Impact of fossil fuel emissions and particulate matter on pulmonary health

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ABSTRACT

In recent decades, several national and international legislative efforts have aimed to improve air quality standards and limit major pollutants, such as carbon monoxide, sulfur dioxide, and nitrogen dioxide, linked to several public health problems. In recent years, particulate matter sources have become an important cause of several pulmonary and systemic diseases. Specifically, several studies examining cigarette smoke particulates have discovered the important contribution that mast cells play in the pathogenesis and progression of smoking-related lung disease and other particulate matter-related lung injury. By understanding the mechanisms of activation and signaling cascades involved in cigarette smoke and mast cell activation, novel pharmacological therapies for particulate matter-induced lung diseases could be developed.

KEYWORDS Air pollution; mast cells; particulate matter; smoking-related lung disease

In recent decades, several national and international legislative efforts have aimed to improve air quality standards and limit major pollutants, such as carbon monoxide, sulfur dioxide, and nitrogen dioxide, linked to several public health problems.¹ The World Health Organization estimated that 1.3 million people die each year from causes directly attributable to outdoor air pollution.² Even more people are affected due to the increased number of hospital admissions for cardiovascular and respiratory diseases related to elevated levels of airborne pollutants. The Clean Air Act identified 188 air toxins, also known as hazardous air pollutants. The US Environmental Protection Agency has identified 21 of these pollutants as mobile source air toxics, which are hazardous air pollutants that require regulation. A subset of six of these compounds was identified as having the greatest influence on health and included benzene, 1,3-butadiene, formaldehyde, acrolein, acetaldehyde, and diesel exhaust particulate matter (PM). The principal pollutants produced from the combustion of fossil fuels are presented in *Table 1*.^{3,4}

PM refers to tiny particles of solid or liquid suspended in a gas that carry toxic substances on their surface.¹ Sources of PM can be natural, including volcanoes, dust storms, and wildfires. However, manmade sources, such as those derived

from burning fossil fuels in vehicles, power plants, industrial processes, and smoking, generate significant amounts of aerosols. Specifically, PM is grouped into three different subsets based on particle size: PM₁₀ refers to particles with a diameter of 2.5–10 µm; PM_{2.5}, known as fine particles, refers to particles <2.5 µm in diameter; and PM_{0.1}, or ultra-fine particles, refers to those with a diameter <0.1 µm.⁵ PM₁₀ is deposited in large airways and is easily removed by mucociliary clearance. Smaller particles (PM_{2.5} and PM_{0.1}) are more harmful and may mediate systemic inflammation.⁵ Once inhaled, PM disseminates through the alveoli and diffuses through the blood-air barrier into the systemic circulation, inducing systemic oxidative stress and inflammation in the heart, liver, brain, and lungs.¹ These PMs accumulate in the lung parenchyma and can exacerbate several pulmonary diseases, including infectious diseases and chronic obstructive pulmonary disease, and reduce lung function.¹

Despite the implementation of pollution control technologies in the USA, smog derived from vehicular and industrial emissions remains a health problem for local communities and national security. Elevated levels of PM_{2.5} and PM₁₀ have been shown to be directly correlated with the level of particulate air pollution in polluted cities.^{3,4,6–10} PM exposure can occur during occupational exposures experienced by

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Table 1. Major pollutants derived from fossil fuel combustion^a

Pollutant	Description
Carbon dioxide (CO ₂)	A colorless, odorless, nontoxic greenhouse gas emitted as a byproduct of combustion, cement production, and respiration.
Carbon monoxide (CO)	A colorless, odorless, nonirritating, but very poisonous gas. It is a byproduct of incomplete combustion of fuels such as natural gas, coal, or wood. Vehicular exhaust is a major source of CO.
Nitrogen oxide (NO ₂)	Emitted from high-temperature combustion and can be seen as the brown haze dome above or plume downwind of cities. It is one of several nitrogen oxides. This reddish-brown toxic gas has a characteristic sharp, biting odor.
Ozone (O ₃)	Formed by reactions between organic compounds and nitrogen oxides. These precursor compounds are emitted by all combustion sources, and in many regions mobile sources, including motor vehicles, are the major source. Ozone violations most often occur in summer (April–October), because strong sunlight and heat are necessary for its formation.
Particulate matter (PM ₁₀ and PM _{2.5})	Airborne particles that are <10 µm (PM ₁₀) or <2.5 µm (PM _{2.5}) in diameter. Particulate matter is both directly emitted and the result of secondary formation based on chemical reactions with nitrogen oxides, VOCs, sulfates, and ammonia, especially with respect to PM _{2.5} . As with ozone, secondary pollution can form some distance away from the precursor emission sources.
Sulfur oxides (SO ₂)	Produced by volcanoes and in various industrial processes. Because coal and petroleum often contain sulfur compounds, their combustion generates sulfur dioxide. Further oxidation of SO ₂ , usually in the presence of a catalyst, such as NO ₂ , forms H ₂ SO ₄ and thus acid rain.
VOCs	An important outdoor air pollutant. VOCs are often divided into the separate categories of methane (CH ₄) and nonmethane. Within the nonmethane VOCs, the aromatic compounds benzene, toluene, xylene, and 1,3-butadiene are hazardous compounds often associated with industrial uses. Methane and other hydrocarbon VOCs are important greenhouse gases that contribute to enhanced global warming via their role in creating ozone.

VOCs indicates volatile organic compounds.

^aSource: PennState: <https://www.e-education.psu.edu/egee102/node/1951>.

firemen or power plant employees.¹¹ Other localized sources contributing to PM exposure include woodstoves, fireplaces, wildfires, volcanic activity, dust, and waste incinerators.

Cigarette smoking remains a significant health burden, killing 7 million people globally, and is the leading risk factor for lung cancer, which accounts for 80% of all lung cancers, and for cardiopulmonary diseases, such as chronic obstructive pulmonary disease, emphysema, hypertension, and coronary artery disease.^{5,12,13} The burning of a cigarette releases a complex aerosol, including liquid tar droplets, volatile compounds, and incomplete combustion gases. When inhaled, the 15,000 to 40,000 µg of PM enters the respiratory tract and increases oxidative stress processes disrupting respiratory epithelium function and integrity.¹⁴ Depending on composition and duration, PM exposure leads to a “loss of pulmonary function, increased bronchial hyperresponsiveness, pathological alterations of emphysema and fibrosis, hemorheological changes, and comorbidities, including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and cancers.”¹⁴ Persistent exposure to PM exacerbates allergic diseases, which are mediated by mast cells.¹⁵ Specifically, several studies examining cigarette smoke particulates have discovered the important contribution that mast cells have in the pathogenesis and progression of smoking-related lung disease and other PM lung injury.

MAST CELLS AND SMOKING

Derived from bone marrow cells, mast cells modulate the innate immune response contributing to the function and

integrity of tissues and organs through the production of proinflammatory mediators, proteases, and cytokines.^{16–18} Mast cells have several stimulatory and inhibitory receptors, which include cross-linked immunoglobulin E binding to the high-affinity immunoglobulin E receptor receptors, toll-like receptors, and formyl peptide receptors.^{19,20} In the lungs, mast cell activity maintains pulmonary function through modulation of the innate and adaptive immune system.²¹ In pathological conditions, stimulation of mast cells releases preformed substances, such as histamine and proteases, and proinflammatory mediators involved in the pathogenesis of rhinitis, asthma, and anaphylaxis.^{19,20} Prolonged activation of mast cells may produce structural and functional remodeling of airways, parenchyma, and vasculature.²² Furthermore, chronic stimulation of mast cells can damage tissues and organs, leading to several pathological conditions, such as chronic obstructive pulmonary disease.²² With the increase in air pollution, several studies have investigated the role of mast cells and PM-related lung disease, specifically smoking-related lung disease.²¹

A clinical study examining asymptomatic smokers showed an increase in mast cells throughout the bronchial mucosa.²³ Specifically, mast cells were found concentrated in the smooth muscle compartment, suggesting bronchial tissue remodeling in response to chronic cigarette smoke exposure.²³ Furthermore, a bronchoalveolar lavage study from smokers showed increases in histamine secretion activity by alveolar macrophages, which increases mast cell degranulation and destruction of bronchial tissue.²⁴ Cigarette smokers also showed decreased nitric oxide secretion from mast cells

through down-regulation of endothelial nitric oxide synthase in the pulmonary artery endothelial cells, which impairs maintenance of the nasal and immune response.²⁵ Mast cells exposed to cigarette smoke increased the production and secretion of proteases, cytokines, and proinflammatory molecules through the high-affinity immunoglobulin E receptor stimulation.^{15,25} Additionally, cigarette smoke toxins, such as acrolein, stimulate mast cell degranulation, releasing cytokines and leukotrienes. Subsequently, the cytokines and leukotrienes activate several cellular processes, increasing the production of free radical species while inhibiting antioxidant mechanisms.²⁶ Cigarette smoke combustion also releases benzene, which inactivates mast cell innate immune response through interference of the PI3 kinase pathways.²⁰

Overall, cigarette smoke increases tissue remodeling and destruction of alveolar structures in smoking-related lung diseases in part through the stimulation of mast cells.²⁷ However, targeting mast cells remains a difficult prospect given the diversity and heterogeneity of mast cell mediators, the multiple mechanisms of mast cell activation, and the phases of disease progression.²² Furthermore, the extent to which PM activation of mast cells affects other pulmonary disease remains an area of active investigation. Therefore, understanding the mechanisms of activation and signaling cascades involved in cigarette smoke and mast cell activation might encourage novel pharmacological therapies for particulate matter-induced lung diseases.

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