Environmental and occupational respiratory disorders

Rostrum

Health effects of air pollution

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The general public, especially patients with upper or lower respiratory symptoms, is aware from media reports that adverse respiratory effects can occur from air pollution. It is important for the allergist to have a current knowledge of the potential health effects of air pollution and how they might affect their patients to advise them accordingly. Specifically, the allergist-clinical immunologist should be keenly aware that both gaseous and particulate outdoor pollutants might aggravate or enhance the underlying pathophysiology of both the upper and lower airways. Epidemiologic and laboratory exposure research studies investigating the health effects of outdoor air pollution each have advantages and disadvantages. Epidemiologic studies can show statistical associations between levels of individual or combined air pollutants and outcomes, such as rates of asthma, emergency visits for asthma, or hospital admissions, but cannot prove a causative role. Human exposure studies, animal models, and tissue or cellular studies provide further information on mechanisms of response but also have inherent limitations. The aim of this rostrum is to review the relevant publications that provide the appropriate context for assessing the risks of air pollution relative to other more modifiable environmental factors in patients with allergic airways disease. (J Allergy Clin Immunol 2004;114:1116-23.)

Key words: Outdoor air pollution, particulate matter, ozone, nitrogen dioxide, sulfur dioxide, diesel exhaust, asthma, exposure, interactions between allergens and pollutants

There have been significant advances in knowledge regarding the effects of air pollutants on human health in the past few years. The general public, especially patients with upper or lower respiratory symptoms, is aware from media reports that adverse respiratory effects can occur from air pollution. These patients are likely to seek information from their allergist or respiratory physician as to the effect on their health. This is often difficult to assess in a patient with concurrent respiratory allergic responses to other outdoor exposures, such as pollens and fungal spores, or who experiences asthma exacerbations from physical factors, such as cold air, dry air, or excessive humidity. Nevertheless, it is important for the allergist or respiratory physician to have current knowledge of the potential health effects of air pollution and how they might affect their patients to advise them accordingly.

Epidemiologic and laboratory exposure research studies each have both advantages and disadvantages. Epidemiologic studies can show statistical associations between levels of individual or combined air pollutants and outcomes, such as rates of asthma, emergency visits for asthma, or hospital admissions, but cannot prove a causative role. Human exposure studies can more easily measure responses in specific high-risk populations, such as asthmatic patients or the elderly, in controlled environments without the presence of the confounding factors often present in epidemiologic studies. Studies have reasonably assessed acute changes in lung function but have just begun to assess the interactions and possible synergism between multiple pollutants or pollutants and allergens. Animal models and tissue or cellular studies provide further information on mechanisms of response, but results might not always be applicable to human effects, and in particular, the exposure concentration delivered to animal lungs might not be equivalent to human exposures.

For allergic patients and their families, important questions regarding air pollution exist. Does air pollution increase the risk of asthma development in my child? Does air pollution exacerbate asthma or allergic rhinitis? Which air pollutants are most commonly associated with adverse health effects, and how can they be reduced or avoided?
responses. Sulfur dioxide (SO2) in high concentrations can cause wheezing and can increase the effects of inhaled allergens associated with an increase in respiratory infection and death from air pollutants.

B. Indoor-outdoor pollutants

(i) Indoor pollutants

(a) Sources: cooking and combustion, particle resuspension, building materials, air conditioning, consumer products, smoking, heating, biologic agents
(b) Products: Combustion products (e.g., tobacco and wood smoke), CO, CO2, SVOC (e.g., aldehydes, alcohols, alkanes, and ketones), microbial agents and organic dusts, radon, manmade vitreous fibers

(ii) Outdoor pollutants

(a) Sources: industrial, commercial, mobile, urban, regional, agricultural, natural
(b) Products: SO2, ozone, NOx, CO, PM, SVOC

C. Gaseous-particulate pollutants

(i) Gaseous: SO2, NOx, ozone, CO, SVOC (e.g., PAH, dioxins, benzene, aldehydes, 1,3-butadiene)
(ii) Particulate: coarse PM (2.5-10 μm; regulatory standard = PM10); fine PM (0.1-2.5 μm; regulatory standard = PM2.5); ultrafine PM (<0.1 μm; not regulated)

NOx: Nitrogen oxides; SVOC: specific volatile organic compounds.

Are allergic individuals with asthma at greater risk of early death from air pollutants?

Some answers to these questions are now available. For example, it has been reported that ozone has been associated with an increased risk of asthma development among children in California playing outdoor sports; ozone can increase airway inflammation and airway responsiveness and also can potentiate the airway response to inhaled allergens. Exposure to nitrogen oxides has been associated with an increase in respiratory infection and wheezing and can increase the effects of inhaled allergen responses. Sulfur dioxide (SO2) in high concentrations with or without exercise is a respiratory irritant, provoking airflow limitations. In some studies SO2, sulfates, and acid aerosols have been associated with increased emergency visits and hospitalizations for asthma.

This rostrum will review relevant publications that provide the appropriate context for assessing the risks of air pollution relative to other more modifiable environmental factors in patients with allergic airways disease. Although air pollutants are present both indoors and outdoors, this overview will be confined to the effects of outdoor pollutants.

CLASSIFICATION OF AIR POLLUTANTS

Air pollution derives from a variety of sources, of which the combustion of fossil-fuel products is the principal source. Air pollutants can be classified by their source, chemical composition, size, and mode of release into indoor or outdoor environments. The examples listed in Table I distinguish between primary versus secondary, indoor versus outdoor, and gaseous versus particulate pollutants. Pollutants directly emitted into the atmosphere are known as primary pollutants, whereas pollutants that form as a result of chemical reactions with other pollutants or atmospheric gases are known as secondary pollutants. This distinction is important from the perspective of abatement. Therefore, although there is a direct relationship between the emission of primary pollutants and their ambient concentrations, a reduction of a precursor does not automatically lead to a proportional decrease in the level of a secondary pollutant. In fact, ozone levels in ambient air might paradoxically increase if the emission of nitrogen oxides is decreased.

Suspended particulate pollutants, designated as ambient particulate matter (PM), are classified into 3 categories. Coarse PM (aerodynamic diameter, 2.5-10 μm) is derived from abraded soil, road dust (e.g., brake and tire dust), construction debris, or aggregation of smaller combustion particles, whereas fine (<2.5 μm) and ultrafine (<0.1 μm) PM is primarily formed during the combustion of fossil-fuel products. The US Environmental Protection Agency has established regulatory standards for ambient PM2.5 and PM10, commonly referred to as particles with aerodynamic diameters of 2.5 μm or less and 10 μm or less, respectively. These standards (Table II) reflect public health concerns about ambient PM because epidemiologic studies show an increase in cardiorespiratory morbidity and mortality with incremental increases in ambient PM2.5 and PM10 levels. Although PM2.5 is a PM10 subset, the former is separately regulated to ensure that the smaller particles, which have less mass but might be more respirable and hence toxic, are adequately controlled. Although a considerable amount of data implicate coarse and fine PM in adverse health effects, much less is known about the risks of ultrafine particles, which are more abundant, potentially more toxic, and not presently amenable to mass standard monitoring. Recent studies have shown that ultrafine particles penetrate the systemic circulation and exert more toxicity than coarse and fine particles because of a higher content of transition metals and redox cycling chemicals.

MECHANISMS OF ADVERSE HEALTH EFFECTS

The exact mechanism or mechanisms by which air pollutants cause adverse health effects are complex and not properly understood. A number of possibilities are listed in Table III. One mechanism of action is how
reactive oxygen species cause inflammation. Fig 1 shows the hierarchic oxidative stress model, in which incremental doses of PM sequentially induce protective and injurious cellular responses.\(^{16}\) Oxidative stress is defined as a depletion of intracellular glutathione, leading to accumulation of oxidized glutathione and a decrease in the glutathione/oxidized glutathione ratio. Oxidative stress initiates redox-sensitive signaling pathways (ie, mitogen-activated protein kinase and the nuclear factor κB cascade), which work synergistically to activate proinflammatory cytokine, chemokine, and adhesion receptor expression through appropriate genetic response elements.\(^{16}\) This model posits that at a lower oxidative stress level (tier 1), PM induces cytoprotective responses through the activation of an antioxidant response element that requires the expression and release of the transcription factor Nrf-2 to the nucleus. Nrf-2 interacts with the antioxidant response element to promote and induce expression of several antioxidant and phase II drug-metabolizing enzymes.\(^{16}\) These enzymes (eg, heme oxygenase 1 and glutathione-S-transferase) exert cytoprotective, antioxidant, and detoxification effects.\(^{16}\) If this layer of protection fails, further escalation of oxidative stress leads to mitogen-activated protein kinase/nuclear factor κB activation and proinflammatory effects.\(^{15}\) At the highest level of oxidative stress (tier 3), perturbation of the mitochondrial function results in cellular apoptosis or necrosis.\(^{15}\) The hierarchic oxidative stress model predicts that a weakened antioxidant defense could increase the propensity toward PM-induced airway inflammation, increased susceptibility to infection, and asthma.\(^{17,18}\) This could explain the existence of susceptible human subsets, who are more prone to experience adverse health effects during pollutant exposure compared with persons with a normal antioxidant defense.

**SPECIFIC POLLUTANTS**

**Diesel exhaust particulate matter**

Recent epidemiologic, human, and animal model studies have demonstrated that diesel exhaust particulates (DEPs) increase airway inflammation and can exacerbate and initiate asthma and allergy. Diesel combustion results in production of DEPs, nitrogen oxides, and precursors of ozone, all of which are harmful to the lung.

Because of the complex nature of diesel exhaust composition, a primary obstacle has been obtaining an accurate measure of exposure. Most studies have used traffic exposure as a proxy. For example, one of the earliest studies showed that cedar pollinosis was significantly higher in individuals living near high-trafficked roads lined with old cedar trees than in those residing near low-traffic roads with similar pollen levels.\(^{15}\) Similar studies have shown that residing near busy roadways is associated with increased asthma hospitalizations, decreased lung function, and increased prevalence and severity of wheezing and allergic rhinitis.\(^{20}\) The view that diesel fumes can increase allergic sensitization and asthma prevalence has been shown by some but refuted by others.\(^{20}\)

Controlled-chamber exposure studies of healthy volunteers exposed to 300 μg/m\(^3\) diesel exhaust or diesel particulates for 1 hour demonstrated increased neutrophil counts in sputum and bronchial biopsy specimens and increases in IL-6, IL-8, and growth-related oncogene α levels, with minimal changes in lung function.\(^{21,22}\) Subsequent studies have shown that similar diesel exposure can increase airway hyperresponsiveness to methacholine and airway resistance in patients with mild asthma.\(^{23,24}\) Animal models have been useful in studying the effects of long-term diesel exhaust exposure. Rats kept in Sao Paulo (a polluted environment with high diesel levels) for 3 months compared with rats residing in Atibaia (a relatively clean diesel region) for 3 months had significantly greater methacholine airway hyperresponsiveness.\(^{25}\) When the Sao Paulo rats were moved to Atibaia for an additional 3 months, this effect disappeared. Diesel exhaust or DEP animal exposure models in the absence or presence of allergen can induce airway inflammation and decrease lung function.\(^{26,27}\) The mechanism by which DEPs induce these effects might be related to the production and release of proinflammatory cytokines and chemokines from human bronchial epithelial cells, which regulate airway hyperresponsiveness.\(^{26,28,29}\) Many effects of DEPs can be attributed to the chemicals that surround the carbon core of the diesel particulates rather than the core itself. For example, carbon black (carbon without chemicals) has no effect on epithelial cells.\(^{30}\)

Enhanced inflammation as a result of diesel exposure might also alter susceptibility to respiratory viral infections.\(^{17}\) Repeated low-dose DEP exposure resulted in downregulation of T cell–mediated immune responses, whereas a single high-dose exposure to DEPs aggravated bacterial infection and triggered strong T cell–mediated immunity, indicating that DEPs can also alter pulmonary immune responses to bacterial infection.\(^{31}\)

Individuals with gene variants for phase II detoxifying enzymes (glutathione-S-transferase P1 and M1), causing the absence or reduced production of these enzymes, have been demonstrated to have increased susceptibility
to the adjuvant effects of DEPs. However, DEPs might also act through mechanisms unrelated to oxidant activity. Recently, in a murine model DEPs were shown to be capable of promoting TH2 cytokine responses directly by stimulating production of inflammatory cytokines through an oxidant-dependent pathway and indirectly by interfering with cytokine-signaling pathways that produce IFN-γ, which is important for down-regulating TH2 responses.

Ozone

Numerous in vitro and animal studies have investigated the inflammatory effects of ozone on the respiratory tract. However, our current understanding of how ozone exerts its adverse health effects has been generated mainly by the multitude of ozone-exposure studies conducted in healthy and asthmatic individuals.

Controlled ozone-exposure studies in healthy human volunteers have consistently demonstrated a decrease in forced vital capacity and FEV1 associated with chest discomfort on inspiration and increased nonspecific airway hyperresponsiveness. Ozone exposure ranging from 0.10 to 0.4 ppm is traditionally accompanied with neutrophilic inflammation as early as 1 hour after exposure and can persist for up to 24 hours.

The effective dose for ozone provocation studies depends on concentration, duration of exposure, and degree of exercise. Ozone exposure of less than 0.50 ppm without exercise typically has no effect on lung function. However, ozone exposure with exercise results in decreased respiratory frequency, FEV1, and forced vital capacity, with an increase in airway resistance and symptoms. For this reason, outdoor exercise on days in which the air-quality index is poor should be avoided by susceptible individuals.

Ozone’s more dramatic effect in asthmatic subjects is most likely a result of existing chronic inflammation in the lower airways. Most studies suggest that ozone worsens airflow in asthmatic patients to a greater extent than in healthy volunteers. However, one study reported that ozone levels as high as 0.4 ppm had no effect on individuals with exercise-induced bronchospasm.

Ozone exposure has been observed to cause an enhanced immediate and late airway response to inhaled allergen, the latter characterized by increased eosinophilia in induced sputum after 6 hours. This effect is more pronounced at higher ozone exposure levels of 0.16 and 0.25 ppm. A more pronounced inflammatory response to ozone has been observed in subjects with mild intermittent asthma compared with those with persistent asthma treated with inhaled corticosteroids, indicating that patients with more severe asthma are either less responsive to ozone or that inhaled corticosteroids are effective at attenuating ozone-induced airway inflammation.

Allergic asthmatic patients challenged intranasally with dust mite allergen coupled with 0.4 ppm ozone exposure had increased eosinophil influx and increased eosinophilic cationic protein and IL-8 levels after 4 hours. Data thus far indicate that the effect of ozone on inhaled allergen challenge is dose dependent and might
involve several mechanistic pathways in addition to mast cell activation.

**Sulfur dioxide and nitrogen dioxide**

Adverse health effects from other gaseous copollutants, such as SO2, nitrogen dioxide (NO2), and carbon monoxide (CO), should not be underappreciated. Recent epidemiologic studies conducted throughout the world have provided valuable insight into the associations between SO2, NO2, and CO exposure and increases in cardiopulmonary mortality, respiratory and cardiovascular hospital admissions, emergency admissions caused by stroke (NO2), and myocardial infarction (NO2 and CO).50-52

Controlled human exposure studies have yielded substantial data on the direct effects of SO2 and NO2 on healthy and diseased individuals over relatively short exposure times. Exposure (5 minutes) to inhaled SO2 induces rapid-onset bronchoconstriction (decreases in FEV1 or increases in airway resistance within 2 minutes of exposure) in both healthy and asthmatic subjects.53 In response to SO2, asthmatic subjects experience increased symptoms and a greater decrease in pulmonary function at lower concentrations (0.25 ppm) compared with nonasthmatic subjects, who are often unresponsive at concentrations of less than 5 ppm.53 Spontaneous recovery from SO2 exposure occurs within 30 minutes, and exposed asthmatic subjects tend to be refractory to the effects of SO2 up to 4 hours after initial exposure.53 Among adult asthmatic subjects, there is considerable interindividual variation in spirometric response to inhaled SO2, suggesting a potential genetic link. Recently, a significant association between the TNF-α promoter polymorphism, known to be associated with asthma, was identified in asthmatic patients who were spirometrically responsive (ie, >12% decrease in FEV1) to inhaled SO2.54 The APHEA studies found that SO2 exposure was associated with increased daily hospital admissions for asthma in children but not in adults or individuals with other respiratory conditions, such as chronic obstructive pulmonary disease.55 Ambient SO2 might contribute to acid aerosol (H2SO4) formation. This could be important because some studies suggest that asthma symptoms are increased on days with high aerosolized acid levels. Finally, exposure to ozone or cold dry air before exposure to SO2 increases bronchial sensitivity to SO2 in asthmatic patients.56

Because NO2 is a precursor to photochemical smog (UV sunlight + hydrocarbons = ozone), its major effect on health as an outdoor pollutant is likely through the formation of ozone. Some epidemiologic studies report an association between indoor NO2 exposure and respiratory symptoms in children, whereas other studies fail to confirm this. More recently, high NO2 personal exposure (21 μg/m3 or 0.02 ppb) the week before the onset of a respiratory viral infection has been linked to increased severity of a resulting asthma exacerbation.57 In challenge studies in healthy subjects and smokers, NO2 exposure (2-6 ppm) induces an inflammatory response in the airways characterized by neutrophil influx and reduced lymphocyte subpopulations.58,59 Compared with its direct effects on the airways, NO2 might play a more prominent role as a sensitizing agent to inhaled allergen. Exposure to 0.4 ppm NO2 for 4 hours enhanced both immediate- and late-phase responses to inhaled allergen.60,61

**INTERACTION BETWEEN ALLERGEN AND POLLUTANTS**

Four major issues concerning the interaction of outdoor pollutants and allergens include the following: (1) epidemiologic studies of pollution and aeroallergens on the genesis of asthma; (2) epidemiologic studies of pollution and aeroallergens on the exacerbation of asthma; (3) experimental studies on the adjuvant effect of pollutant particulates (DEPs) on specific T12 responses; and (4) the role of pollution and global warming on natural allergen production.

Since 1997, there have been a number of epidemiologic studies in Europe and Japan concerning the incidence and persistence of respiratory diseases, primarily asthma, in urban sites of known high pollution.52-67 Most of these studies focused on automobile-related pollutants in heavily traveled expressways and their relationship to asthma symptoms caused by seasonal allergens. They have generally concluded that high vehicle traffic is associated with asthma, cough, and wheeze in children with known allergic sensitization.52-67

Epidemiologic and laboratory studies investigating the role of allergen-pollutant combinations as triggers of asthmatic attacks have revealed that ozone, NO2, and aeroallergens were independently or interactively related with asthma symptoms and changes in peak flow rates. The most familiar of these studies involving ozone and fungal spores revealed that they were cofactors associated with increased asthma symptoms and inhaler use.66,67 The interesting observation that increased asthma admissions were associated with thunderstorms was originally attributed to peak fungal spore counts preceding or during the weather front but not to concomitant increases in air pollutants.70-74 Several more recent studies failed to show an association with thunderstorms but instead found a positive association between asthma admissions and higher levels of ozone at these times. As previously discussed, controlled challenge studies all have demonstrated that inhaled ozone, NO2, and SO2, individually or in combination, might enhance the airway response to inhaled allergens, thereby inducing asthma exacerbations.75

It has been proposed that DEPs synergize with allergen in the human upper respiratory mucosa to enhance allergen-specific IgE production by initiating a T12 cytokine environment.76 Thus it is possible that the adjuvant properties of DEPs are directly associated with the worldwide increased prevalence of asthma that is concurrent with the rapid increase in diesel-powered transportation around the globe.

The probability that shifts in aeroallergen ecology might be caused by changes in global climate has also
been recently investigated. A study assessing the role of climatic change on pollen production of common ragweed found that ragweed plants grew faster, flowered earlier, and produced significantly greater amounts of pollen in urban locations (where carbon dioxide [CO₂] concentrations and temperatures were higher) than in rural locations. It has also been shown that doubling the atmospheric CO₂ concentrations stimulated ragweed pollen production by 61%. These studies suggest that significant increases in allergenic pollen will occur in the future if global warming continues.

CONCLUSIONS

Although early epidemiologic studies of the effects of air pollution on human health provided only associative data, the body of current scientific data now clearly delineates the role of pollutant-mediated adverse interactions in human allergic diseases.

The allergist–clinical immunologist should be keenly aware that both gaseous and particulate outdoor pollutants might aggravate or enhance the underlying pathophysiology of both the upper and lower airways. Although the health effects of gaseous pollutants were of chief concern during the last half of the 20th century, particulate pollutants might prove to be even more formidable health hazards for several reasons discussed in this rostrum.

How can this new information be used in a pragmatic way by practicing clinicians? Patients should be advised to minimize outdoor activity during days with high pollution or smog levels. In choosing new residential locations, patients should give preference to sites remote from heavy automobile traffic or chemical manufacturing plants. Finally, as patient advocates, physicians, both individually and as members of large health organizations, should support societal control of air pollution and rally against attempts to weaken science-based regulatory air pollution standards. To this end, the physician should become familiar with current exposure guidelines for compounds considered to be risks for inducing or exacerbating asthma, as determined by the Environmental Protection Agency and nongovernmental agencies, such as the American Conference of Governmental Industrial Hygienists.

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