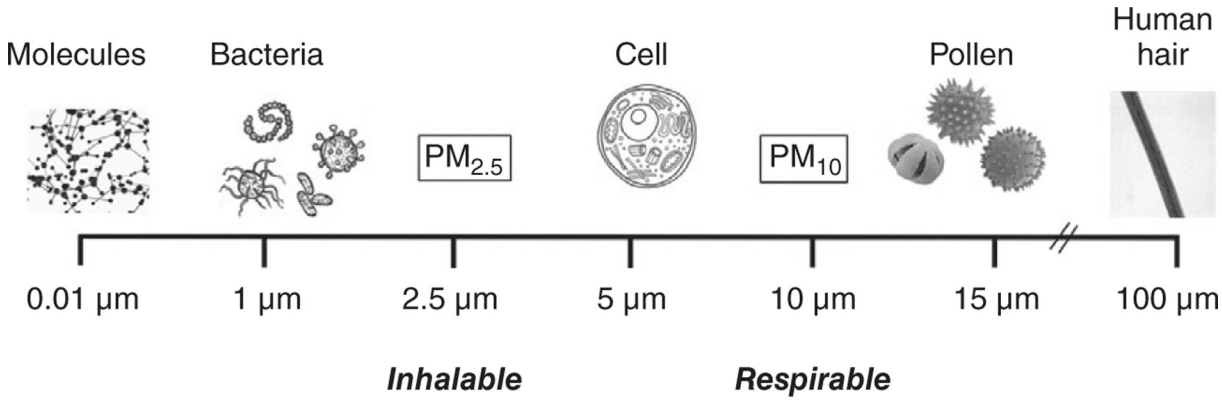

Figure 2. Comparison of particle size fractions including particulate matter (PM), bioaerosols and reference particles.

Adapted, with permission, from Kaiser J, 2005 (66).

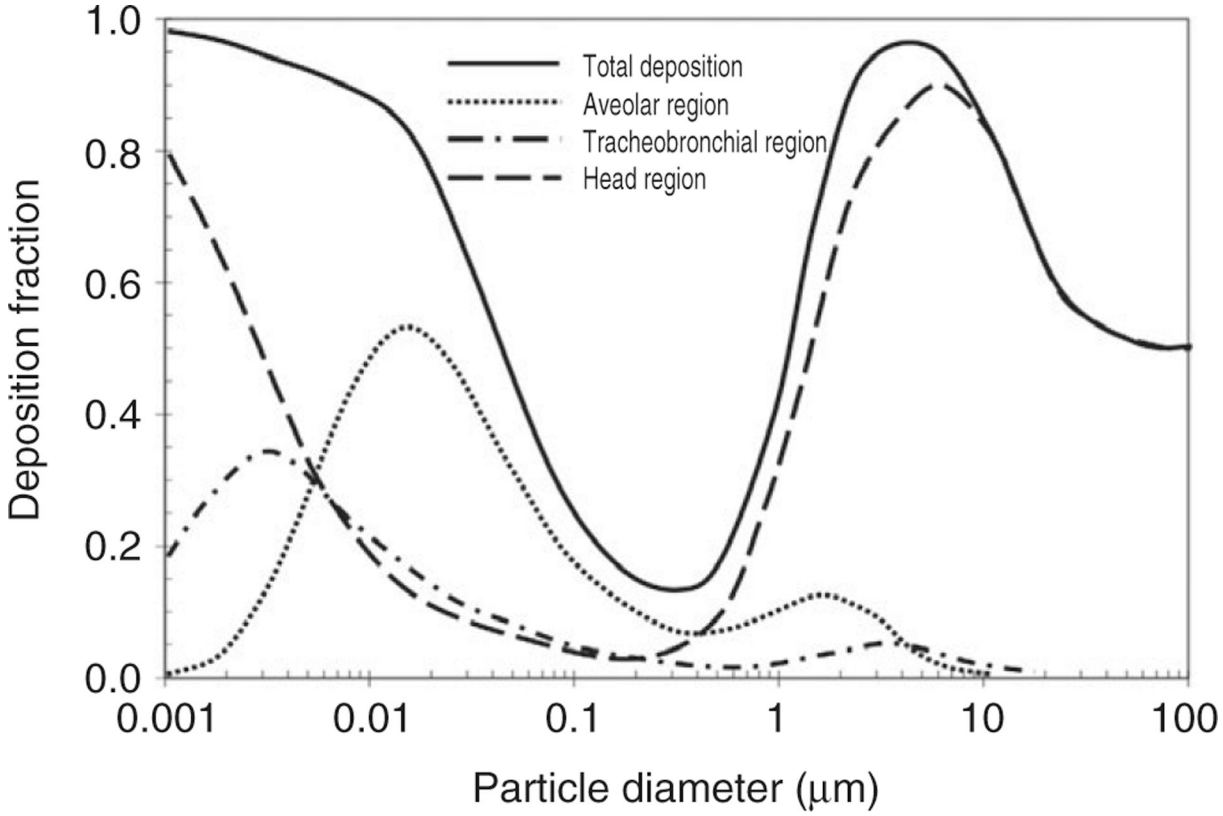

Figure 3. Probability of particle deposition in different regions of the respiratory tract.
This graph is modeled after an adult exposed to spherical particles with a density of 1000 kg/m^3, respiring during light exercise (25 L/min). Adapted, with permission, from Madl AK, et al., 2010 (83).

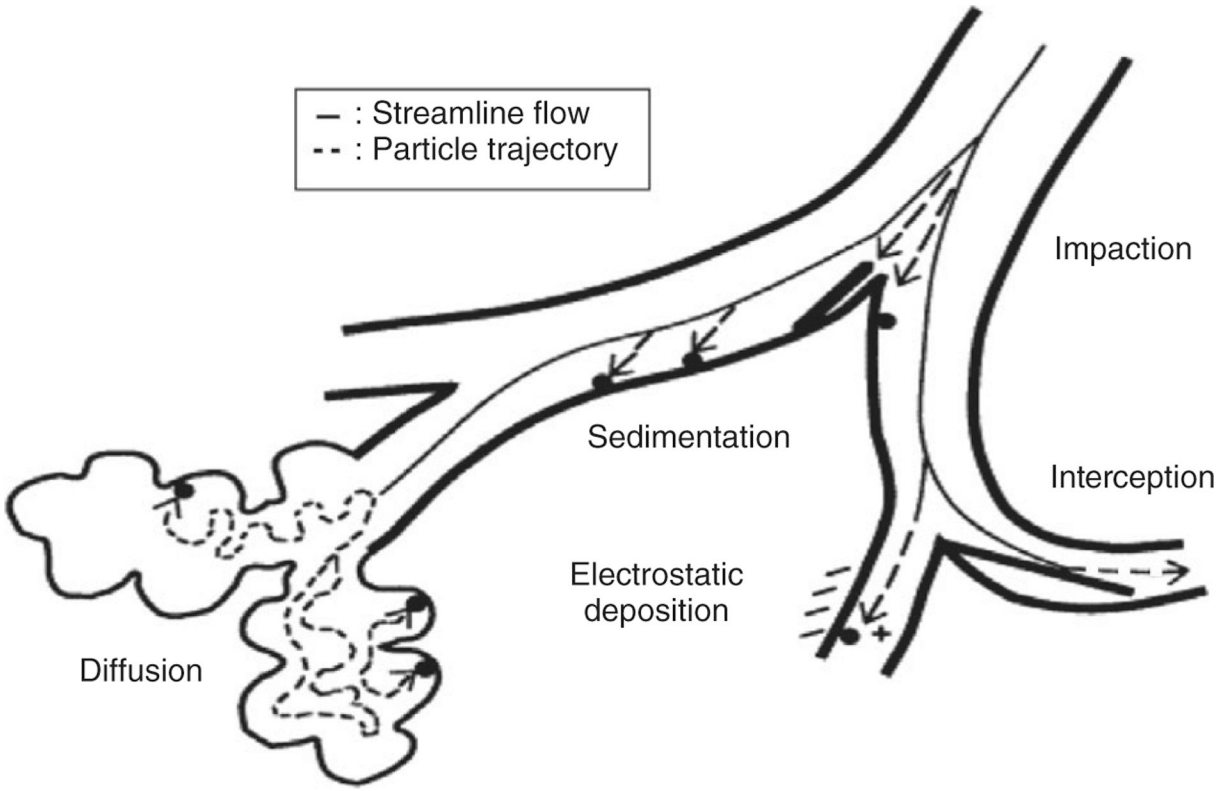

Figure 4. Impaction, sedimentation, interception, diffusion, and electrostatic deposition are the main mechanisms of particle deposition.

Impaction and sedimentation are dependent on the inertia of the particle size and shape, whereas diffusion is dependent on the properties of the aerosol and the trumpet effect of the alveolar space. Interception is dependent on an edge of a particle touching the tract surface and thus changing the final particle trajectory. Electrostatic deposition is dependent on particle charge. Adapted, with permission, from Madl AK, et al., 2010 (83).

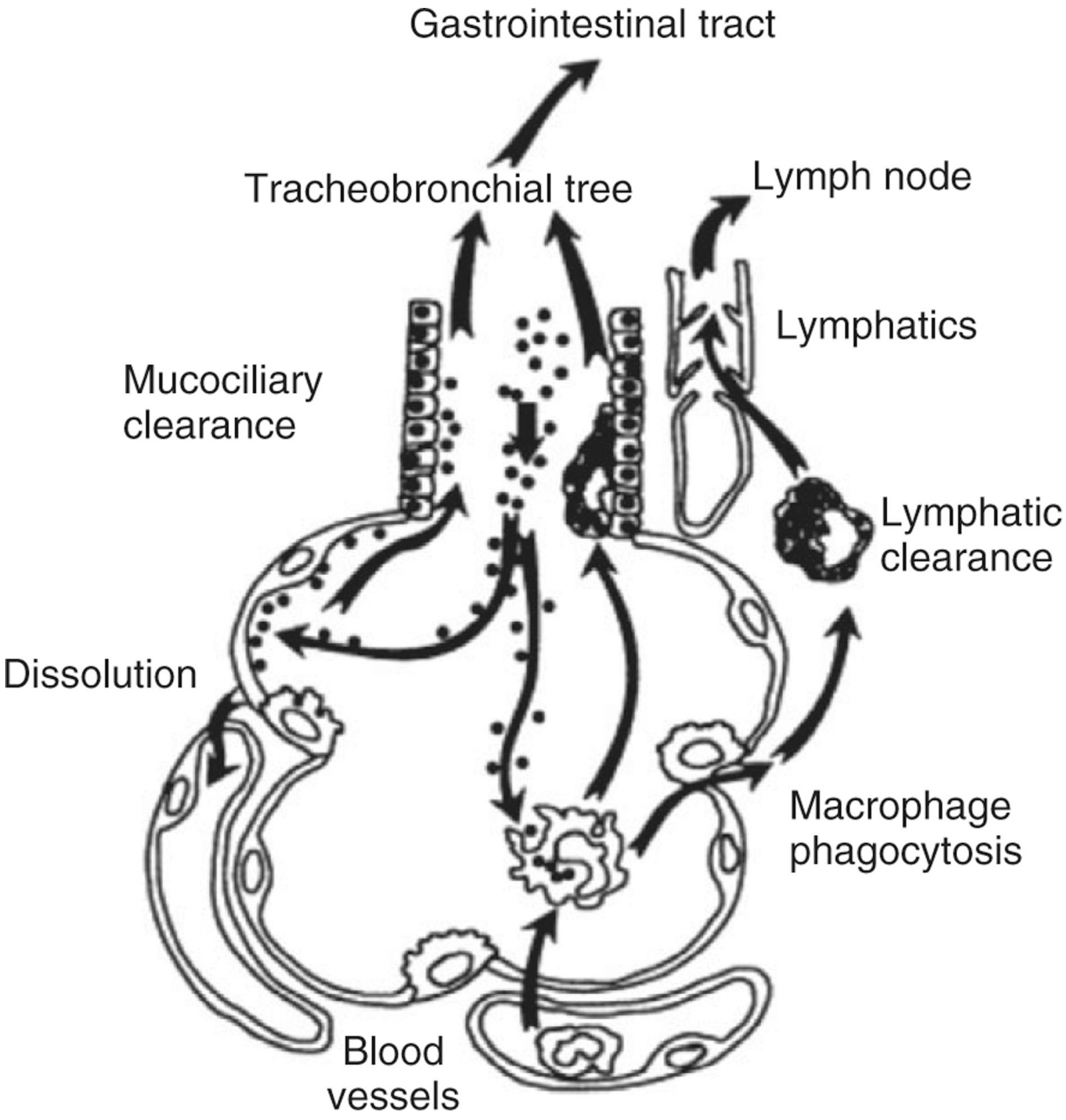

Figure 5. Clearance of particles from the tracheobronchial tree.

Mechanisms include (i) sneezing, coughing, and transport of mucin to the nasopharyngeal region where it is swallowed; (ii) direct mucociliary transport of particles up the tracheobronchial tree and subsequent passage to the gastrointestinal tract; (iii) macrophage uptake and transport up the bronchiolar airways or across the alveolar epithelium and clearance through the pulmonary circulation or interstitial lymphatics; and (iv) physicochemical processes, including dissolution, leaching, and physical breakdown of particles. Courtesy of Dr. Patrick J. Haley, Nycomed R&D, Inc., Collegeville, PA, from an original drawing.

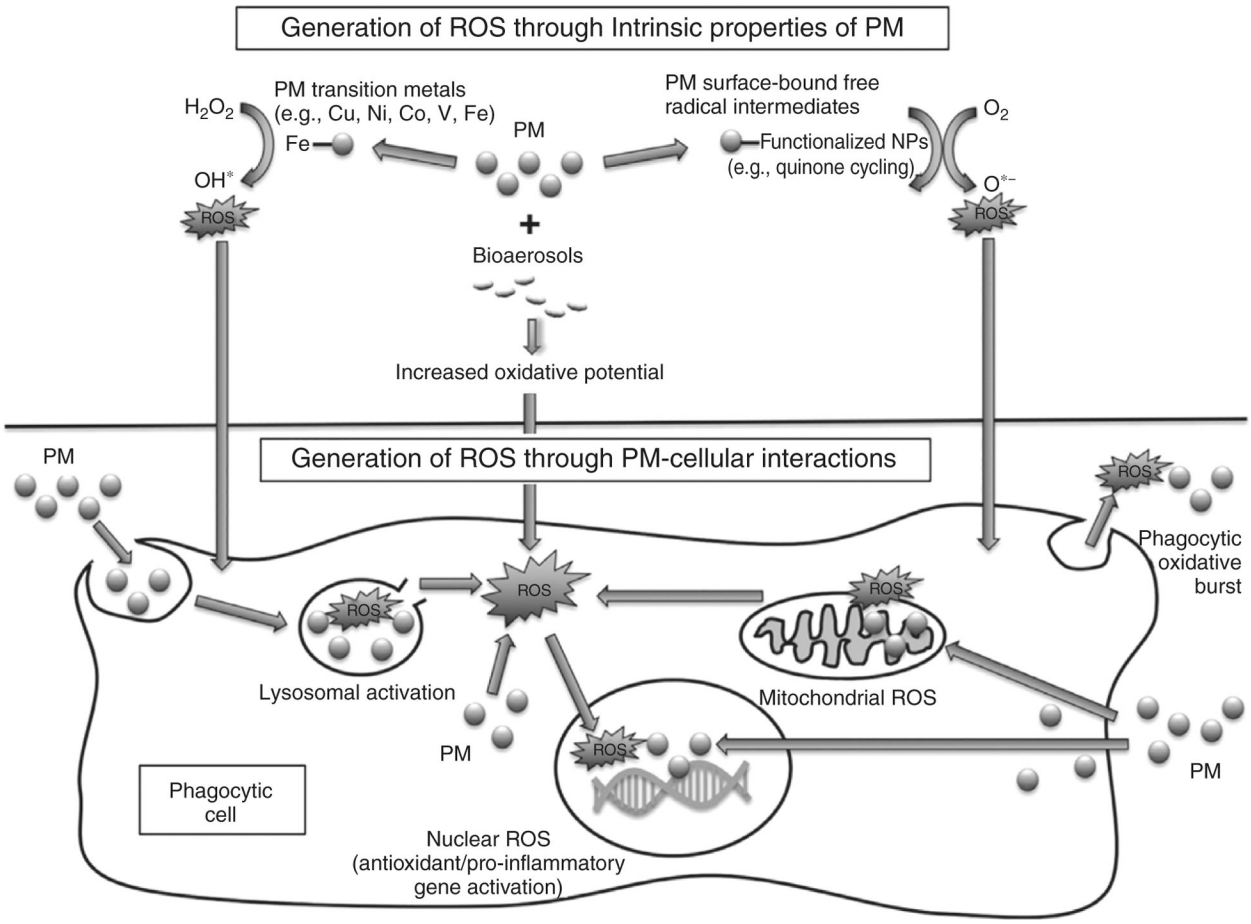

Figure 6. Mechanisms of reactive oxygen species (ROS) generation due to the intrinsic properties and cellular interactions of particulate matter (PM).

PM containing transition metals, free radicals, or pieces of organic bioaerosols can generate ROS intrinsically. PM also interacts with cellular surface proteins and internal cellular components prior to and after phagocytosis. Adapted, with permission, from Madl AK, et al., 2014 (84).

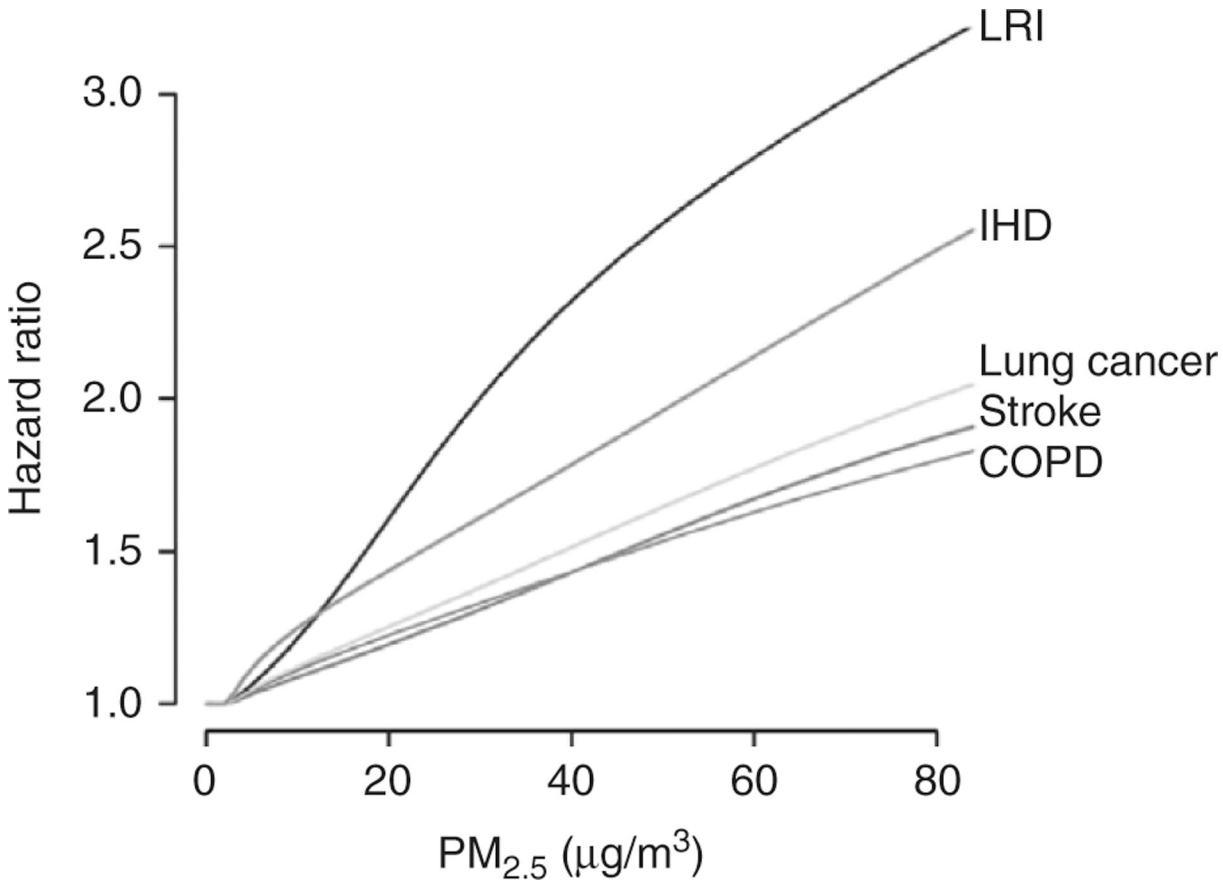

Figure 7. Mortality hazard ratio for PM-related diseases.

Abbreviations: LRI, lower respiratory infection; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease. Adapted, with permission, from Burnett R, et al., 2018 (18).