

REVIEW ARTICLE

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Air Pollution Induced Asthma and Alterations in Cytokine Patterns

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ABSTRACT

In recent decades, clinicians and scientists have witnessed a significant increase in the prevalence of allergic rhinitis and asthma. The factors underlying this phenomenon are clearly complex; however, this rapid increase in the burden of atopic disease has occurred in parallel with rapid industrialization and urbanization in many parts of the world.

Consequently, more people are exposed to air pollutants than at any point in human history. Worldwide increases in allergic respiratory disease have mainly been observed in urban communities. Epidemiologic and clinical investigations have suggested a strong link between particulate air pollution and detrimental health effects, including cardiopulmonary morbidity and mortality. The purpose of this review is to provide an evidence-based summary of the effects of air pollutants on asthma, focusing on particulate matter PMs, diesel exhaust particles (DEPs), and ozone as major air pollutants. An overview of observational and experimental studies linking these pollutants with asthma will be provided, followed by consideration of the mechanisms underlying pollutant induced immune response and inflammation. The cytokine response will be viewed in depth and a brief discussion of future research and clinical directions is provided.

Key words: Air Pollution; Asthma; Cytokines

INTRODUCTION

Acute air pollution is a major environmental challenge in contemporary times. Urban and industrial areas in many parts of the world, particularly in the developing countries are exposed to pollutants which have adversely affected air quality and human health.¹ Many efforts have been made to control and curb air pollution through regulation of emissions from industries and vehicles. Although in many industrialized countries decades-long air pollution abatement programs have resulted in better air quality, continual

and emerging issues in these areas as well as the ongoing challenge in urban air in developing countries still poses a significant global health problem. Tehran is a mega-city that experiences inversion and smog many days a year. Although major air pollution abatement plans are successfully underway, its air pollution problem will persist for several years before up to standard ambient air quality is achieved.²

Cardiovascular and respiratory diseases, asthma and allergy, immunological disorders, and cancer are among the complications listed in current scientific literature related to air pollution. Respiratory illness alone account for hundreds of million person days of restricted activity and lost work each year. Hence, any agent which impairs normal respiratory function is likely to have a significant social and economic impact.

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With this concern in mind, numerous epidemiological, clinical and basic studies have been undertaken to determine the effects of air pollution on health parameters (Figure 1).

Pyramid of New York City, NY Annual Adverse Ozone Impacts Avoided By The Implementation Of The Proposed New Standard (vs. "As Is")*

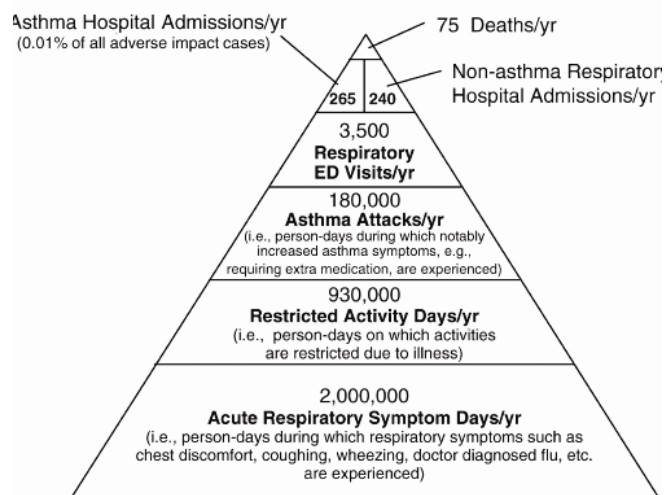


Figure 1. Estimated number of acute adverse health effects avoided by meeting the 1997 US EPA Ozone Ambient Air Quality standard. Reprinted with permission from the prepared statement of Dr George D. Thurston from clean Air Acc Ozone and particulate matter standards. Hearings before the subcommittee on clean Air.

Motor vehicle emissions and industrial emissions are a major source of airborne pollutants. The combustion of fossil fuels produces a number of unhealthy substances, including carbon monoxide, nitrogen oxides, benzene, sulfur dioxides, and particulate matter (PM). Airborne pollutants may enter the respiratory tract as 1) volatile gases: such as, carbon monoxide, ozone, and benzene 2) liquid droplets: sulfuric acid, oxides of nitrogen 3) particulate matter: components of diesel exhaust and poly aromatic hydrocarbons.^{2,3}

PM

PM is a general term that refers to a mixture of solid particles or liquid droplets of varying chemical composition and physical properties suspended in the air. Deposition in the respiratory tract varies with particle size. Combustion and secondary particles are usually very small (1 μ m in diameter) and are present in children respiratory system because of their frequent mouth breathing, and these particles are especially of

concern because they usually contain more toxic compounds and can penetrate deeper into the lung than the larger PM generated by natural processes (eg, windblown soil particles). Particles larger than 10 microns in diameter do not typically pass beyond the larynx, but because of their frequent mouth-breathing behavior, these particles can more often deposit in the respiratory tract of children.⁴⁻⁶

PM₁₀ is composed of both fine and coarse particles. Coarse particles in the PM₁₀ are 2.5 to 10 μ m in diameter and can include dust generated from the breakdown of rocks, soil, and dust. Fine particles, including those that are formed in the atmosphere from gaseous pollutants, are less than 2.5 μ m in diameter (PM_{2.5}) and result from the combustion of fuels used in motor vehicle, power plant, and industrial operations, as well as the combustion of wood (eg, in wood-burning stoves) and other organic materials. Of major concern are nano particles because they can remain suspended in the atmosphere, as they settle out relatively slowly. The formation and increase of atmospheric aerosols from the combination of natural (e.g., animal) and anthropogenic sources are a major air-quality concern.⁷⁻⁹

Diesel Exhaust Particles

The largest single source of airborne PM from vehicles is derived from diesel exhaust. Diesel fuel combustion results in the production of diesel exhaust particles (DEPs), as well as gaseous compounds, including nitrogen oxides and precursors of ozone. DEPs consist of an elemental carbon core with a large surface area to which hundreds of chemicals and transition metals are attached. Most mechanistic studies have attributed the proinflammatory and adjuvant effects of DEPs to these chemical constituents. The majority of DEPs are classified as fine (2.5-0.1 μ m) or ultrafine (0.1 μ m) particles, but these primary DEPs can coalesce to form aggregates of varying sizes. It has been postulated that because smaller particles have a greater relative surface area, they can carry proportionally more chemicals and have greater biologic effects.^{5,10,11}

Sox

Sulfates are a major component of the water-soluble fraction of suspended PM containing the sulfate ion, but not limited to strong acids, and sulfate salts. Sulfates also contribute to acid rain and can often be

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seen in the air as a milky white summertime haze that impairs visibility, seen in the downwind of coal-fired power plants that emit a large portion of sulfur oxide emissions and their resultant secondary sulfates.^{10,11}

NO_x

Diesel- and gasoline-powered vehicular engines and coal- and oil-fired power plants are the main sources of ambient emissions of oxides of nitrogen (NO_x), which typically result from the fixation of nitrogen in the air during high-temperature combustion. The available epidemiologic studies are often difficult to interpret because of the high degree of co variation between NO₂ and other outdoor air pollutants. However, they suggest a possible synergistic role by NO₂ with other air pollutants in mediating lower respiratory tract illnesses among children.^{10,12}

Smog and O₃

The term smog a combination of smoke and fog has been employed in scientific texts since the mid twentieth century to denote the photochemical phenomena that ensues inversion of layers of polluted air and a new combination of pollutants resulting in high levels of ozone O₃ which causes proinflammatory reactions in airways and lungs.¹³ It has subsequently been found that ozone occurs in the polluted air of most, if not all, urban areas throughout the world.¹¹

Ozone is not emitted directly by any man-made source in significant quantities. Instead it arises from chemical reactions in the atmosphere through the action of sunlight on oxygen molecules. The photochemistry involved in the generation of ozone is complicated and usually involves three reaction mechanisms: photo-activation, photodecomposition and free radical chain reactions.¹⁰ Its formation in the photochemical complex is essentially cyclic and is dependent upon the following factors. First, the photodecomposition and regeneration of nitrogen dioxide (NO₂) and oxygen (O₂); second, interactions of nitric oxide. NO and NO₂ with other radical species in the complex, and third, the input of sunlight at wavelengths between 295 and 430 nm.^{11,12}

Epidemiological and Clinical Studies

Global statistics indicate a correlation between the degree of exposure to pollutants and incidence of asthma and allergy. In 1873, when Charles Harrison Blackley reported that "hay-fever" or "hay-asthma"

was actually caused by grass pollen, he also observed that it was more common in urban than in rural settings, an observation since confirmed in numerous studies.¹³⁻¹⁶ Studies in some areas indicate that up to 30% of the population in industrialized areas have allergic symptoms. Exposure to outdoor air pollutants, including ozone (O₃), particulate matter (PM) and hazardous air pollutants (HAPs), are also known risk factors for developing respiratory diseases, including asthma.^{4,17,18.}

In the late 1950s by examining the total deaths attributable to cardiovascular or respiratory failure in Los Angeles county in relation to the maximum oxidant levels, a significant association was found between ozone concentrations and mortality,¹⁹ Later studies also indicated small but significant associations between daily mortality and the ambient concentrations of pollutants.²⁰ In a study performed in Tehran a correlation was observed between the number of hospital admissions for asthma and the weekly mean concentration of nitrogen dioxide (P < 0.05). The 3-day and 10-day mean concentrations of sulphur dioxide were also found to be directly associated with the number of asthma admissions during this period.²¹ A study performed in Isfahan, an industrial city in Iran with a history of air pollution also indicated more susceptibility to asthma among children living in urban settings.²² Children living in Seattle area who are exposed to 10 microg/m³ increase in particulate matter (less than or equal to 2.5 micron) for more than one day, show 1.2 times increased odds of having serious asthma attack. This study also showed that 10 micron particulates increase was also associated with more serious asthma attacks.⁹ Studies done in Iran indicate that diesel exhaust might also enhance allergic and inflammatory responses to antigens and might facilitate development of new allergies.²¹⁻²³

Acquisition of 'hard mortality' data is a difficult task, but attempts to compile such figures in recent years have been made. In the UK, the COMEAP (committee on medical effects of air pollutants) concluded that up to 12 500 deaths are hastened each year after only ozone peaks were observed.²⁴ Hence, these new studies suggest that the impact of ozone on mortality is best considered as a contributing factor in the 'hastening of death'. That is, exposure to ozone accelerated death in those already ill, but did not directly cause it. A number of epidemiological studies have demonstrated a significant negative association

between the concentrations of ambient ozone and other pollutants and pulmonary function particularly in children.^{25,26}

Another approach that has been used to assess the impact of ozone on respiratory health has been examining hospital admission records around the time of a major episode. Many studies using this approach have demonstrated a negative association between ambient ozone concentrations and hospital admissions²⁷ later studies did not confirm the link.²⁸

It is now generally accepted that studies which include all individuals are difficult to interpret, especially as many air pollution episodes contain complex mixtures of pollutants. As a counter to this problem, attention is now beginning to focus on vulnerable subgroups of the population, such as those with cardio-respiratory disease. In this respect, those with chronic obstructive airways diseases are recognized as a sensitive subgroup.²⁷

Basic and Clinical Studies

The effect of various pollutants on lung and immune parameters has been studied extensively in both clinical and basic aspects. These studies elucidate some of the mechanisms through which pollutants exert their effects on respiratory and immune systems.

Ozone

Exposure of human subjects to ozone, either during an air pollution episode, or under controlled chamber conditions, has been shown to elicit a wide spectrum of responses.²⁹ The symptoms include subjective perceptions of respiratory discomfort (substernal soreness and pain on deep inspiration); putative alterations in lung function; the development of airway inflammation; as well as tissue injury, with altered airway permeability and subsequent epithelial re-modeling.^{29,30}

Increased airway reactivity to non-specific bronchoconstrictors (histamine, metacholine) has been reported in subjects following ozone exposure. Bronchial hyper-reactivity has been shown to double after exposure to 0.12 ppm ozone in chamber studies³⁰ and dose-dependent increases in metacholine responsiveness have been observed after exposure to 0.08±0.12 ppm ozone.³¹ Numerous studies on humans and laboratory animals have demonstrated that exposure to ozone increases bronchial responsiveness to allergen.³² Ozone exposure has been shown to increase bronchial responsiveness to inhaled allergen in

atopic asthmatics and allergic airway responses have been reported to be increased due to ozone (0.25 ppm for 3h) in asthmatics, though not in subjects with allergic rhinitis.³³ Ozone exposure has also been shown to augment symptomatic and allergic responses in the nasal airways of asthmatics.³⁴ Despite the evidence presented in these studies, the issue of whether air pollutants can increase bronchial responsiveness to allergen remains equivocal.

Diesel Exhaust

The specific effects of diesel exhaust and its particles on allergic respiratory disease have been explored in a number of animal, in vitro, and human clinical studies (Table 1).

The most consistent finding in these investigations is the profound adjuvant effects of DEPs on the development and intensity of allergic inflammation. Animal studies have demonstrated an increase in total and antigen-specific IgE levels, as well as increases in IL-4, IL-5, and GM-CSF levels in response to DEP exposure.³⁵⁻³⁷ In addition, DEPs reproducibly induce increased airway eosinophilic inflammation, goblet cell hyperplasia, and airway hyperreactivity (AHR) in murine models of asthma.³⁸⁻³⁹

Table 1. Direct effects of DEPs and their extracts on multiple cell types

A. Bronchial and nasal epithelial and endothelial cells:
Increase expression of chemokines and cytokines (IL-8, eotaxin, RANTES, GM-CSF, and IL-6)
Increase expression of histamine 1 receptor
Upregulate expression of adhesion molecules (ICAM-1)
Increase phase 2 enzyme expression
B. Eosinophils
Enhance adhesion to nasal epithelial cells
Induce eosinophil degranulation
C. Mast cells
Enhance IgE-mediated histamine release
Enhance cytokine production (IL-4, IL-6)
D. Basophils
Induce histamine release in the absence of IgE
Enhance cytokine production (IL-4)
E. PBMCs
Induce chemokine production (IL-8, RANTES)
Synergize with allergen to increases in IL-8, RANTES, and TNF- α production
F. B cells
Enhance IgE production after IL-4 and anti-CD40 stimulation
G. Monocytes-macrophages
Modulate cytokine production (eg, inhibits IL-12p40 production)
Inhibit prostaglandin E2 release
Increase phase 2 enzyme express

NO_x

Studies in London, Japan and the US have associated increased ambient NO₂ with risks of respiratory tract symptoms,^{35,40} Whereas in Santa Clara, California, NO₂ levels were associated with childhood asthma exacerbations.⁴¹ In a fourth-grade cohort of southern California children, exposure to NO₂ was associated with reduced lung function growth.^{38,40} Controlled-exposure studies of persons with asthma have shown that 30-minute exposures to NO₂ can enhance the allergic response after subsequent challenge with allergens. Enhancement was seen at concentrations as low as 0.26 ppm, a level experienced in some American communities on a short-term basis, despite compliance with current federal regulation, similar results were also observed in French school children.^{35,42}

PM

In recent studies across the globe PM10 exposure has been increasingly associated with infant respiratory illness and infant death⁴². Woodruff et al⁴³ found an association with infant deaths in the United States, even when they excluded neonatal deaths. This excess risk seemed to be principally from respiratory illness, although sudden infant death syndrome rates were also increased. Bobak and Leon⁴⁴ also found a similarly significant association between infant death rates and particle and SO₂ concentration in the Czech Republic.

Mechanisms of Pollutants Effects

The underlying mechanisms by which pollutants and DEPs exert biologic effects are an area of ongoing investigation. Oxygen species generated on exposure to pollutants and the subsequent generation of oxidative stress has been the focus of many studies.³ Also research indicates that the inhibitory effect on particle phagocytosis mediated by four different receptors suggests that air pollution particles cause a general inhibition of macrophage phagocytosis.³⁵ Their specific effects on the lung, airways and immune system which are related to allergy and asthma are essential issues in this field. Here we will focus on the specific effect of pollutants on the cytokine patterns in the lung and the role of cytokines in pollution induced allergy and asthma

Cytokines

Cytokines are low weight regulatory proteins that play a major role in cell to cell communication, in

regulating the development and function of immune effector cells and in regulating the production and function of other cytokines.

Cytokines act locally and bind to the specific receptors on target cell membrane with high affinity with dissociation constants ranging from 10⁻¹⁰ to 10⁻¹² M. They act upon other cells in autocrine, paracrine and endocrine forms. They display the following attributes: pleiotropy, redundancy, synergy, antagonism and cascade induction. Considering their important regulatory role the effect of air pollutants on the expression, production, secretion and effectory roles of cytokines must not be underestimated.⁴⁵

Data from both animal and cell culture experiments have subsequently confirmed that ozone exposure stimulates the production of both neutrophil and monocyte chemoattractants early after exposure.⁴⁶

Notably a causal relationship between the production of these species and airway neutrophilia has never been conclusively shown in vivo. Much attention has focused on IL-8 as a key promoter of neutrophil chemotaxis. Numerous in vitro studies have demonstrated increased production/secretion of this cytokine after ozone exposure^{47,48} and its concentration has been shown to be elevated in human lavage fluid obtained after ozone challenge.⁴⁹ Recent work on primates has shown that IL-8 message is increased in airway epithelial cells and alveolar macrophages early (1 h) after exposure to 0.96 ppm ozone (8 h), returning to control levels at 24 h post-exposure.⁵⁰ The profiles of the PGE₂ and IL-6 response after ozone appear to fit the profile of the developing neutrophilia more closely than IL-8.⁵¹

The release of platelet activating factor from ozone-exposed epithelial cells in vitro has also been demonstrated.⁵² Recently, this lipid mediator has been shown to play a key regulatory role in ozone-induced inflammation in mice, where acute inflammation could be attenuated through administration of PAF receptor antagonists.⁵³ Currently, no data on the response of this lipid mediator in humans exposed to ozone have been published.

Many studies have demonstrated increased concentrations of GM-CSF at 18 h post-exposure and equated this increase with neutrophil activation.⁵⁴ Though GM-CSF has been shown to be involved in neutrophil activation in vitro,⁵⁵ the assumption of a clear association in vivo is far from established. Exposure to 0.2 ppm ozone for 2 h has also been shown

to induce an increase in submucosal mast cells of healthy subjects 1.5 h post-ozone exposure.⁵⁶ A similar increase in submucosal mast cell numbers has recently been reported after exposure to diesel exhaust⁵⁷. Mast cells are an important source of several pro-inflammatory cytokines such as TNF α , GM-CSF, TGF β , IL-1, IL-3 and IL-6 and may therefore play a role in modulating the recruitment of neutrophils to the interstitium. As stated earlier, repeated exposures to ozone result in an attenuation of the observed pulmonary response. Attenuation of airway inflammation with successive exposures has also been reported in animal models⁵⁸ and decrease in IL-6 not IL-8 production in humans is also reported.⁵⁹

Studies show DEPs also enhance histamine induced IL-8 and GM-CSF levels from human airway epithelial cells *in vitro*.⁶⁰ Extracts from DEPs effectively enhance human eosinophil adhesion to nasal epithelial cells and induce eosinophil degranulation.⁶¹ In addition, PBMCs from allergic subjects co-cultured with DEPs and allergen show synergistic increases in IL-8, RANTES, and TNF- α production.⁶² These cytokines are over expressed in asthmatic bronchoalveolar lavage fluids and are believed to enhance airway inflammatory responses.^{63,64}

Cultured BECs bronchial epithelial cells from asthmatic patients constitutively release greater amounts of IL-8, GM-CSF, RANTES, and soluble intercellular adhesion molecule 1 (ICAM-1) compared with levels in non-asthmatic individuals. Exposure to low DEP concentrations (10 mg/mL) significantly increases release of these cytokines from BECs of asthmatic subjects, whereas BECs of non-asthmatic subjects require higher concentrations of DEPs (50-100 mg/ml) to cause significant increases in IL-8 and GM-CSF production.⁶⁵ *In vivo* studies support a proinflammatory role for DEPs.

Increases in lymphocytes, monocytes-macrophages, and neutrophils are observed after nasal challenge of subjects with DEPs, and this is accompanied by an increase in levels of the CC chemokines RANTES, macrophage inflammatory protein 1a (MIP-1a), and monocyte chemoattractant protein 3 (MCP-3).⁶⁶

In addition, IL-6 and IL-8 expressions are increased, as is expressions of the adhesion molecules ICAM-1 and vascular cell adhesion molecule 1.⁵⁷ In addition, DEPs can interact with allergen to augment allergen-induced responses, so that allergen-specific IgE levels are up to 50- fold greater in allergic subjects

challenged with DEPs plus allergen than in those receiving allergen alone. In addition, diesel particles have been shown to broadly stimulate cytokines when administered alone, but when administered with allergen, they induce a TH2 cytokine profile and a concomitant decrease in IFN- γ levels in the nasal environment. DEPs also appear to affect immediate responses through direct effects on mast cell and basophils.^{67,68}

Thus if administered with DEPs, only 20% of the amount of intranasal dust mite allergen normally required will result in a symptomatic response. In the real world this effect is probably compounded because DEPs can also increase histamine 1 receptor mRNA expression in human airway epithelial and endothelial cells.⁶⁰ Subsequent studies have focused on the role of DEPs in increasing the rate of primary allergic sensitization. There is strong evidence that PM, DEPs, and their resident chemicals can induce mitogen-activated protein kinase and nuclear factor kB activation⁶⁹⁻⁷² and that this can result in gene transcription for IL-4, IL-5, IL-13, TNF- α , ICAM-1, and vascular cell adhesion molecule 1.⁷³

In a recent study, Monn and Becker (1999) assessed water-soluble components of PM_{2.5} and PM₁₀ in indoor and outdoor air and showed that cytokine production by human monocytes was restricted to eluates of PM₁₀, and cytokine induction was inhibited by measures that inactivate endotoxin (ETOX). The study showed that outdoor air contained more soluble ETOX/m³ air than indoor air.⁷⁴ Several studies have implicated ETOX as a health concern in the indoor environment.⁷⁵ Other studies have shown that ETOX will prime macrophages to further stimulation with particulate PM_{2.5}.⁷⁴

In a recent study cytokines IL-6, TNF- α , and MCP-1 were found to be induced by in soluble PM₁₀ to a much higher extent (>50-fold) than soluble PM₁₀. Previous studies have indicated that endotoxin (ETOX) is a component of soluble PM₁₀ responsible for cytokine production.⁷⁵ Recently, it has been shown that ETOX is also a cytokine-inducing moiety in insoluble PM₁₀. In addition to inducing cytokines, exposure to insoluble PM₁₀, but not the other PM fractions, also inhibited phagocytosis and oxidant generation in response to yeast. The decrease in host defenses may be the result of apoptosis in the alveolar macrophage population, which was also found to be specifically caused by insoluble PM₁₀. These results show that the

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functional capacity of alveolar macrophages is selectively modulated by insoluble components of coarse PM, including the biocontaminant ETOX.⁷⁶

Conclusions and Future Prospects

As the understanding that contemporary air pollution poses a major Public Health threat improves, it is increasingly attracting the attention of both the political and scientific communities. For those actively involved, a number of major goals lie ahead. A better understanding and definition of sensitive groups within the population is required, as is a better understanding of the mechanisms underlying sensitivity. It is only when we have this information appropriate strategies can be applied to protect all the public.

By taking a synoptic view, the researchers have been able to give us a useful summary of the possible mechanisms of pollutant-associated adverse health effects these include the direct effect of pollutants on inflammation of airways, oxidative stress generated by transition metals and organic chemicals, covalent modification of intracellular proteins, and direct effects of other biologic compounds, such as endotoxins, which might have effects on the innate immune system and thereby influence airways inflammation. Other possible mechanisms include direct effects on the autonomic nervous system, perhaps explaining some of the cardiac toxicity and issues surrounding heart rate variability or alternative effects on coagulation, which might explain the increased risk of acute cardiovascular events. Particles can also serve as vectors for allergenic material or as adjuvants, altering the way that the immune system views allergenic particles. Allergists are particularly likely to be consulted by patients asking for information on this area, and although the causes of pollution are not within our direct sphere of influence, we can continue to give our patients the information they need, and we can also keep air pollution on the policy-makers' agenda through our interactions as patient advocates and members of larger health organizations and political structures.

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