Rostrum

Health effects of air pollution

Editor: **Jonathan A. Bernstein, MD[a]**
Contributors: **Neil Alexis, PhD,[b] Charles Barnes, PhD,[c] I. Leonard Bernstein, MD,[a] Jonathan A. Bernstein, MD, Andre Nel, MD, PhD,[d] David Peden, MD,[b] David Diaz-Sanchez, PhD,[d] Susan M. Tarlo, MB, BS,[e] and P. Brock Williams, PhD[c]**

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*

Abbreviations used
CO: Carbon monoxide
CO_2: Carbon dioxide
DEP: Diesel exhaust particulate
NO_2: Nitrogen dioxide
PM: Particulate matter
SO_2: Sulfur dioxide

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?

From [a]the Department of Internal Medicine, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, Cincinnati, Ohio; [b]the Department of Pediatrics, University of North Carolina-Chapel Hill, Chapel Hill, NC; [c]the Department of Pediatrics, Children's Mercy Hospital, Kansas City, Mo; [d]the Department of Internal Medicine, UCLA School of Medicine, Los Angeles, Calif; and [e]the Department of Internal Medicine, Toronto Western Hospital, Toronto, Ontario, Canada.

Received for publication March 31, 2004; revised July 19, 2004; accepted for publication August 17, 2004.

Reprint requests: Jonathan A. Bernstein, MD, 231 Albert Sabin Way, ML #563, Cincinnati, OH 45267-0563. E-mail: Jonathan.Bernstein@uc.edu.

0091-6749/$30.00

doi:10.1016/j.jaci.2004.08.030

TABLE I. Classification of air pollutants

A. Primary-secondary pollutants
  (i) Primary: pollutants emitted directly into the atmosphere (eg, SO_2, some NO_x species, CO, PM)
  (ii) Secondary: pollutants that form in the air as a result of chemical reactions with other pollutants and gases (eg, ozone, NO_x, and some particulates)
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 (eg, tobacco and wood smoke), CO, CO_2, SVOC (eg, 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: SO_2, ozone, NO_x, CO, PM, SVOC
C. Gaseous-particulate pollutants
  (i) Gaseous: SO_2, NO_x, ozone, CO, SVOC (eg, PAH, dioxins, benzene, aldehydes, 1,3-butadiene)
  (ii) Particulate: coarse PM (2.5-10 μm; regulatory standard = PM_{10}), fine PM (0.1-2.5 μm; regulatory standard = $PM_{2.5}$); ultrafine PM (<0.1 μm; not regulated)

NO_x, 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.[1,2] Exposure to nitrogen oxides has been associated with an increase in respiratory infection and wheezing and can increase the effects of inhaled allergen responses.[3] Sulfur dioxide (SO_2) in high concentrations with or without exercise is a respiratory irritant, provoking airflow limitations. In some studies SO_2, sulfates, and acid aerosols have been associated with increased emergency visits and hospitalizations for asthma.[4-6]

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. Thus 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.[7]

TABLE II. Standards for air pollutants as imposed by the US Environmental Protection Agency

Pollutant	Time period	
PM_{10} (μg/m^3)	150 (24 h)	50 (annual)
$PM_{2.5}$ (μg/m^3)	65 (24 h)	15 (annual)
Ozone (ppm)	0.12 (1 h)	0.08 (8 h)
NO_2 (ppm)		0.053 (annual)
SO_2 (ppm)	0.14 (24 h)	0.03 (annual)

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 (eg, 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 $PM_{2.5}$ and PM_{10}, 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 $PM_{2.5}$ and PM_{10} levels.[8-10] Although $PM_{2.5}$ is a PM_{10} 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.[8-12] 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.[12-15]

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

TABLE III. Possible mechanisms of pollutant-associated adverse health effects

1. PM- or ozone-induced pulmonary inflammation
2. Free radical and oxidative stress generation by transition metals and organic chemical compounds (eg, PAH)
3. Covalent modification of key intracellular proteins (eg, enzymes)
4. Biologic compounds, such as endotoxin and glucans, which induce inflammation and innate immune effects
5. Stimulation of nocioreceptor and autonomic nervous system activity, which regulates heart rate variability and airway reactivity
6. Adjuvant effects in the immune system (eg, DEPs and transition metals enhancing responses to common environmental allergens)
7. Procoagulant activity by ultrafine particles after access to the systemic circulation
8. Suppression of normal defense mechanisms (eg, suppression of alveolar macrophage functions)

PAH, Polyaromatic hydrocarbons.

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 (tier 2) 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-traffic roads lined with old cedar trees than in those residing near low-traffic roads with similar pollen levels.[19] 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 $\mu g/m^3$ 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

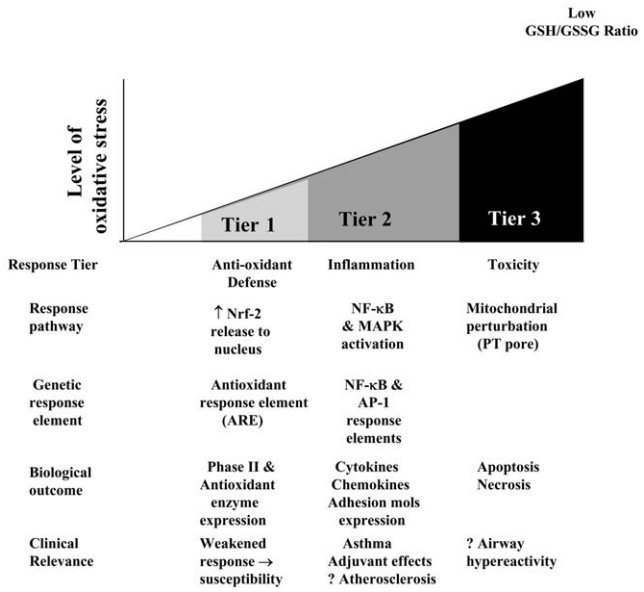

FIG 1. Hierarchic oxidative stress model to PM. At tier 1, antioxidant enzymes restore cellular redox homeostasis. At tier 2, proinflammatory responses are induced. At tier 3, cellular apoptosis-necrosis occurs. *GSH*, Glutathione; *GSSG*, oxidized glutathione; *NF-κB*, nuclear factor κB; MAPK, mitogen-activated kinase; *AP-1*, Activator protein 1.

to the adjuvant effects of DEPs.[32] However, DEPs might also act through mechanisms unrelated to oxidant activity. Recently, in a murine model DEPs were shown to be capable of promoting T_H2 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 downregulating T_H2 responses.[33]

Ozone

Numerous *in vitro* and animal studies have investigated the inflammatory effects of ozone on the respiratory tract.[34-38] 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 FEV_1 associated with chest discomfort on inspiration and increased nonspecific airway hyperresponsiveness.[39] 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.[40]

The effective dose for ozone provocation studies depends on concentration, duration of exposure, and degree of exercise.[41] 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, FEV_1, and forced vital capacity, with an increase in airway resistance and symptoms.[1,42] 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.[43] Most studies suggest that ozone worsens airflow in asthmatic patients to a greater extent than in healthy volunteers.[44] However, one study reported that ozone levels as high as 0.4 ppm had no effect on individuals with exercise-induced bronchospasm.[45]

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.[46] This effect is more pronounced at higher ozone exposure levels of 0.16 and 0.25 ppm.[47] 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.[48]

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.[49] 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 SO_2, nitrogen dioxide (NO_2), and carbon monoxide (CO), should not be underappreciated. Recent epidemiologic studies conducted throughout the world have provided valuable insight into the associations between SO_2, NO_2, and CO exposure and increases in cardiopulmonary mortality, respiratory and cardiovascular hospital admissions, emergency admissions caused by stroke (NO_2), and myocardial infarction (NO_2 and CO).[50-52]

Controlled human exposure studies have yielded substantial data on the direct effects of SO_2 and NO_2 on healthy and diseased individuals over relatively short exposure times. Exposure (5 minutes) to inhaled SO_2 induces rapid-onset bronchoconstriction (decreases in FEV_1 or increases in airway resistance within 2 minutes of exposure) in both healthy and asthmatic subjects.[53] In response to SO_2, 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 SO_2 exposure occurs within 30 minutes, and exposed asthmatic subjects tend to be refractory to the effects of SO_2 up to 4 hours after initial exposure.[53] Among adult asthmatic subjects, there is considerable interindividual variation in spirometric response to inhaled SO_2, 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 FEV_1) to inhaled SO_2.[54] The APHEA studies found that SO_2 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 SO_2 might contribute to acid aerosol (H_2SO_4) 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 SO_2 increases bronchial sensitivity to SO_2 in asthmatic patients.[56]

Because NO_2 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 NO_2 exposure and respiratory symptoms in children, whereas other studies fail to confirm this. More recently, high NO_2 personal exposure (21 $\mu g/m^3$ 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, NO_2 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, NO_2 might play a more prominent role as a sensitizing agent to inhaled allergen. Exposure to 0.4 ppm NO_2 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 T_H2 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.[62-67] 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.[62-67]

Epidemiologic and laboratory studies investigating the role of allergen-pollutant combinations as triggers of asthmatic attacks have revealed that ozone, NO_2, 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.[68,69] 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, NO_2, and SO_2, 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 T_H2 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 [CO_2] concentrations and temperatures were higher) than in rural locations.[77] It has also been shown that doubling the atmospheric CO_2 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.[78]

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 airways 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.

REFERENCES

1. McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Ghunderman WJ, et al. Asthma in exercising children exposed to ozone: a cohort study. Lancet 2002;359:386-91.
2. Parnia S, Brown JL, Frew AJ. The role of pollutants in allergic sensitization and the development of asthma. Allergy 2002;57:1111-7.
3. D'Amato G, Liccardi G, D'Amato M, Cazzola M. Respiratory allergic diseases induced by outdoor air pollution in urban areas. Monaldi Arch Chest Dis 2002;57:161-3.
4. Sunyer J, Atkinson R, Ballester F, LeTertre A, Ayers JG, Forastiere F, et al. Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. Occup Environ Med 2003;60:e2.
5. Lin M, Chen Y, Villeneuve PJ, Burnett RT, Lemyre L, Hertzman C, et al. Gaseous air pollutants and asthma hospitalization of children with low household income in Vancouver, British Columbia, Canada. Am J Epidemiol 2004;159:294-303.
6. Wong GW, Lai CK. Outdoor air pollution and asthma. Curr Opin Pulm Med 2004;10:62-6.
7. Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-9.
8. Sarnat JA, Schwartz J, Suh HH. Fine particulate air pollution and mortality in 20 U.S. cities. N Engl J Med 2001;344:1253-4.
9. Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 2000;343:1742-9.
10. Utell MJ, Frampton MW. Acute health effects of ambient air pollution: the ultrafine particle hypothesis. J Aerosol Med 2000;13:355-9.
11. de Hartog JJ, Hoek G, Peters A, Timonen KL, Ibald-Mulli A, Brunkreef B, et al. Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol 2003;157:613-23.
12. Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage. Environ Health Perspect 2003;111:455-60.
13. Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, et al. Passage of inhaled particles into the blood circulation in humans. Circulation 2002;105:411-4.
14. Ghio AJ, Samet JM. Metals and air pollution particles. In: Holgate S, Samet J, Koren H, et al, editors. Air pollution and health. San Diego (CA): 1998. p. 653-72.
15. Xiao GG, Wang M, Li N, Loo JA, Nel AE. Use of proteomics to demonstrate a hierarchical oxidative stress response to diesel exhaust particles in a macrophage cell line. J Biol Chem 2003;278:50781-90.
16. Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma: a paradigm for the role of oxidative stress in PM-induced adverse health effects. Clin Immunol 2003;3:250-65.
17. Harrod KS, Jaramillo RJ, Rosenberger CL, Wang SZ, Berger JA, McDonald JD, et al. Increased susceptibility to RSV infection by exposure to inhaled diesel engine emissions. Am J Respir Cell Mol Biol 2003;28:451-63.
18. Bucchieri F, Puddicombe SM, Lordan JL, Richter A, Buchanan D, Wilson SJ, et al. Asthmatic bronchial epithelium is more susceptible to oxidant-induced apoptosis. Am J Respir Cell Mol Biol 2002;27:179-85.
19. Ishizaki T, Koizumi K, Ikemori R, Ishiyama Y, Kushibiki E. Studies of prevalence of Japanese cedar pollinosis among the residents in a densely cultivated area. Ann Allergy 1987;58:265-70.
20. Diaz-Sanchez D, Proietti L, Polosa R. Diesel fumes and the rising prevalence of atopy: an urban legend? Curr Allergy Asthma Rep 2003;3:146-52.
21. Salvi SS, Nordenhall C, Blomberg A, Rudell B, Pourazr J, Kelly FJ, et al. Acute exposure to diesel exhaust increases IL-8 and Gro-alpha production in healthy human airways. Am J Respir Crit Care Med 2000;161:550-7.
22. Stenfors N, Nordenhall C, Salvi SS, Mudway I, Soderberg M, Blomberg A, et al. Different airway inflammatory responses in asthmatic and healthy humans exposed to diesel. Eur Respir J 2004;23:82-6.
23. Nordenhall C, Pourazar J, Blomberg, Levin J-O, Sandstrom T, Adelroth E. Airway inflammation following exposure to diesel exhaust: a study of time kinetics using induced sputum. Eur Respir J 2000;15:1046-51.
24. Nordenhall C, Pourazar J, Ledin M-C, Levin J-O, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. Eur Respir J 2001;17:909-15.
25. Pereira P, Saldiva PH, Sakae RS. Urban levels of air pollution increase lung responsiveness in rats. Environ Res 1995;69:96-101.
26. Ohta K, Yamashita N, Tajima M, Miyasaka T, Nakano J, Nakajima M, et al. Diesel exhaust particulate induces airway hyperresponsiveness in a murine model: essential role of GM-CSF. J Allergy Clin Immunol 1999;1004:1024-30.
27. Hao M, Comier S, Wang M, Lee JJ, Nel A. Diesel exhaust particles exert acute effects on airway inflammation and function in murine allergen provocation models. J Allergy Clin Immunol 2003;112:905-14.
28. Fahy O, Senechal S, Pene J, Scherpereel A, Lassalle P, Tonnel AB, et al. Diesel exposure favors Th2 cell recruitment by mononuclear cells and alveolar macrophages from allergic patients by differentially regulating macrophage-derived chemokine and IFN-gamma-induced protein-10 production. J Immunol 2002;168:5912-9.
29. Ritz S, Cundall AMJ, Gajewska BU, Alvarez D, Gutierrez-Ramos JC, Coyle AJ, et al. Granuolcyte macrophage colony-stimulating factor-

driven respiratory mucosal sensitization induces Th2 differentiation and function independently of interleukin-4. Am J Respir Cell Mol Biol 2002;27:428-35.
30. Baulig A, Sourdeval M, Meyer M, Marano F, Baeza-Squiban A. Biological effects of atmospheric particles on human bronchial epithelial cells. Comparison with diesel exhaust particles. Toxicol In Vitro 2003; 17:567-73.
31. Yin XJ, Dong CC, Ma JY, Antonini J, Roberts JR, Stanley CF, et al. Suppression of cell-mediated immune responses to *Listeria* infection by repeated exposure to diesel exhaust particles in Brown Norway rats. Toxicol Sci 2004;77:263-71.
32. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Estela del Rio-Navarro B, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. Thorax 2004;59:8-10.
33. Finkelman FD, Yang M, Orekhova T, Clyne E, Bernstein J, Whitekus M, et al. Diesel exhaust particles inhibit Interferon-γ production by inhibiting cytokine effects on NK and NKT cells. J Immunol 2004;172:3808-38.
34. Kafoury RM, Pryor WA, Squadrito GL, Salgo MG, Zou X, Friedman M, et al. Induction of inflammatory mediators in human airway epithelial cells by lipid ozonation products. Am J Respir Crit Care Med 1999;160: 1934-42.
35. Longphre M, Zhang L, Harkema JR, Kleeberger SR. Ozone-induced pulmonary inflammation and epithelial proliferation are partially mediated by PAF. J Appl Physiol 1999;86:341-9.
36. Wagner JG, Van Dyken SJ, Wierenga JR, Hotchkiss JA, Harkema JR. Ozone exposure enhances endotoxin-induced mucous cell metaplasia in rat pulmonary airways. Toxicol Sci 2003;74:437-46.
37. DeLorme MP, Yang H, Elbon-Copp C, Gao X, Barraclough-Mitchell H, Bassett DJ. Hyperresponsive airways correlate with lung tissue inflammatory cell changes in oxone-exposed rats. J Toxicol Environ Health 2002;65:1453-70.
38. Pearson AC, Bhalla DK. Effects of ozone on macrophage adhesion in vitro and epithelial and inflammatory responses in vivo: the role of cytokines. J Toxicol Environ Health 1997;50:143-57.
39. Koren HS, Devlin RB, Graham DE, Mann R, McGee MP, Horstman DH, et al. Ozone-induced inflammation in the lower airways of human subjects. Am Rev Respir Dis 1989;139:407-15.
40. Nightingale JA, Rogers DF, Barnes PJ. Effect of inhaled ozone on exhaled nitric oxide, pulmonary function, and induced sputum in normal and asthmatic subjects. Thorax 1999;54:1061-9.
41. McDonnell WF, Stewart PW, Andreoni S, Seal E Jr, Kehrl HR, Horstman DH, et al. Prediction of ozone-induced FEV1 changes. Effects of concentration, duration, and ventilation. Am J Respir Crit Care Med 1997;156:715-22.
42. Cartellejos M, Gold DR, Damokosh AI, Serrano P, Allen G, McDonnell WF, et al. Acute effects of ozone on the pulmonary function of exercising school children from Mexico City. Am J Respir Crit Care Med 1995;152: 1501-7.
43. Vagaggini B, Taccola M, Cianchetti S, Carnevali S, Bartoli ML, Bacci E, et al. Ozone exposure increases eosinophilic airway response induced by previous allergen challenge. Am J Respir Crit Care Med 2002;16: 1073-7.
44. Fernandes AL, Molfino NA, McClean PA, Silverman F, Tarlo S, Raizenni M, et al. The effect of pre-exposure to 0.12 ppm of ozone on exercise-induced asthma. Chest 1994;106:1077-82.
45. Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, et al. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. Lancet 1991;338:199-203.
46. Ball BA, Folinsbee LJ, Peden DB, Kehrl HR. Allergen bronchoprovocation of patients with mild allergic asthma after ozone exposure. J Allergy Clin Immunol 1996;98:563-72.
47. Kehrl HR, Peden DB, Ball B, Folinsbee LJ, Horstman D, Taccola M, et al. Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. J Allergy Clin Immunol 1999;104:1198-204.
48. Vagaggini B, Carnevali S, Macchioni P, et al. Airway inflammatory response to ozone in subjects with different asthma severity. Eur Respir J 1999;13:274-80.
49. Peden DB, Setzer RW Jr, Devlin RB. Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics. Am J Respir Crit Care Med 1995;151:1336-45.
50. Koken PJ, Piver WT, Ye F, Elixhauser A, Olsen LM, Portier CJ. Temperature, air pollution and hospitalization for cardiovascular diseases among elderly people in Denver. Environ Health Perspect 2003;111:1312-7.
51. Tsai SS, Goggins WB, Chiu HF, Yang CY. Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. Stroke 2003;34:1-5.
52. Tarlo SM, Broder I, Corey P, Chan-Yeung M, Ferguson A, Becker A, et al. The role of symptomatic colds in asthma exacerbations: influence of outdoor allergens and air pollutants. J Allergy Clin Immunol 2001;108:52-8.
53. Horstman DH, Folinsbee LJ. Sulfur dioxide-induced bronchoconstriction in asthmatics exposed for short durations under controlled conditions: a selected review. In: Utell MJ, Frank R, editors. Susceptibility to inhaled pollutants. Philadelphia: American Society for Testing and Materials; 1989.
54. Winterton DL, Kaufman J, Keener CV, Quigley S, Farin FM, Williams PV, et al. Genetic polymorphisms as biomarkers of sensitivity to inhaled sulfur dioxide in subjects with asthma. Ann Allergy Asthma Immunol 2001;86:232-8.
55. Sunyer J, Spix C, Quenel P, Ponce-de-Leon A, Ponka A, Barumandzadeh T, et al. Urban air pollution and emergency admissions for asthma in four European cities: the APHEA Project. Thorax 1997;52:760-5.
56. Linn WS, Shamoo DA, Vinet TG, Spier CE, Valencia LM, Anzar UT, et al. Combined effect of sulfur dioxide and cold in exercising asthmatics. Arch Environ Health 1984;39:339-46.
57. Chauhan AJ, Inskip HM, Linaker CH, Smith S, Schreiber J, Johnston SL, et al. Personal exposure to nitrogen dioxide (NO_2) and the severity of virus-induced asthma in children. Lancet 2003;361:1939-44.
58. Sandstrom T, Stjernberg N, Eklund A, Ledin MC, Bjermer L, Kolmodin-Hedman B, et al. Inflammatory cell response in bronchoalveolar lavage fluid after nitrogen dioxide exposure of healthy subjects: a dose-response study. Eur Respir J 1991;4:332-9.
59. Sandstrom T, Ledin MC, Thomasson L, Helleday R, Stjernberg N. Reductions in lymphocyte subpopulations after repeated exposure to 1.5 ppm nitrogen dioxide. Br J Ind Med 1992;49:850-4.
60. Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. Lancet 1994;344:1733-6.
61. Strand V, Rak S, Svartengren M, Bylin G. Nitrogen dioxide exposure enhances asthmatic reaction to inhaled allergen in subjects with asthma. Am J Respir Crit Care Med 1997;155:881-7.
62. Janssen NA, Brunekreef B, van Vliet P, Aarts F, Meliefste K, Harssema H, et al. The Relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. Environ Health Perspect 2003;111: 1512-8.
63. Venn AJ, Lewis SA, Cooper M, Hubbard R, Britton J. Living near a main road and the risk of wheezing illness in children. Am J Respir Crit Care Med 2001;164:2177-80.
64. de Hartog JJ, van Vliet PH, Brunekreef B, Knape MC, Janssen NA, Harssema H. [Relationship between air pollution due to traffic, decreased lung function and airway symptoms in children]. Ned Tijdschr Geneeskd 1997;141:1814-8.
65. Wyler C, Braun-Fahrlander C, Kunzli N, Schindler C, Ackermann-Liebrich U, Perruchoud AP, et al. Exposure to motor vehicle traffic and allergic sensitization. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Epidemiology 2000; 11:450-6.
66. Shima M, Nitta Y, Adachi M. Traffic-related air pollution and respiratory symptoms in children living along trunk roads in Chiba Prefecture, Japan. J Epidemiol 2003;13:108-19.
67. Nicolai T, Carr D, Weiland SK, Duhme H, von Ehrenstein O, Wagner C, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. Eur Respir J 2003;21:956-63.
68. Delfino RJ, Coate BD, Zeiger RS, Seltzer JM, Street DH, Koutrakis P. Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am J Respir Crit Care Med 1996;154: 633-41.
69. Delfino RJ, Zeiger RS, Seltzer JM, Street DH, Matteucci RM, Anderson PR, et al. The effect of outdoor fungal spore concentrations on daily asthma severity. Environ Health Perspect 1997;105:622-35.

70. Higgins BG, Francis HC, Yates C, Warburton CJ, Fletcher AM, Pickering CA, et al. Environmental exposure to air pollution and allergens and peak flow changes. Eur Respir J 2000;16:61-6.
71. Rutherford S, Simpson R, Williams G, Mitchell C, McCall B. Relationships between environmental factors and lung function of asthmatic subjects in south east Queensland, Australia. J Occup Environ Med 2000;42:882-91.
72. Anderson W, Prescott GJ, Packham S, Mullins J, Brookes M, Seaton A. Asthma admissions and thunderstorms: a study of pollen, fungal spores, rainfall, and ozone. QJM 2001;94:429-33.
73. Dales RE, Cakmak S, Judek S, Dann T, Coates F, Brook JR, et al. The role of fungal spores in thunderstorm asthma. Chest 2003;123:745-50.
74. Marks GB, Colquhoun JR, Girgis ST, Koski MH, Treloar AB, Hansen P, et al. Thunderstorm outflows preceding epidemics of asthma during spring and summer. Thorax 2001;56:468-71.
75. D'Amato G, Liccardi G, D'Amato M, Cazzola M. Respiratory allergic diseases induced by outdoor air pollution in urban areas. Environ Res 2003;91:21-8.
76. Bastain TM, Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Intra-individual reproducibility of nasal allergic responses to diesel exhaust particles indicates a susceptible phenotype. Clin Immunol 2003;109: 130-6.
77. Ziska LH, Gebhard DE, Frenz DA, Faulkner S, Singer BD, Straka JG. Cities as harbingers of climate change: common ragweed, urbanization, and public health. J Allergy Clin Immunol 2003;111:290-5.
78. Wayne P, Foster S, Connolly J, Bazzaz F, Epstein P. Production of allergenic pollen by ragweed (*Ambrosia artemisiifolia* L.) is increased in CO2-enriched atmospheres. Ann Allergy Asthma Immunol 2002;88: 279-82.