# Associations between Criteria Air Pollutants and Asthma

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The evidence that asthma is increasing in prevalence is becoming increasingly compelling. This trend has been demonstrated not only in the United States, but also in the United Kingdom, New Zealand, Australia, and several other Western countries. In the United States, the increase is largest in the group under 18 years of age. There is mounting evidence that certain environmental air pollutants are involved in exacerbating asthma. This is based primarily on epidemiologic studies and more recent clinical studies. The U.S. Clean Air Act of 1970 provides special consideration to the class of outdoor air pollutants referred to as criteria pollutants, including $O_3$, sulfur dioxide ($SO_2$), particulate matter (PM), $NO_x$, CO, and Pb. Standards for these pollutants are set by the U.S. Environmental Protection Agency with particular concern for populations at risk. Current evidence suggests that asthmatics are more sensitive to the effects of $O_3$, $SO_2$, PM, and $NO_2$, and are therefore at risk. High $SO_2$ and particulate concentrations have been associated with short-term increases in morbidity and mortality in the general population during dramatic air pollution episodes in the past. Controlled exposure studies have clearly shown that asthmatics are sensitive to low levels of $SO_2$. Exercising asthmatics exposed to $SO_2$ develop bronchoconstriction within minutes, even at levels of 0.25 ppm. Responses are modified by air temperature, humidity, and exercise level. Recent epidemiologic studies have suggested that exposure to PM is strongly associated with morbidity and mortality in the general population and that hospital admissions for bronchitis and asthma were associated with $PM_{10}$ levels. In controlled clinical studies, asthmatics appear to be no more reactive to aerosols than healthy subjects. Consequently, it is difficult to attribute the increased mortality observed in epidemiologic studies to specific effects demonstrated in controlled human studies. Epidemiologic studies of hospital admissions for asthma have implicated $O_3$ as contributing to the exacerbation of asthma; however, most study designs could not separate the $O_3$ effects from the concomitant effects of acid aerosols and $SO_2$. Controlled human clinical studies have suggested that asthmatics have similar changes in spirometry and airway reactivity in response to $O_3$ exposure compared to healthy adults. However, a possible role of $O_3$ in worsening atopic asthma has recently been suggested in studies combining allergen challenge following exposure to $O_3$. Attempts at identification of factors that predispose asthmatics to responsiveness to $NO_2$ has produced inconsistent results and requires further investigation. In summary, asthmatics have been shown to be a sensitive subpopulation relative to several of the criteria pollutants. Further research linking epidemiologic, clinical, and toxicologic approaches is required to better understand and characterize the risk of exposing asthmatics to these pollutants. — Environ Health Perspect 103(Suppl 6):235–242 (1995)

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## Introduction

Asthma is a diffuse, inflammatory chronic airway disease generally associated with hyperreactivity to nonspecific bronchoconstrictor drugs, in which eosinophils are prominent among inflammatory cells. The eosinophils and their specific products are responsible in part for bronchial hyperreactivity and for airway epithelial damage and desquamation.

Many patients with asthma are atopic, i.e., have a genetically determined type of immune reactivity that favors IgE response to multiple environmental antigens. These individuals may or may not develop clinical asthma despite the existence of IgE-mediated mucosal and skin reactivity to common environmental antigens. Allergic asthma is, most commonly, an immediate onset reaction (within 1 hr and often within minutes of exposure) and results from the local release of inflammatory mediators. Such reactions are usually, although not exclusively, affected by IgE antibody. Asthmatic reactions may also be persistent or have a late onset and it is possible that other types of immune reactions play a part (*1–3*). Recently it has been apparent that cytokines play a role of particular importance in the regulative antibody responses (*4*). Interleukin 4 (IL-4) and interferon γ (IFNγ) are the most important cytokines with respect to the regulation of IgE antibody. In mice, the initiation and maintenance of IgE responses is dependent on the availability of IL-4 (*5*). In contrast, IFNγ inhibits IgE production (*6*). In humans, IL-4 and IFNγ also have similar reciprocal effects on IgE antibody (*7*). Interestingly, there exists a functional heterogeneity among T helper ($T_H$) cells, the class of T lymphocytes required for B lymphocytes to respond to antigen and develop into antibody-producing plasma cells. Two populations of $T_H$ cells have been described, designated $T_{H1}$ and $T_{H2}$, which differ in respect to the spectrum of cytokines they produce following activation (Figure 1). Although both populations secrete interleukin 3 (IL-3) and granulocyte/macrophage colony-stimulating factor (GM-CSF), only $T_{H1}$ cells produce interleukin 2 (IL-2), tumor necrosis factor (TNF-β), and IFNγ, and only $T_{H2}$ cells produce interleukins 4, 5, 6, and 10 (IL-4, IL-4, IL-6, and IL-10) (*8*). Heterogeneity among $T_H$ cells has recently been confirmed in humans (*9*), and there is emerging evidence that immediate-onset allergic reactions in man are associated with the selective activation of $T_{H2}$ cells. It appears that conditions that favor the activation of

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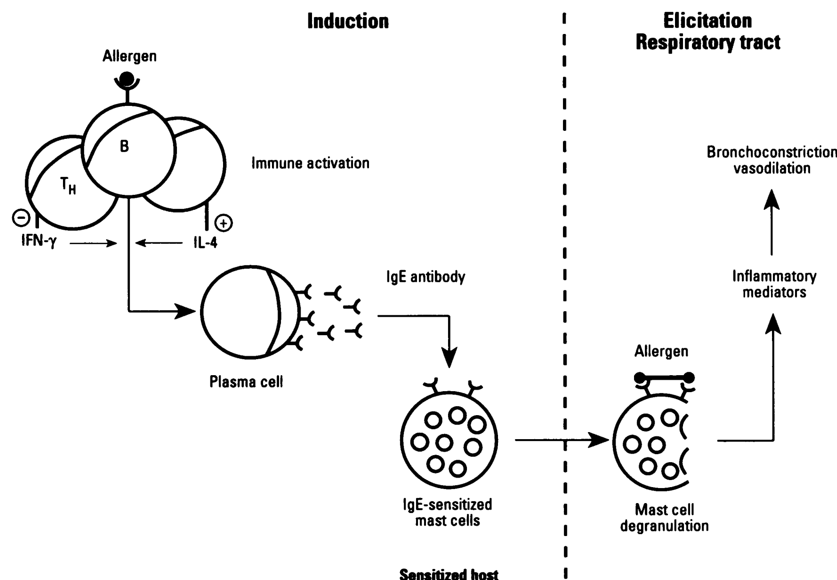


**Figure 1.** Induction and elicitation of respiratory allergy.

$T_{H2}$ cells and IL-4 production will facilitate IgE antibody responses and the development of respiratory sensitization. Variables that might affect the induction of $T_{H2}$-type responses include the nature of antigen, the route and duration of exposure, genetic predisposition, and possibly environmental factors.

Air pollution does not affect the health of exposed persons with equal severity. Certain subgroups of people potentially exposed to air pollution can be identified as particularly at-risk from the adverse health effects of airborne pollutants. The U.S. Environmental Protection Agency (U.S. EPA) has described the population at-risk as "...a segment of a defined population exhibiting characteristics associated with significantly higher probability of developing a condition, illness, or other abnormal status...." These subgroups have been identified through clinical, field, and epidemiologic studies of the health effects of the six criteria pollutants. The specific at-risk subgroups described for each pollutant are based on information contained in the recent U.S. EPA criteria documents used to set the National Ambient Air Quality Standards (NAAQS) and other sources (Table 1). For example, there is very strong scientific evidence that asthmatics are much more sensitive (i.e., respond with symptoms at relatively low concentrations) to the effects of sulfur dioxide ($SO_2$) than the general healthy population.

In the United States, the Clean Air Act of 1970 established the public health basis of the nation's effort to control air pollution and established the U.S. EPA. Section 108 requires the U.S. EPA to identify air pollutants that "...may reasonably be anticipated to endanger public health," and to issue air quality criteria documents for such pollutants that reflect "the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health and welfare which may be expected from the presence of such pollutants in the ambient air." The six criteria pollutants, the primary standards, and their permissible levels are shown in Table 1. In the 1990 Amendments to the Clean Air Act, Congress gave the U.S. EPA authority to impose technology-based standards to control specific toxic substances (air toxics). The ultimate goal is to regulate the list of 189 pollutants based on known or anticipated health risks.

There is mounting evidence that asthma prevalence, morbidity, and mortality are increasing in the United States and many other western countries. The reasons for these trends are not clear but are probably complex and involve a number of factors. According to our present understanding, the development of clinical asthma requires the presence of host factors and environmental factors. Work in laboratory animals (*10*) and epidemiologic evidence (*11*) both support the existence of an intimate relationship between atmospheric pollution and IgE-mediated sensitization to environmental antigens. The issue of whether air pollution can increase the severity of asthma in an already sensitized population is not resolved; this topic has recently been reviewed (*12*). Respiratory viruses also seem to be an important cofactor, but their role is unclear. The evidence that asthma is increasing in prevalence is becoming increasingly compelling based on trends demonstrated in the United States, across Europe, New Zealand, Australia, and several other countries (*13*). In the United States, the increase is largest among children and adolescents (*14*). It is still not completely clear how much of the increase

**Table 1.** National ambient air quality standards.

| Pollutant | Primary standards[a] | Type of average | At-risk populations |
|---|---|---|---|
| $O_3$ | 0.12 ppm (235 μg/m$^3$) | Maximum daily 1 hr average | Persons with preexisting respiratory disease, elderly persons, preadolescent children |
| $PM_{10}$ | 50 μg/m$^3$<br>150 μg/m$^3$ | Annual arithmetic mean<br>24 hr | Preadolescent children (≤ 13 years old), elderly persons (≥ 65 years old), persons with preexisting respiratory disease (COPD[b] and asthma) |
| $SO_2$ | 0.03 ppm (80 mg/m$^3$)<br>0.14 ppm (365 μg/m$^3$) | Annual arithmetic mean<br>24 hr[c] | Preadolescent children, persons with preexisting respiratory disease, elderly persons |
| $NO_2$ | 0.053 ppm (100 μg/m$^3$) | Annual arithmetic mean | Preadolescent children, persons with preexisting respiratory disease |
| CO | 9 ppm (10 mg/m$^3$)<br>35 ppm (40 mg/m$^3$) | 8 hr[c]<br>1 hr[c] | Pregnant women, persons with preexisting coronary heart disease |
| Pb | 1.5 μg/m$^3$ | Maximum quarterly average | Children ≤ 5, pregnant women |

Abbreviations: $O_3$, ozone; $PM_{10}$, particulate matter less than 10 μm aerodynamic diameter; $SO_2$, sulfur dioxide; $NO_2$, nitrogen dioxide; CO, carbon monoxide; Pb, lead. [a]The primary standard is to protect against adverse health effects. [b]Chronic obstructive pulmonary disease, including emphysema and chronic bronchitis. [c]Not to be exceeded more than once a year.

in prevalence is due to a real increase and how much is due to increased recognition on the part of the lay public and health professionals. Asthma hospitalizations increased during the 1970s and levelled off during the 1980s for all but a few age groups (*14*). These increases come at a time when hospitalization for most conditions has been decreasing, and greater use has been made of extended emergency room units and short-stay admissions. Asthma mortality increased in the United States during the 1980s for all ages (*14*). It is important to note, however, that asthma mortality in the United States is among the lowest for the countries that have reliable mortality statistics (*13*). Nevertheless, a continuing trend toward increasing mortality is worrisome. It will take a number of years to sort out why these trends for asthma are occurring. Attention must be focused on finding the causes and risk factors for asthma so that appropriate intervention strategies can be developed.

The purpose of this report is to review the available data that provides evidence for an association between asthma and exposure to selected criteria pollutants and that focuses on clinical studies using physiological and biochemical end points.

## Responses of Asthmatics to Criteria Pollutants

Not all criteria pollutants have been shown to have an effect on asthmatics (Table 1). Therefore, the discussion below will focus on those criteria pollutants that have been shown to have pulmonary effects on asthmatics, namely $SO_2$, particulate matter less than 10 µm aerodynamic diameter ($PM_{10}$), $O_3$, and $NO_2$.

### Sulfur Dioxide

Sulfur dioxide ($SO_2$) is emitted primarily by coal- and oil-fired plants and by industrial processes involving fossil fuel combustion, as sulfur is a natural contaminant of these fossil fuels. $SO_2$ and particles are directly regulated under the Clean Air Act whereas the possibility of a standard for acid aerosols has only recently been considered by the U.S. EPA. Even though particles, sulfur oxides ($SO_x$), and acid aerosols are chemically distinct, they are all released by fossil fuel combustion processes and are usually present together as components of a complex mixture.

Epidemiologic data indicate an association between particles and acid aerosols and increased mortality, although the association is notably weaker for $SO_2$. The epidemiologic studies are limited in that the effects of these different pollutants cannot be assessed separately. This can, however, be addressed in controlled chamber exposure studies.

$SO_2$ is a respiratory irritant that does not cause substantial acute or chronic adverse effects in animals exposed to ambient concentrations (*15,16*). Because $SO_2$ is 50 times more soluble than $CO_2$ in water at 30° C, it is mostly absorbed in the upper airways in subjects at rest, although increasing ventilation results in deposition in deeper parts of the lung. Controlled human studies of healthy subjects exposed to $SO_2$ at rest or with exercise have failed to demonstrate effects on respiratory mechanics at levels up to 1.0 ppm (*17–20*). In contrast, exposure to low levels of $SO_2$ does alter the lung function of asthmatics (*21,22*). Asthmatic subjects exercising in air containing $SO_2$ develop bronchoconstriction within minutes, even at levels as low as 0.25 ppm. When asthmatic subjects are briefly exposed to $SO_2$, many develop significant increases in airway resistance, especially with oral breathing at a minute ventilation greater than 40 l/min (*23–26*). Spirometric functions (e.g., forced expiratory volume in 1 sec; $FEV_1$) were also decreased in response to exposure to 0.4 to 1.0 ppm $SO_2$. The data indicate heterogeneity in the response to $SO_2$ among asthmatics (*27*) and that individual responses are relatively reproducible (*27,28*). $SO_2$ can be considered to have comparable effects to those of nonsensitizing bronchoconstrictors, such as histamine and methacholine, but are not comparable to those of specific antigens and certain occupational chemicals that can provoke so-called late reactions.

The predominant acid aerosols are sulfate and bisulfate ions that are found in solution in water droplets in the atmosphere. Because of the abundance of ammonia in the atmosphere, sulfate is usually found in one of the two above-mentioned forms. Some short-term controlled inhalation studies suggest that asthmatics are more sensitive than normal subjects to $H_2SO_4$ aerosols at concentrations in excess of the high range of observed ambient levels of acid aerosols in the United States (*29,30*). Other studies, however, have failed to confirm the susceptibility of asthmatics (*31–33*). One reason for the difference in the results obtained from different laboratories may be that endogenous respiratory $NH_3$ provides protection against inhaled acidic pollutants. High oral respiratory levels of $NH_3$ have been shown to inhibit bronchoconstriction induced by $H_2SO_4$ in exercising asthmatics (*34*). Taken together, these studies show that an effect of acid aerosols clearly occurs in some asthmatics, but with less consistency than the $SO_2$ response. The variation in response of asthmatics to acid aerosols among various laboratories awaits explanation.

### Particulate Matter

The initial reference method for total suspended particles (TSP) measured mass of all suspended particles. In 1987, the EPA restricted the NAAQS to the mass concentration of inhalable particles less than 10 µm aerodynamic diameter ($PM_{10}$) (*35*) (Table 1). The NAAQS for PM does not specify chemical composition of particles. The 10 µm size cutoff focuses monitoring and regulatory efforts on particles of a size that would be deposited in and could damage the lower airways and gas-exchanging portions of the lung. So far, most of the human health effects data of PM is based on epidemiologic data. High particulate and $SO_2$ concentrations were associated with substantial short-term increases in morbidity and mortality during dramatic air pollution episodes of the past (*36–41*). The obvious increases in morbidity and mortality that accompanied these episodes and the frequency and severity of respiratory complaints left little doubt that pollution exposure caused the adverse effects. Exposure to particulates was associated with increases in respiratory symptoms during the 1960s in Londoners with chronic obstructive lung disease (COPD) (*37*). Daily total mortality has recently been reported to be positively associated with TSP concentrations. An analysis of data from Steubenville, Ohio, for 11 years (1974–1984) showed a statistically significant increase in daily total mortality associated with TSP concentrations of the previous day (*42*). A similar association was shown in a study conducted in Philadelphia (*43*). Analysis of cause-specific mortality in Philadelphia showed the strongest association with respiratory mortality and, secondarily, with cardiovascular mortality. Relatively few studies have specifically assessed the association between PM and asthma. Daily reports of respiratory symptoms were collected among a panel of 209 adult asthmatics residing in Denver, Colorado (*44*). Hydrogen ion and $PM_{2.5}$ levels were associated with moderate to severe cough and shortness of breath, both of which are indicators of asthma.

Asthma medication use increased with increasing $PM_{10}$ in a panel of asthma patients living in the Utah Valley (*45,46*).

The biological effect of particles is determined by the physical and chemical nature of the particle, the physics of the deposition in the respiratory tract, and the biologic events occurring in response to the particle. There is a general belief that a disturbing aspect of the epidemiologic findings thus far is that effects appear independent of the chemical composition of the particles. Approaches to understanding the mechanism(s) responsible for the biologic effects of particles include *in vivo* instillation and inhalation of particles followed by analyses of tissues and fluids for toxicological changes indicative of a disease and *in vitro* exposures of particles to pulmonary cell types including macrophages and epithelial cells. Intratracheal instillation of particle suspensions directly into the lung of rodents has been used to study direct cytotoxic effects (*47*). Bronchopulmonary lavage in animals at various times postexposure has enabled the performance of assays of inflammation and edema for various particles (*48,47*). *In vitro* study of particles is a useful approach to assess the response of cells that may contribute to the inflammatory process as it relates to interactions with particles. Several studies describing the responses of alveolar macrophages (*49,50*) to particles such as $SiO_2$ and $TiO_2$ have been described. So far none of these studies involved the use of pulmonary cells obtained from asthmatic individuals. It is noteworthy that recent studies with normal human subjects exposed to instilled particles followed by bronchoalveolar lavage (BAL) at different times revealed an inflammatory response for 2 days following the instillation of the particles as indicated by neutrophilic infiltrates (*51*). Inflammation may be exacerbated by alteration in the deposition characteristics of particles in compromised lungs. Again, no such experiments have so far been performed with asthmatic subjects.

Collectively, the epidemiologic studies provide provocative evidence for adverse pulmonary health effects associated with particulate pollution. The association between PM and acute mortality and morbidity has primarily been demonstrated with people who have cardiopulmonary disease and asthma. Clearly, there is a need to better understand the underlying mechanisms responsible for these effects by performing *in vivo* and *in vitro* exposure studies with a variety of particles comparing the responses of asthmatics to normal subjects.

## Ozone

Ozone ($O_3$) is a gas that occurs with other photochemical oxidants and fine particles in the complex mixture called smog. Ozone is formed by a series of sun-driven reactions involving nitrogen oxides ($NO_x$) and volatile organic compounds (VOC) arising largely from mobile and stationary combustion sources (*52–54*). As a potent oxidant, $O_3$ is capable of reacting with a variety of extracellular and intracellular molecules, particularly those containing thiol or amine groups or unsaturated C=C bonds (*55*).

Bates and Sizto (*56*) studied hospital admissions in southern Ontario, Canada, an area with a population of 7 million people and observed increased rates of admissions for asthmatic subjects in the summer, which correlated with both $O_3$ and suspended sulfates. These results implicate $O_3$ as a contributing cause of asthma admissions; however, the study design could not separate the $O_3$ effects from concomitant effects of acidic aerosol and $SO_2$ (*56,57*). A more recent study by Spektor et al. (*58*) found significant decreases in peak flow and $FEV_1$ in children in summer camp, although the $O_3$ concentration during the study period did not exceed 0.12 ppm. None of the children were reported to have a history of lung disease or atopy.

Over the last 15 years, controlled human exposure studies have clearly demonstrated that the lung responds to $O_3$ exposure by irritative cough and substernal chest pain on inspiration; decrements in forced vital capacity (FVC) and $FEV_1$; increase in specific airway resistance (SRaw) and airway responsiveness; and neutrophilic inflammation of the airway submucosa accompanied by increased level of mediators and cytokines in the BAL (*59*). Even among homogeneous study populations, there has been a wide range of susceptibility to these effects (*60,61*).

Many clinical studies have failed to show that subjects with asthma are more sensitive to $O_3$ than are healthy subjects (*62–64*). These studies have typically involved subjects with clinically mild asthma performing mild exercise, and those studies focused on spirometric abnormalities. Recent data suggest that if more intense exercise is imposed, asthmatic subjects show increased SRaw to a 2-hr exposure to 0.4 ppm $O_3$ (*65,66*), which is in excess of the response seen in nonasthmatics.

A number of studies have addressed the effects of $O_3$ following an exposure to or in the presence of other pollutants. A few controlled human exposure studies addressing the interaction between $O_3$ and other criteria pollutants have been performed. Prior exposure of healthy individuals to other pollutants may modify the response to $O_3$ (*67*). Similarly, preexposure to $O_3$ may change a response to other pollutants. Recently, preexposure to 0.12 ppm $O_3$ for 45 min followed by 0.10 ppm $SO_2$ for 15 min elicited greater bronchial hyperreactivity in adolescent asthmatics than $SO_2$ alone or $O_3$ exposure followed by $O_3$ (*68*). Exposures to mixtures containing acid aerosols and $O_3$ have shown modestly increased effects (*20,69*). For example, lung function, as measured by spirometry was worse (*70*) when $O_3$ was inhaled with $SO_2$ than with either alone, although this study has not been replicated. Very few studies focusing on the effects of exposure to mixtures on asthmatics have been carried out so far. However, the concept of influencing the asthmatic response by combining exposure to $O_3$ with a challenge of a specific allergen has created a lot of interest in the potential indirect effects of $O_3$ exposure. In one study, individuals with allergic rhinitis were initially exposed to clean air or 0.5 ppm $O_3$ for 4 hr (*71*). The high level exposure to $O_3$ did not enhance the acute response to antigen in the nose under these experimental conditions. In a more recent study, Molfino et al. (*72*) examined the effect of $O_3$ without exercise on the airway response to inhaled allergen in adult subjects with asthma. They reported $O_3$-induced increases in bronchial responsiveness to inhaled ragweed or grass pollen as measured by allergen bronchoprovocation tests. This is a very provocative study that needs to be confirmed. Along the same line of experiments, studies are currently being conducted examining the effects of preexposure to $O_3$ and exercise followed by a nasal allergen challenge (using house dust mite as antigen) on atopic asthmatics (*73*). Preliminary data from those studies suggest that the exposure to $O_3$ before the nasal challenge caused a shift in the dose of allergen needed to induce symptoms and caused an increase in the levels of inflammatory cytokines detected in the nasal lavage.

In developing future programs intended to better understand the effects of $O_3$ on asthma, there is a need to do longitudinal and cross-sectional population studies, clinical exposure studies including nasal and bronchial challenges with allergen, and *in vitro* studies that will be primarily done to address mechanistic aspects of environmental asthma and how the epithelial cells from asthmatics may differ from normal epithelial cells. Future studies should also recognize the fact that $O_3$ is not only an outdoor air pollutant, but is also present in the indoor air environment (albeit at lower concentrations) where we spend most of our time.

## Nitrogen Dioxide

Nitrogen dioxide ($NO_2$) is an oxidant that contaminates ambient air in many urban and industrial locations and indoor air in homes with unvented combustion appliances. The present NAAQS refers to the annual average concentration; a short-term standard is not in place. However, some evidence, largely from studies of the effects of acute exposure to $NO_2$ on lung function and airway responsiveness of asthmatics, suggests that a new standard governing short-term concentrations may be warranted.

During high temperature combustion, oxygen reacts with nitrogen to generate nitric oxide (NO) and, to a lesser extent nitrogen dioxide ($NO_2$) and other nitrogen oxides. $NO_2$ is highly reactive and, in the presence of sunlight, it participates with hydrocarbons and oxygen in the complex reactions that form $O_3$ and other photochemical oxidants. The principal source of NO and $NO_2$ in outdoor air is motor vehicle emissions, but power plants and fossil-fuel-burning industries also contribute. In most U.S. cities, ambient levels of $NO_2$ vary with traffic density. Of 163 counties reporting $NO_2$ monitoring data, only Los Angeles County did not meet the NAAQS of 0.053 ppm annual arithmetic mean. In contrast to other criteria pollutants, $NO_2$ is a widespread contaminant of indoor as well as outdoor air, and indoor levels can exceed those outdoors. Indoor sources of $NO_2$ include cooking ranges (*74*) and kerosene space heaters (*75*). Because over one-half of the residences in the United States have gas cooking stoves and Americans spend a large proportion of time in their homes, the residential environment has generally been found to be the most important contributor to the population's total exposure to $NO_2$ (*76,77*). The toxicity of $NO_2$ is generally attributed to oxidative capabilities (*78,79*), although as an oxidant it is less reactive than $O_3$ (*78,80*). Empirical and theoretical studies indicate that $NO_2$ penetrates to the lung periphery, with the centriacinar region as its primary deposition site, and has a somewhat greater airway deposition than $O_3$ due to its higher solubility in water (*81,82*).

Only a few epidemiologic studies have directly addressed the association between $NO_2$ concentration in outdoor air and respiratory illness. Much more extensive information is available from studies examining the effects of indoor exposures resulting from emissions from gas cooking stoves and space heaters (*83–85*). The evidence for a relationship between exposure to $NO_2$ and respiratory illness from studies of indoor exposure does not consistently indicate an increased incidence of more severe illness in children and adults classified as having higher exposures to $NO_2$ (*85–87*). The evidence is more abundant for children. While several studies showed significantly increased risk of respiratory illness for children living in homes with gas stoves compared with children living in homes with electric stoves (*88,89*), other studies did not (*84,90–93*). Metaanalysis summarizing data from 11 epidemiologic studies of health effects associated with $NO_2$ showed a significant association between estimated $NO_2$ exposure and illness (*94*).

Studies examining responses of healthy volunteers to acute exposure to $NO_2$ ($\leq 1$ ppm) have generally failed to show alterations in lung mechanics of healthy volunteers (*95,96*). Several recent observations indicate that $NO_2$ exposures in the range of 1.5 to 2.0 ppm cause small but significant increases in airway reactivity. Mohsenin (*97*) found that a 1-hr exposure to 2 ppm $O_2$ increased responsiveness to methacholine, as measured by changes in airway responsiveness, without directly affecting lung function.

Early findings (*98*) brought attention to the intriguing possibility that a relatively brief exposure of asthmatics to low-level $NO_2$ (0.1 ppm) might enhance subsequent responsiveness to bronchial challenge with a bronchoconstricting drug, although these results could not be replicated in a later study (*99*). Kleinman et al. (*100*) have shown that inhalation of 0.2 ppm $NO_2$ for 2 hr, although not causing alterations in flow rates or airway resistance, resulted in increased reactivity to methacholine. Bauer et al. (*101*) reported that $NO_2$ inhalation produced significant decrements in forced expiratory flow rates after exercise and increased responsiveness to cold air challenge. Despite this evidence of hyperresponsiveness of asthmatics to low levels of $NO_2$, considerable controversy remains because of the inconsistency of the results (*59*). The effects of $NO_2$ exposure on $SO_2$-induced bronchoconstriction have been examined, but with inconsistent results. Collectively, the findings reported above differ from those of Linn et al. (*102,103*), for asthmatics inhaling concentrations of $NO_2$ as high as 4.0 ppm. It is evident that a wide range of responses occur among asthmatics exposed to $NO_2$. This variation may in part reflect differences in subjects and exposure protocols. However, the consistency of responses of asthmatics to $NO_2$ across a 1-year interval suggests that some asthmatics are inherently more responsive and implies a need for better understanding of $NO_2$ and asthma (*104*).

$NO_2$ appears to be much less potent than $O_3$ in eliciting a neutrophilic inflammatory response in normal subjects. Two preliminary reports (*105,106*) describe increases in numbers of PMNs obtained by BAL following a single 4- or 6-hr exposure to 2.0 ppm $NO_2$. Devlin et al. (*105*), observed the increase in PMN only in the cells recovered from the bronchial lavage aliquot. The effect of $NO_2$ on challenges with a specific allergen in atopic asthmatics is of considerable interest considering the recent data by Molfino et al. (*72*) and Peden et al. (*73*).

Responses to $NO_2$ exposure in clinical studies are characterized by marked variability, which directs attention toward identifying determinants of susceptibility. Characterizing these and other factors may hold the key to understanding the risks of $NO_2$ exposure, especially to sensitive subpopulations such as asthmatics.

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