Human Health Effects of Air Pollution

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Over the past three or four decades, there have been important advances in the understanding of the actions, exposure-response characteristics, and mechanisms of action of many common air pollutants. A multidisciplinary approach using epidemiology, animal toxicology, and controlled human exposure studies has contributed to the database. This review will emphasize studies of humans but will also draw on findings from the other disciplines. Air pollutants have been shown to cause responses ranging from reversible changes in respiratory symptoms and lung function, changes in airway reactivity and inflammation, structural remodeling of pulmonary airways, and impairment of pulmonary host defenses, to increased respiratory morbidity and mortality. Quantitative and qualitative understanding of the effects of a small group of air pollutants has advanced considerably, but the understanding is by no means complete, and the breadth of effects of all air pollutants is only partially understood.

Introduction

Community air pollution is a problem that is as old as civilization, and on a smaller scale must date back to prehistoric cultures. Surely the black linings of caves inhabited by some of our ancestors are evidence of indoor air pollution with wood or coal smoke, pollutants which have drawn more attention recently as a significant risk factor in the development of lung cancer (*1*). Understandably, smoke was the first pollutant to be regulated (*2*). In the present century, there have been several major air pollution "disasters" (Meuse Valley, Belgium, 1930; Donora, PA, 1948; London, 1952). To the extent that real changes in the control of air pollution occurred in the United States, these episodes apparently did not generate sufficient political or public health interest in the health effects of air pollutants. The Clean Air Act of 1963 and its subsequent amendment in 1970, along with formation of the Environmental Protection Agency led to implementation of National Ambient Air Quality standards for several major pollutants (photochemical oxidants [ozone], sulfur oxides, nitrogen oxides, carbon monoxide, hydrocarbons, and particulate matter; lead was added later, and hydrocarbons were incorporated in the ozone standard). The passage of the Clean Air Act sparked a renewed interest in the health effects of air pollutants that has continued to the present.

The investigation of the effects of air pollution on human health has followed a multidisciplinary approach using animal toxicology, epidemiology, controlled human exposure studies, and, more recently, molecular and cell biology. Air pollutants may, in addition to other responses, cause lung cell damage, inflammatory responses, impairment of pulmonary host defenses, and acute changes in lung function and respiratory symptoms as well as chronic changes in lung cells and airways. Substances subsequently absorbed into the blood, such as lead or carbon monoxide, can have a variety of effects on other tissues. Acute and chronic exposure to air pollutants is also associated with increased mortality and morbidity. The focus of this review is on the human health effects of air pollutants as determined through controlled human exposure studies and emphasizes the responses that have been shown with ozone, sulfur dioxide, and carbon monoxide. An effort was made to include key studies that added important insight into the health effects of air pollutants and which led to use of these findings in the establishment of regulations. A comprehensive review of the biological responses to air pollutants is presented in the Air Quality Criteria Documents (*3–8*) and in the National Acid Precipitation Assessment Program review (*9*), which fills numerous volumes.

Ozone

Ozone has received a great deal of scientific attention over the past 25 years, and much is now known about how this compound affects lung function and lung morphology. The discovery of the physiological effects of ozone was first reported by Schönbein in 1851 (*10*). He described typical symptoms including cough and pain in the chest, which are still reported today, although in his case the symptoms were quite severe because of the higher ozone concentrations which he breathed. In 1876, Richardson (*11*) pointed out the possible community-wide effects of ozone when he suggested that there may be times when the ambient ozone level may be high enough to cause symptoms. Despite these early observations and the subsequent investigation of occupational health risks associated with ozone, the realization of potential health effects from ambient ozone dates back primarily to the 1950s.

An important observation was made in 1967 by Wayne and coworkers (*12*), who reported that the seasonal improvement in race times of high school cross-country runners was inversely related to the ambient ozone concentration. Although lung function and respiratory symptoms were not examined in this study, it was known that considerably higher concentrations of ozone

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could cause alterations in lung function in resting subjects (*13–15*). The importance of this study (*12*) was that it indicated that heavily exercising, healthy, young men could experience adverse effects at relatively low ozone levels commonly found in the ambient air. The observation that exercise during high-concentration ozone exposure caused a marked increase in toxicity to rats had been made many years previously by Stokinger and colleagues (*16*).

Subsequently, Bates and associates (*17*), in a controlled chamber exposure study, demonstrated that ozone exposure that included mild, intermittent exercise caused a markedly increased pulmonary function response in humans compared to a resting exposure. This study underscored the point that individuals are often active when exposed to air pollutants and that the increased ventilation associated with exercise was an important factor in the delivery of air pollutants to the pulmonary target tissues. The intermittent exercise exposure protocol used in this study, designed to simulate moderate outdoor activity, was later adopted by many other investigators. These findings were extended and confirmed by others (*18–23*) who showed that increasing the exercise intensity or exposure duration further exacerbated the pulmonary function responses.

In addition to pulmonary function responses, Folinsbee et al. (*24*) found an alteration of the breathing pattern during exercise as well as a decline in maximum oxygen uptake after ozone exposure (*25*). Alterations in lung function, breathing pattern, and exercise performance have now been confirmed in heavily exercising subjects exposed to ozone concentrations as low as 0.12 ppm (*23,26,27*). The dose–response study by McDonnell et al. (*27*) has provided important data [see also Kulle et al. (*28*) and Avol et al. (*29*)] for the risk analysis used to support the 1-hr ozone standard. Additional studies from EPA's Clinical Research Branch of the effects of prolonged exposures to low ozone concentrations (*23,30,31*) will be useful in analyzing the need for a multihour ozone standard.

These studies have been instrumental in shifting from a simplistic concentration–response evaluation of controlled exposure data to more complex risk analyses that consider activity patterns, pollutant concentration, respiratory tract uptake, and other factors. These data have also been useful in modifying and verifying models used to estimate responses to ozone and other air pollutants (*32,33*). An important step in using animal data to estimate human responses (animal to human extrapolation), essential to the evaluation of many pollutants for which controlled human exposures are impossible, was to determine differences in respiratory tract ozone uptake between man and animal (*34,35*). Concentration response studies at different exercise levels (*22,27,29,30*) have illustrated the importance of ozone concentration in the prediction of response (*36*). Comparisons of responses to ambient exposures either in uncontrolled "camp" studies (*37,38*) or in controlled exposures to ambient air (*29*) have demonstrated the validity of chamber exposures.

Sensitive Subjects

In the context of setting air quality standards, a key issue in the evaluation of the health effects of air pollutants is to determine the individuals who are at greatest risk from exposure to air pollutants. The most likely candidates for this distinction often include children, the elderly, patients with lung disease such as asthma and chronic obstructive lung disease (COPD), smokers, and patients with other diseases; many such individuals have undergone controlled ozone exposures. The pulmonary function responses of children exposed to ozone are similar to those of healthy adults (*38–40*), except that children have fewer respiratory symptoms. Ambient ozone exposure is associated with increased asthma attacks in asthmatics (*41*). However, asthmatics (*42,43*) have similar changes in spirometry and airway reactivity, although somewhat larger changes in airway resistance than healthy adults. Patients with COPD have not shown remarkable changes in lung function (*44*), but the potentially more important changes in lung host defenses and airway inflammation have not been evaluated. Smokers (*21*) and healthy older adults (*45*) appear to be less responsive to ozone than healthy young adults. However, there is a broad range of responsiveness among healthy adults (*27,46*) and responses are reproducible (*47*). Factors that predict individual sensitivity to ozone have yet to be defined, despite attempts to do so (*48*), although it is clear that increasing age (*45,48*) is associated with decreased responsiveness to ozone. A group of healthy individuals at increased risk from ozone exposure are those who engage in vigorous outdoor work or exercise (*23,49*) or athletic competition (*26,50*).

Repeated Exposure

In 1956, Stokinger et al. (*16*) demonstrated that a 6-hr exposure to 1 ppm ozone was lethal to rats. However, animals that were preexposed to 1 ppm ozone at rest developed "tolerance" and were not killed even by several successive days of exposure with exercise. Although research had been directed at the effect of residing in areas encumbered by oxidants (e.g., Los Angeles) on respiratory symptoms (*51–53*), no serious attempts have been made to determine the chronic effects of oxidant air pollution on lung function, despite the pronouncement by Bates (*54*) that an "urgent need [for these data] has been evident for some years." Although there have been investigations of chronic effects of oxidant pollutants (*55*), we seem to be not much closer to an answer to this question now than 20 years ago. Apparent differences in response to ozone between residents of Los Angeles and of other cities (*56*) led to an examination of the effects of repeated ozone exposure in humans (*57*). Although these and other studies illustrated a compensatory response to repeated ozone exposure, it remains unclear whether continuous residence in a polluted environment such as the Los Angeles Basin will cause premature "aging" of the lung or increased incidence of chronic respiratory disease.

Repeated exposure to higher ozone doses results initially in an enhanced pulmonary function response within 12–48 hr (*58,59*) but after 3–5 days of exposure leads to an attenuated pulmonary function responsiveness. This attenuated response persists for up to a week (*46,60,61*) but may last considerably longer for other ozone-induced responses. The increased responsiveness to methacholine or histamine that is caused by ozone exposure may be attenuated (*60,62*) with repeated exposure or may persist (*63*). Rats repeatedly exposed to ozone demonstrate attenuated functional responses but show a pattern of progressive damage to epithelial cells and airway inflammation with increasing numbers of inflammatory cells in the terminal bronchiolar region (*64*). These observations emphasize that the attenuation

of symptoms and functional response to ozone does not imply a beneficial compensatory response.

One of the effects of repeated ambient exposure may be a persistent change in responsiveness to ozone. Linn et al. (*65*) demonstrated that Los Angeles residents who were sensitive to ozone in the spring were less responsive to ozone exposure after the summer and fall oxidant air pollution seasons. However, after a winter of relatively low ozone levels, they had regained their responsiveness by the following spring. This important finding, which confirms previous anecdotal reports, strongly suggests that some long-term response is causing an alteration in the sensitivity to ozone exposure. In rats and monkeys repeatedly exposed to ozone for prolonged periods, cellular remodeling of the lung occurs, resulting in a thickened airway epithelium and a persistent inflammatory lesion (*66–68*). Similar responses in humans may be responsible for the seasonal decrease in ozone response.

Inflammation and Airway Hyperresponsiveness

Damage to airway epithelial cells leads to a cascade of events that results in airway hyperresponsiveness (AH) and airway inflammation. Exposure of dogs (*69*) or guinea pigs (*70*) to ozone has been shown to cause AH to histamine. Holtzman et al. (*71*) also demonstrated AH in humans after ozone exposure and showed that the induction of AH to nonimmunologic stimuli did not appear to be related to other factors known to be associated with AH such as atopy or allergy. It was subsequently shown (*72*) that ozone-damaged epithelial cells could elaborate mediators (prostaglandins E_2 and $F_{2\alpha}$, leukotriene B_4) responsible for AH, airway smooth muscle shortening, or airway inflammation, and it is well established that ozone causes damage to epithelial cells (*73,74*). A number of animal studies have demonstrated that airway inflammation is temporally associated with ozone-induced AH (*75,76*). The temporal association of inflammation and AH is not observed in all species (*77,78*) and does not imply a causal relationship.

In ozone-exposed humans, Seltzer et al. (*79*) showed AH to methacholine 1 hr after exposure and the presence of increased levels of neutrophils in bronchoalveolar lavage (BAL) fluid taken about 3 hr after exposure. Also increased were several arachidonic acid metabolites including prostaglandins PGE_2, $PGF_{2\alpha}$, and thromboxane. Elevated plasma $PGF_{2\alpha}$ has also been shown after ozone exposure (*80*). Elevated levels of cellular damage markers such as protein and lactate dehydrogenase indicated a disruption of the barrier function of the lung. Increased clearance of labeled diethyltriamine pentaacetic acid (DTPA) from the lung after ozone exposure (*81*) provides further evidence of epithelial permeability. Seltzer's (*79*) observations have been confirmed and extended by Koren et al. (*82*), Devlin et al. (*83*), and Graham et al. (*84*), who have shown airway inflammatory responses from 1 to 18 hr after ozone exposure at concentrations as low as 0.10 ppm as well as nasal inflammatory responses at higher ozone concentrations. In addition to increased numbers of neutrophils, these investigators reported elevated levels of fibronectin, known to be involved in the cellular repair process and to be chemotactic for lung fibroblasts, and interleukin-6, which may play an important role in the induction of inflammatory responses.

Examination of ozone-response mechanisms in humans have been limited, although numerous studies have been performed in animals (*69,75–78*). The primary mechanism causing changes in spirometry after ozone exposure is a limitation of deep inspiration leading to decreased vital capacity (*18,88*). These responses appear to be related to the cough and pain on deep inspiration which are typical symptoms of ozone exposure. Bronchoconstriction is not necessary for the changes in spirometry seen in healthy adults exposed to ozone. Atropine inhibits the increase in airway resistance, indicating the parasympathetic reflex nature of this response (*87*). The spirometry responses are not altered by atropine, although they are partially inhibited by lidocaine sprayed into the upper airway (*88*). Preexposure treatment with cyclooxygenase inhibitors (indomethacin, ibuprofen) causes a reduction or inhibition of pulmonary function and respiratory symptom responses to ozone (*85,86*; M. J. Hazucha, personal communication), indicating the importance of arachidonic acid metabolites to the induction of some ozone responses. The mechanisms of airway hyperresponsiveness in humans are the subject of ongoing study, but the complex nature of this response has not yet been elucidated.

Sulfur Dioxide

Sulfur dioxide has polluted the atmosphere for most of the earth's history. However, concern over SO_2 as a modern pollutant was heightened in the middle of this century by the London "fogs," of which SO_2 was a major component. In 1953, Amdur and co-workers (*89*) examined the responses of men breathing up to 8 ppm SO_2 in one of the first controlled studies of humans exposed to air pollutants. They demonstrated that SO_2 caused a change in respiratory pattern and that the effect was concentration dependent. This study is important because it represents the emergence of physiological measurements as markers of the effects of air pollutants. The authors noted that some subjects became tolerant of even the highest concentration (8 ppm), whereas others could only tolerate the lowest levels (1–2 ppm). It was also found that individuals habitually exposed to SO_2 did not respond in the same way as those exposed acutely.

Even though the breathing pattern responses were not subsequently replicated (*90*), the lessons of individual variability and tolerance with continued or repeated exposure have been rediscovered on a number of occasions since. Frank and colleagues (*90*) subsequently studied a larger group of subjects in a more rigorous fashion. They demonstrated that SO_2 caused increased airway resistance, which was later shown to be due to reflex bronchoconstriction (*91*). They confirmed that the response to SO_2 was rapid, dose dependent, and tended to reach a peak after about 10 min or so. In this study, the authors alluded to the possible differences in oral versus nasal breathing and that the mode of breathing might alter responses. Subsequent studies (*92*) confirmed that mouth breathing of SO_2 caused greater changes in pulmonary resistance than the same concentrations breathed through the nose. SO_2, even at relatively high concentrations, was almost completely removed by the nasal mucosa during resting breathing. In a series of experiments performed on dogs, removal of SO_2 was shown to be dependent on the upper-airway breathing path (i.e., nose or mouth) as well as the air flow rate (*93*).

These initial studies of SO_2 exposure in humans were conducted at rest. To model these responses and conduct appropriate risk assessments, it was necessary to examine responses in active

subjects as well as other factors that could increase or decrease responses to SO_2. The increased ventilation due to exercise is one determinant of the volume of pollutant delivered to various target tissues within the respiratory tract. In the case of SO_2, the upper airway route traversed by the inhaled SO_2 is also very important. Although people may breathe through their nose during mild exercise, they typically breathe oronasally during heavier exercise, although this transition is variable within and among individuals. At a ventilation of about 35 L/min (*94*) most people have shifted from strictly nasal breathing to oronasal breathing, thus increasing the relative amount of air breathed through the mouth. However, even in heavy exercise, some 40–60% of the inspired air is breathed through the nose. For persons with impediments to nasal breathing such as a deviated nasal septum or allergic rhinitis (*95*), the transition to oronasal breathing will occur at a lower ventilation. SO_2 does not appear to increase nasal resistance in either asthmatics or individuals with allergic rhinitis (*96*) and would not therefore alter the proportion of oral versus nasal breathing.

Sensitive Subjects

The observation that asthmatics were more sensitive to SO_2 than healthy subjects was an important advance in the understanding of human SO_2 responses, although it is somewhat surprising that it was almost 30 years after the London fog episodes that these responses were finally studied. In addition to previous studies of asthmatics exposed to ozone and NO_2, this hypothesis was alluded to by Kreisman et al. (*97*). However, confirmation of this hypothesis was provided in a series of experiments by Sheppard and co-workers (*98–102*) and was examined concurrently by Koenig et al. (*103*). It was shown that asthmatics were more responsive to inhalation of SO_2 than healthy subjects and that this effect was clearly exacerbated by simultaneous exercise, over and above the known effect of exercise-induced bronchoconstriction. Numerous papers (*104–108*) extended and confirmed these observations, showing that higher ventilations increased the airway response to a given SO_2 concentration, and mouth breathing, as opposed to nasal breathing, exaggerated the response (*109,110*). Inhalation of SO_2 in air with a low water vapor content (either cold or dry) also increased SO_2 responsiveness in asthmatics (*102,111*), possibly due to drying of the upper airway mucosa leading to decreased scrubbing of SO_2 by the mucosa. An alternative explanation is that dissolved SO_2 or its reaction products could have been concentrated in the airway surface fluids because of evaporation of water.

At SO_2 exposure levels exceeding 0.5 ppm, bronchoconstriction will typically occur in exercising asthmatics (*104,110*). Horstman et al. (*105*) examined the SO_2 concentration–specific airway resistance (SR_{aw} response relationship in a group of moderately exercising asthmatics and found that the median concentration producing a 100% increase in SR_{aw} was approximately 0.75 ppm. About 20% of the subjects did not respond to SO_2 levels even as high as 2.0 ppm, although the provocative concentration was less than 0.50 ppm in the most sensitive 20% of the subjects.

In contrast to some other pollutants, the acute response to SO_2 is rapid; a near maximal response in asthmatics occurs in about 5–10 min, and significant increases in airway resistance can be seen with exposures as brief as 2 min (*112,113*). Spontaneous recovery often occurs within about 30–60 min. Healthy subjects typically experience responses within about the first 30 min of exposure to higher concentrations (*90*); extended exposures to relatively low concentrations (0.75 ppm) do not tend to cause increased responses (*114*).

Repeated exposure of asthmatics to low levels of SO, ($<$ 1.0 ppm) results in a diminished responsiveness to SO_2 (tolerance) (*101,104*). Roger et al. (*104*) demonstrated that, in asthmatics, the response to SO_2 was diminished with repeated exercise during exposure to SO_2. This decrease in response is at least partly due to the well-known response to repeated exercise in asthmatics that induces a period of refractoriness to exercise-induced bronchoconstriction. The diminished response to SO_2 is evident in about 30 min, but initial responsiveness is restored within 6 hr (*115*). The blunted response is not caused by diminished nonspecific airway responsiveness because the response to histamine is unchanged at the time when SO_2 response is reduced (*101*). Furthermore, there is no convincing evidence that SO_2 alters nonspecific airway responsiveness, although there may be a weak relationship between nonspecific airway responsiveness and responsiveness to SO_2 among asthmatics (*105,116,117*).

The mechanisms of response to SO_2, have been addressed in several studies. Because of the rapid onset and reversibility, it is likely that the SO_2-induced increase in airway resistance is caused by reduced airway caliber subsequent to smooth muscle contraction via a parasympathetically mediated reflex (*91,98*). Muscarinic blocking agents have been shown to be effective in inhibiting SO_2-induced bronchoconstriction (*118*). Cromolyn sodium also inhibits SO_2-induced bronchoconstriction (*99,119*), presumably due to inhibition of mast cell degranulation and histamine release. Cromolyn also blocks release of leukotrienes and prostaglandins, which could lead to decreased SO_2-induced bronchoconstriction.

Because SO_2 is deposited primarily in the nose of individuals at rest, one would expect the impact on nasal tissues to be most pronounced. In 1942, Cralley (*120*) observed that 25 ppm SO_2 increased the transit time for red dye to traverse from the nares to the nasopharynx. In a series of studies, Andersen et al. (*121,122*) confirmed that nasal mucociliary transport was indeed slowed by exposure to as little as 1 ppm SO_2. Carson et al. (*123*) showed that the nasal cilia were damaged by SO_2, providing a structural basis for these observations. Despite cell damage and the reduction in nasal mucociliary clearance, SO_2 exposure did not cause increased rhinovirus infectivity (*122*).

Nitrogen Dioxide

Nitrogen dioxide is the main precursor of ozone and as such it is a major component of oxidant air pollution. The major health end points that have been associated with NO_2 are increased incidence of lower respiratory tract infections in children and increased airway responsiveness in asthmatics. The small airways are the primary site of NO_2-induced damage. In controlled exposure studies, at levels of less than 1 ppm, NO_2 does not induce pulmonary function responses (*124,125*) or changes in airway responsiveness (*126,127*) in healthy subjects, although little, if any, functional evaluation of small airways has been performed. NO_2 causes an increase in airway responsiveness to methacholine or histamine in healthy subjects (*128*) and in asthmatics (*129,130*). Unfortunately, the database for human exposures to NO_2 lacks consistency and reproducibility. For example,

two groups that initially reported small changes in lung function associated with NO_2 exposure in asthmatics (*131,132*) were unable to replicate their findings. Nevertheless, asthmatics and COPD patients appear to be most susceptible to NO_2 (*126,133*).

Long-term exposure to NO_2, typically in homes with gas-burning appliances, appears to be associated with increased susceptibility to lower respiratory tract illness (*134,135*). This observation is strongly supported by acute and chronic animal exposure studies (*136–140*). In these studies, mice exposed to NO_2 experienced greater mortality from induced bacterial or viral infections than mice not exposed to NO_2. These effects may be associated with impaired mucociliary clearance mechanisms and depression of alveolar macrophage function (*141*). Investigation of host defense responses in NO_2-exposed humans is in the early stages, and, although there appears to be some decrease in inactivation of virus by macrophages (*142*), further work will be necessary to confirm these findings. NO_2 does not appear to cause an inflammatory response like the other common oxidant, ozone. However, there has not been sufficient examination of the cellular response to NO_2 to make any conclusions at this time.

Carbon Monoxide

Carbon monoxide is an odorless, colorless gas created primarily by incompletely combusted fuels. CO has a high affinity for hemoglobin, interferes with oxygen transport to the tissues, and is well known to cause poisoning at high concentrations. However, such high levels are of little interest to those concerned with health effects of community air pollution. Because of its association with combustion, death associated with poorly ventilated fires (and hence from CO poisoning) was surely known to prehistoric man. There are numerous records, dating back to the time of Roman civilization (*143*), that have associated fire in enclosed spaces with accidental death or suicide.

In the context of community air pollution, interest has centered on susceptible subjects who include patients with cardiovascular disease as well as healthy nonsmokers engaged in heavy exercise. CO exposure occurs in urban areas near roadways, smoke-filled rooms, and poorly ventilated areas impacted by combustion appliances and other combustion sources such as in parking garages and traffic tunnels.

The high affinity of CO for hemoglobin (Hb) was studied in a series of experiments by Haldane (*144*) before the turn of the century. In experiments conducted on himself and his colleagues he established that the relative affinity of CO for Hb was about 250–300 times that of oxygen. More recently, Roughton (*145*) reported a figure of about 245-fold greater affinity. This high affinity is important in clearing endogenously produced CO from the tissues. Carboxyhemoglobin (COHb) levels are normally less than 1% in nonsmokers. However, when ambient CO levels are increased, oxygen binding sites on Hb become occupied by CO and cause a corresponding decrease in oxygen-carrying capacity. The increase in COHb also results in a leftward shift in the oxyhemoglobin dissociation curve, resulting in decreased unloading of oxygen at the tissue level (*146*).

The clearance of CO from the blood is relatively slow with a half-time for excretion of about 3–5 hr (*147*). CO can accumulate in the blood as a result of prolonged exposure to low concentrations (10–30 ppm) or brief exposure to high concentrations (> 100 ppm) of the gas. After 1 hr of exercise in the midst of traffic congestion (mean levels of ~ 10–15 ppm CO), COHb levels could reach 3–4%. Once COHb is elevated, relatively modest levels of CO (10 ppm) will slow the clearance of CO from the blood by reducing the gradient for excretion via the lung. The dynamics of CO uptake and excretion are well described by the equation developed by Coburn et al. (*148*).

Increased COHb levels can impair exercise performance by reducing maximal oxygen uptake ($\dot{V}O_2max$) (*149,150*). $\dot{V}O_2max$ is decreased about 10% in sea-level nonsmokers as a result of increasing the COHb level to about 10%. Analysis of numerous studies of CO's effect on $\dot{V}O_2max$ (*151,152*) indicates a linear relationship between percent COHb and percent decrease in $\dot{V}O_2max$, although no statistically significant effects on exercise performance have been observed below about 4–5% COHb. Carbon monoxide reduces peak $\dot{V}O_2$ primarily by reducing the oxygen-carrying capacity of the blood and causing a leftward shift of the oxygen–hemoglobin dissociation curve (*146*). Moderate submaximal exercise performance (30–60% maximum) in healthy individuals is unimpaired, with COHb levels below about 15%, as a compensatory increase in cardiac output maintains tissue oxygen delivery (*153*).

Sensitive Subjects

Patients with cardiovascular disease are at increased risk from CO exposure. The decrease in oxygen-carrying capacity and the impediment to tissue oxygen unloading imposed by the shift in the oxygen dissociation curve combine to contribute to tissue hypoxia in patients whose compensatory cardiovascular responses may be limited. Individuals with healthy coronary circulations compensate for increased COHb levels by increasing coronary flow to maintain oxygen delivery. The inability of many cardiac patients to substantially increase coronary flow means that increased COHb levels present the threat of myocardial hypoxia (*154*).

Initial observations of angina patients exposed to CO in heavy freeway traffic (*155*) indicated marked increases in COHb (up to about 5%). Subsequently, it was shown that angina patients exposed to CO (*156*) had a more rapid onset of exercise-induced angina and increased ischemic changes in the electrocardiogram. There has been a reevaluation of these early studies in a large multicenter trial of CO exposure in 63 patients with angina and documented coronary artery disease (*157*). The decrease in exercise time before onset of ischemia was confirmed, although the response was considerably less than previously reported. For each 1% increase in COHb above the background level of about 1% there was a 4% decrease in time before ischemic changes. Thus, at a COHb level of 4%, a 12% decrease in time to onset of ischemic changes and a 7% decrease in time to onset of angina was observed. Similar or possibly higher levels of COHb may occur in freeway commuters (*158*), police officers, auto tunnel workers (*159*), or garage attendants. At slightly higher COHb levels of 6%, Adams et al. (*160*) found a reduction in left ventricular ejection fraction in addition to reduced exercise duration and time to angina, but these responses were not observed at lower COHb levels (3.8%) (*161*).

Cardiac patients with electrical instability of the myocardium leading to frequent arrhythmias are at increased risk of sudden death. Low levels of carboxyhemoglobin (< 5% COHb) do not appear to be arrhythmogenic (*162,163*), but a significant increase

in exercise-related arrhythmias, both single and multiple premature ventricular depolarizations, was seen in cardiac patients with only slightly higher COHb levels (6%) (*164*). Although the mechanism is not understood, the increased mortality from arteriosclerotic heart disease in traffic tunnel workers (*159*) could be related to CO-induced arrhythmias.

Neurobehavioral Studies

There has been considerable interest in the effect of CO exposure on neurobehavioral performance. A number of early studies suggested that CO, at levels below 20% COHb caused changes in visual sensitivity (*165*) or time estimation (*166*). However, more recent efforts using well-controlled studies with larger groups of subjects have been unable to confirm these observations (*167–169*). Indeed, Benignus et al. (*170*) concluded from a meta-analysis of studies of CO and neurobehavior that only small responses would be observed in healthy young subjects below a COHb level of about 20%, a level which would not be reached during ambient exposure. One of the hypotheses advanced for the purported neurobehavioral effects of CO was that reduced oxygen delivery to the brain would cause cerebral hypoxia. However, when COHb levels are increased, there is a compensatory increase in cerebral blood flow (*171*) so that the low arterial oxygen content does not lead to a reduction in overall oxygen delivery. Despite the numerous studies of neurobehavioral response to CO exposure, there is a need for a better understanding of the mechanisms of action of CO on the nervous system.

Particulate Matter and Acidic Pollutants

Airborne Acid

Sulfuric acid is thought to be one of the main ingredients in the London "killer fogs" of the 1950s. Today, in addition to H_2SO_4, nitric acid vapor is recognized as a significant component of airborne acidity. Despite the fact that investigations of the effects of sulfuric acid aerosols began in 1952 (*172*), little is known about the possible mechanisms by which acid aerosols could contribute to increased mortality (*173*). Increased interest in sulfuric acid aerosols developed in 1975 (*174*) with the advent of catalytic converters, early models of which produced substantial amounts of acid aerosol. More recent emphasis on acid rain and its important ecological effects (*9*) has renewed interest in the human health effects of acid aerosols.

The most sensitive physiological end point for effects of sulfuric acid in healthy adults is a change in mucociliary clearance (*175*), apparently induced by increased airway acidity. Responses in humans have been reported at levels as low as 100 $\mu g/m^3$ (*176,177*). In healthy adults, there have been few lung function responses seen at acid levels below 500 $\mu g/m^3$, a level approximately 10-fold greater than the highest ambient levels measured. At these levels, H_2SO_4 also causes an increase in airway responsiveness (*178*). Recent work suggests that prolonged, repeated exposures to acid aerosols may induce increased airway responsiveness and changes in clearance (W. S. Linn et al. and T. R. Gerrity et al., personal communication). Adolescent allergic asthmatics are more sensitive to H_2SO_4, and responses have been observed at levels as low as 70–100 $\mu g/m^3$ (*177,178*). The broad range of response to acid aerosols may be in part attributable to the substantial and highly variable capability for neutralization of acid by airway ammonia, primarily from oral bacteria (*181*).

Studies of exposure to HNO_3 vapor have been performed only recently (*180*; S. Becker, personal communication). These studies suggest possible pulmonary function responses in asthmatics and some alterations of macrophage function. Because HNO_3 vapor is taken up almost entirely in the upper airways, it will be important to examine responses in the nose, an area that has at present been overlooked.

More work is necessary to understand the effects of acid inhalation on mucus-producing cells, mucus rheology and buffering capacity. Increased secretory cells are seen in rabbits after prolonged acid exposure (*182*), and increased frequency of bronchitis and respiratory illness has been associated with particulate sulfate exposure in children (*183*). It has also been postulated that there is a relationship between acid inhalation and the exacerbation of chronic bronchitis. Such a connection is speculative at this time but could possibly explain, in part, the relationship between particulate exposure and increased mortality (*173*).

Particulate Matter

Acute exposure to airborne particles is associated with increased mortality (*3,173,184*). The 1952 London fog was associated with about 4000 excess deaths, primarily among those with preexisting cardiovascular or respiratory disease (*185*). Schwartz and Dockery (*184*) examined daily mortality and total suspended particulate (TSP) levels in Philadelphia using a Poisson regression model controlling for serial correlations and found a significant association of TSP level and mortality on the following day. The association was stronger for persons over the age of 65 and for respiratory deaths (COPD and pneumonia).

Exposure to particulate matter (PM) is also strongly associated with morbidity. Dockery et al. (*186*), as part of the Harvard Six-Cities study, demonstrated a decrease in pulmonary function that was associated with episodes of PM and SO_2 pollution. These decrements in lung function appear to persist for several weeks after the episode. Recent studies of children in a Utah community showed that respirable particulate (PM < 10 μm or PM_{10}) levels of 150 $\mu g/m^3$ were associated with a 3–6% decline in peak expiratory flow, an effect that persisted for up to 3 days (*187*). Furthermore, Ware et al. (*183*) showed that the prevalence of cough and bronchitis was positively associated with ambient particulate concentrations. Recent and very convincing evidence supports these observations. Pope (*188,189*) demonstrated a doubling of respiratory hospital admissions for bronchitis and asthma associated with the operation of a steel mill, responsible for production of up to 70% of the regional PM_{10}. Asthma and bronchitis admissions were also twice as high as in adjacent areas not impacted by the steel mill; these differences were much smaller when the steel mill was closed. These observations support an emerging view that particulate pollution is an important risk factor for acute changes in lung function and respiratory symptoms, increased acute and chronic respiratory illness, and death among high risk groups.

Lead

Lead can enter the body by either inhalation, dermal absorption, or ingestion; the effects generally cannot be differentiated

between exposure routes. Although the effects of ingested lead were evident in ancient times (*190*), the public health significance of airborne lead dates back primarily to the extensive use of lead in gasoline, which may have accounted for as much as 90% of airborne lead before the mandated elimination of lead in motor vehicle fuels. Some of the most important health end points associated with low-level lead exposure are the complex of neurological deficits (*191*), particularly in children, modest elevations in blood pressure in adults, and developmental problems. Controlled human exposures have played little if any important role in determining these problems, although more effort must be expended to understand the mechanisms of these responses in the future.

High blood lead (PbB) concentrations cause frank brain damage and slowing of nerve conduction (*192,193*). Intelligence (IQ) deficits in children have been associated with PbB levels as low as 10–15 μg/dL (*5,194–196*), and there appears to be no evidence of a threshold for the effect (*197*). In addition, hearing is adversely affected by increased PbB levels (*198,199*) also with no evidence for a threshold. Other electrophysiological responses have been reported in children with elevated PbB levels (*198,200*) and lead exposure in young monkeys has been shown to cause scotopic visual deficits (*201*).

Elevated PbB levels are also associated with developmental abnormalities including fetal neurologic damage (*202*), reduced birth weight (*203*), reduced stature (*204*), and slower attainment of developmental milestones (*199*). The positive association of PbB levels with blood pressure has been noted in several epidemiologic investigations (*205–207*). Modest elevations in pressure have been associated with PbB levels in the range of 30 μg/dL, although the mechanism of this response has not been established.

Ambient Air and Pollutant Mixtures

One of the problems of relating health effects of exposures to single pollutants in an environmental chamber to responses experienced in the ambient environment is that ambient air is a complex mixture of several gaseous and particulate pollutants that varies markedly from location to location and from day to day. Numerous chamber studies have been performed using gas–gas mixtures or gas–aerosol mixtures. In addition, field studies that take the controlled exposure methodology (minus the environmental controls) into the ambient environment have been important in validating chamber responses and vice versa.

One early study (*208*) used the interesting approach of trying to generate a smog mixture directly from automotive engine exhaust piped through a transparent tube exposed to sunlight. Although this technique failed to catch on, the issue of aging or temporal changes in the makeup of pollutant mixtures has not been well studied. One of the early studies of gas–gas mixtures was the report of Hazucha and Bates (*209*), which purported to show a striking interactive effect of ozone and SO_2 in combination. Pulmonary function responses to ozone were increased substantially by the addition of SO_2 to the chamber atmosphere. Numerous attempts (*210,211*) were made to replicate this study but none showed this striking "synergistic" response in healthy subjects. On the other hand, asthmatics exposed first to a low level of ozone and subsequently to SO_2 showed a significant drop in the forced expiratory volume in 1 sec (FEV_1), where the SO_2 alone caused no response (*212*). The principal investigators of all these studies would have perhaps saved valuable time and effort if they had examined the ambient air monitoring information and discovered, as Lefohn et al. (*213*) did, that there are very few occasions when SO_2 and ozone coexist at near equivalent concentrations. Because of the complexities of the ambient air mixtures, it is, for all practical purposes, impossible to examine every possible mixture and temporal combination of gases and aerosols in a dose–response fashion. It is important to study mixtures, but primarily those that are likely to be present, and in a similar time frame, as they occur in the ambient environment.

Mixtures of ozone and NO_2 in controlled human exposures have typically yielded similar responses in pulmonary function as are seen with ozone alone (*124,214*). Mouse infectivity studies, on the other hand, have shown additive or synergistic effects of this mixture on pulmonary bacterial infections (*140,215*). Koenig et al. (*216*) found no increase in response to SO_2 in allergic adolescents when a sodium chloride droplet aerosol, hypothesized to enhance SO_2 transport to the lower airways, was added to the SO_2. Neither sequential (*217*) nor simultaneous (*218*) exposures to ozone and H_2SO_4 change the pulmonary function response from that which would be expected alone. The absence of an additive effect for one end point does not imply that other responses, not easily measured noninvasively, will not show additive or synergistic responses. However, a presumably more interesting end point to examine for a synergistic response to ozone plus H_2SO_4 would be mucociliary clearance, which is known to be altered by acid aerosol exposure (*176*).

Field studies have, in general, supported the findings of controlled exposure studies. The ozone dose–response study of Avol et al. (*29*), involved controlled ozone exposures performed in a group of subjects also exposed to ambient air. The similarity of response between ambient air and purified air containing a similar ozone concentration suggested that the other pollutants in Los Angeles air did not add significantly to the pulmonary function response seen with ozone alone. Field studies of children attending summer camps in the northeastern United States (*37,38*) have shown spirometric responses that are similar to those seen in controlled exposures to ozone.

In general, mixtures of pollutants tend to produce effects that are additive. The acute responses to ambient air can typically be estimated by the sum of the responses to controlled levels of the pollutants. A more important question relates to the response to chronic ambient air pollution. With the continuing improvements in air quality in many areas of the globe, the answers to such questions may be forthcoming from studies of regions with more severe air pollution problems such as China, Eastern Europe, or Mexico City.

Summary

Over the past three decades, important advances in the understanding of the health effects of air pollutants have been made. Dose–response functions for several pollutants are sufficiently refined in many cases to allow adequate risk characterization, although for many air pollutants and many markers of air pollutant-induced injury, the exposure response database needs to be expanded. The understanding of response mechanisms has improved greatly but remains incomplete, even for pollutants

such as ozone and sulfur dioxide, which have been studied more comprehensively. The understanding of the human health effects of many "toxic" air pollutants will not be attained through controlled exposure studies and will be forced to rely on animal-to-human extrapolation using animal toxicology, *in vitro* human lung cell exposures, and occupational or epidemiological studies. The continued development of *in vitro* exposure techniques and appropriate comparisons to *in vivo* human exposures will be helpful in the understanding of mechanisms of response to air pollutants and in the improvement of dosimetry models necessary to the improvement of the extrapolation process.

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