

The role of air pollution in asthma and other pediatric morbidities

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A growing body of research supports the role of outdoor air pollutants in acutely aggravating chronic diseases in children, and suggests that the pollutants may have a role in the development of these diseases. This article reviews the biologic basis of children's unique vulnerability to highly prevalent outdoor air pollutants, with a special focus on ozone, respirable particulate matter (PM_{2.5} [$<2.5 \mu\text{m}$ in diameter] and PM₁₀ [$<10 \mu\text{m}$ in diameter]), lead, sulfur dioxide, carbon monoxide, and nitrogen oxides. We also summarize understanding regarding health effects and molecular mechanisms of action. Practitioners can significantly reduce morbidity in children and other vulnerable populations by advising families to minimize pollutant exposures to children with asthma, or at a broader level by educating policymakers about the need to act to reduce pollutant emissions. Management of children with asthma must expand beyond preventing exposures to agents that directly cause allergic reactions (and therefore can be diagnosed by means of skin tests) and must focus more attention on agents that cause a broad spectrum of nonspecific, generalized inflammation, such as air pollution. (*J Allergy Clin Immunol* 2005;115:689-99.)

Key words: Asthma, particulate matter, lead, sulfur dioxide, carbon monoxide, nitrogen oxides, children's environmental health

Outdoor air pollution has become a subject of increasing concern for child health professionals, epidemiologists, environmental policy makers, and families alike. Levels of outdoor air pollutants in the United States have shown general improvement since 1970, when the Clean Air Act

Abbreviations used

CO: Carbon monoxide
EPA: Environmental Protection Agency
NO₂: Nitrogen dioxide
NO_x: Nitrogen oxides
O₃: Ozone
PM: Particulate matter
PM_{2.5}: Particulate matter $<2.5 \mu\text{m}$ in aerodynamic diameter
PM₁₀: Particulate matter $<10 \mu\text{m}$ in aerodynamic diameter
SO₂: Sulfur dioxide
WTC: World Trade Center

was implemented. However, progress has slowed in recent years, and air quality in some areas has actually worsened.¹ Indeed, in 2002, some 146 million persons in the United States lived in counties in which pollution levels remained higher than the National Ambient Air Quality Standards for at least one of the 6 regulated ambient air pollutants.²

A growing body of research supports the role of these air pollutants in acutely aggravating chronic diseases, such as asthma, and suggests that they might be contributing to the development of these diseases, including as a result of exposure to developing fetuses and children. Policy makers must now confront evidence that current safety thresholds might not be sufficiently protective, especially for susceptible populations, such as children. Generalists and specialists alike are, with increasing frequency, facing management dilemmas in the care of children with asthma whose exacerbations are the product of inflammation mediated by respiratory irritants. Parents frequently request information about the environmental origins of asthma and ask for evidence-based guidance to prevent hospitalizations, especially in urban areas, where studies have consistently documented unusually prevalent and severe asthma.³

This article reviews the biologic basis of children's unique vulnerability to highly prevalent outdoor air pollutants, with a special focus on ozone (O₃), fine particulate matter (PM; PM_{2.5} [$<2.5 \mu\text{m}$ in aerodynamic diameter]), thoracic PM (PM₁₀ [$<10 \mu\text{m}$ in aerodynamic diameter]), lead, sulfur dioxide (SO₂), carbon monoxide (CO), and nitrogen oxides (NO_x), and summarizes understanding regarding the health effects and molecular mechanisms of action of the major criteria air pollutants. Data for individual pollutants are presented separately,

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although in reality these pollutants exist in ambient air as a complex mixture and might exert their effects in a synergistic fashion as well.

Practitioners can significantly reduce morbidity in children and other vulnerable populations by advising families to minimize air contaminant exposures to children with asthma, or at a broader level by educating policy makers about the societal need to act to reduce pollutant emissions. Physicians are among the most esteemed members of our society, and their advice can strongly influence decisions by policy makers, such as local school boards, that can have a great influence on air pollutant exposures to our children. Moreover, management of children with asthma must expand beyond preventing exposures to agents that directly cause allergic reactions (and therefore can be diagnosed by means of skin tests) and focus more attention on agents that cause a broad spectrum of nonspecific generalized inflammation, such as air pollution.

SOURCES AND PATHWAYS OF EXPOSURE

Outdoor air pollutants can come from many sources and include both gaseous and particulate pollution. Air pollution arises in 2 ways: as primary pollutants emitted directly out of exhaust pipes and stacks (including the gaseous pollutants NO_x and SO_2 , as well as PM, such as soot), and as secondary pollutants formed from the primary pollutants in the atmosphere in the copresence of sunlight, moisture, or both (including O_3 and secondary particles, such as sulfates). The dominant anthropogenic origin of all these pollutants is the combustion of fossil fuels. In most urban areas, and increasingly in suburban areas, traffic-related emissions are a major source of air pollution. Truck, car, and bus traffic produces a complex mixture of toxic chemicals (eg, benzene from unleaded gasoline and the organic chemicals in diesel exhaust), PM, and a variety of irritant gases (including nitrogen dioxide [NO_2], SO_2 , and O_3). These compounds can arise from the pumping of gasoline, exhaust from the combustion of fuel, and the resuspension of settled road dust particles by moving vehicles. Increasing use of motor vehicles will lead to an increase in the amount of these toxicants, despite recent efforts to make internal combustion engines cleaner and more efficient. Other sources can include large industrial facilities, such as coal-fired power plants; smaller industrial operations, such as dry cleaners; nonpoint sources, such as aircraft, locomotives, and lawn mowers; residential wood-burning stoves; and natural sources, such as O_3 caused by lightning and PM from wildfires. The relative importance of these different sources varies among pollutants over time and from one community to another, but in the United States the principal air pollution contributors are industries and electric power plants that burn coal and oil, and motor vehicles burning gasoline and diesel fuels.

The primary route of exposure to air pollutants is through inhalation. These substances, however, can also contaminate water and soil through atmospheric deposi-

tion and precipitation. Some pollutants can accumulate and persist in the soil and sediments of streams because they do not degrade quickly. Children, the elderly, and persons with preexisting respiratory conditions, such as asthma, are among those most affected by air pollution. Children spend more time outdoors and exercise more, and therefore they breathe a greater amount of pollution per pound of body weight than adults. Also, their bodies are growing and can be more affected by pollutants that impair organogenesis and other developmental processes. It is more difficult for individuals to control their air pollution exposures than exposures through other environmental routes because it is impractical to carry clean air or to cease breathing when in polluted air. Since the vast majority of air pollution's effects on children are mediated through inhalation, this review is limited to the childhood health effects that result from this pathway.

BIOLOGIC BASES FOR CHILDREN'S UNIQUE VULNERABILITY TO AIR POLLUTION

Organogenesis of the lung begins in fetal life and is especially rapid in early childhood. The number of alveoli in the human lung increases from 24 million at birth to 257 million at the age of 4 years,⁴ and changes in the lung continue through adolescence.⁵ Exposure to air pollution alters the normal process of lung development, which is guided by a complex and precisely timed sequence of chemical messages.⁶ This suggests that air pollution might have a lasting effect on respiratory health. The lung epithelium's incomplete development poses the further problem of greater permeability of the epithelial layer in young children, which can result in more significant damage resulting from a given exposure.^{7,8} At the same time, the child's lung is developing, and the child's immune system, which is immature at birth, is also developing. Molecular mechanism studies have suggested that environmental exposures influence the development of T_H2 (humoral immunity dominant) versus T_H1 (cellular immunity dominant) phenotypes.⁹

Children also have greater activity levels than adults and therefore are likely to have increased personal exposures relative to adults because of an enhanced personal cloud of particles. In part, this is the result of the air intake of a resting infant being twice that of an adult.^{10,11} In one study comparing activity patterns in Californian children and adults,^{12,13} children spent an average of 124 minutes per day participating in active sports, walking-hiking, or outdoor recreation, or more than 5 times the 21 minutes per day spent by adults engaging in the same activities. In personal exposure studies in The Netherlands, children experienced a much higher personal exposure than adults exposed to the same outdoor concentrations of PM_{10} . Although children were exposed to similar outdoor concentrations as those experienced by adults in the study (41.5 vs 38.5 $\mu\text{g}/\text{m}^3$ for adults), children's personal exposures averaged 66.8 $\mu\text{g}/\text{m}^3$ above ambient levels versus 26.9 $\mu\text{g}/\text{m}^3$ above ambient levels for adults.^{14,15}

Largely for anatomic reasons, the peripheral airways of infants are more susceptible to inflammatory narrowing than are those of adults.¹⁶ Thus, irritation caused by breathed air pollution can also result in proportionally greater airway obstruction than in adults. Children might also present with more severe asthmatic symptoms associated with air pollution exposure because they may not cease activity even when they are symptomatic. Two other factors form the biologic basis of children's unique vulnerability: their differential ability to metabolize, detoxify, and excrete environmental agents^{10,17} and their higher number of remaining years of life. Many chronic diseases, including cancer and neurodegenerative diseases, are thought to arise through a series of changes within cells that require many years to evolve from initiation to actual manifestation of illness. Exposures to environmental agents early in life, including prenatal exposures, appear more likely to produce chronic disease than similar exposures encountered later.^{18,19}

THE EFFECTS OF INDIVIDUAL POLLUTANTS ON CHILDREN'S HEALTH

Air pollution episodes have provided the starkest evidence of their potential health consequences for children. A landmark event in the recognition of the disastrous effect of air pollution on child health occurred from December 1 through 5, 1952, in London. Trapped coal smoke in the Thames valley accumulated as a result of a stationary high-pressure cell accompanied by wind speeds near zero. Approximately 4000 excess deaths occurred in London that week,²⁰ and excess deaths continued for weeks afterward,²¹ indicating that there were delayed, as well as prompt, effects. Although most of the deaths were among older adults, infant mortality was also strongly affected, with postneonatal deaths doubling during that period.²² Death rates fluctuated in a highly consistent way with the ebb and flow of the pollutants. Other causes for this epidemic, such as influenza, can be readily excluded. Influenza was not prevalent in England until more than 1 month after the episode, and in other towns in England, where the weather was as cold or colder but no inversion occurred, no increase in deaths was observed.

More recently, there were regional air pollution episodes of PM from massive forest fires in Southeast Asia and Mexico in the 1990s, shutting down businesses, schools, and airports. As recently as 1998, schools in Tehran, Iran, were shut down because automobile exhaust caused O₃ air pollution levels to increase to 6 times above acceptable levels, causing some residents to wear masks when venturing outdoors. Thus, pollution episodes can still occur today, especially in rapidly developing nations.

Although relationships between more routine levels of air pollution and adverse health outcomes are not as obvious, recent epidemiologic studies have found statistically significant associations between multiple individual pollutants and a wide range of significant adverse and preventable sequelae at present-day pollutant levels

in the United States, sometimes even in areas with pollution levels less than current air pollution standards (Table I).²³⁻⁴⁸ The acute adverse health effects of air pollution have been shown to include reduced lung function, inflammation in the lung, increased numbers of asthma attacks, excess respiratory and cardiac hospital admissions, and even premature death. The documentation of the adverse effects of chronic exposure to air pollution is not as extensive as for acute effects, but it has been reported to cause the induction of respiratory diseases, such as bronchitis and asthma, as well as to cause premature mortality.

O₃

O₃ is a highly reactive gas that results primarily from the action of sunlight on hydrocarbons and NO_x emitted in fuel combustion. It oxidizes lung tissues on contact, acting as a powerful respiratory irritant at the levels frequently found in most of the nation's urban areas during summer months.⁴⁹ Epidemiologic and clinical studies have shown that O₃ exposure is associated with worsening of athletic performance, reductions in lung function, shortness of breath, chest pain with deep inhalation, wheezing and coughing, and asthma exacerbations among those with asthma.²³ Despite this evidence, air pollution remains one of the most underappreciated contributors to asthma exacerbations.

In one recent study of the effect of air exposure on children with asthma, Gent et al²⁴ followed 130 New Haven area children who used maintenance medications for asthma and 141 children with asthma who did not use medications; the former group was considered to have more severe asthma. In the group using maintenance medication, the level of O₃ exposure was significantly associated with worsening of symptoms and an increase in the use of rescue medication. Each 50-ppb increase in 1-hour average O₃ was associated with an increased likelihood of wheezing (by 35%) and chest tightness (by 47%).

In the northeastern United States, O₃ levels are closely associated with levels of sulfate particles, both of which are components of summertime haze. These pollutants might account in part for the associations reported in the New Haven study. However, the authors directly addressed the issue of the possibly confounding effects of other air pollutants. In their copollutant models, O₃ levels, but not fine particles, were significantly associated with respiratory symptoms and rescue medication use among children with maintenance medication. This finding is supported by another recent study of 13,246 hospital admissions for asthma in Brisbane, Australia, that showed a strong association between hospital admissions for asthma and O₃ in the absence of aerosolized sulfate, strengthening the causative link between O₃ exposure and asthma exacerbations.²⁵ Similar associations have been demonstrated with hospital admissions and emergency department visits in Atlanta^{26,27} and with hospitalizations in Toronto, Ontario.²⁸

Other cohort studies have found similar associations between acute O₃ exposure and adverse effects in children.

TABLE I. Health effects of air pollution on children

Air pollutant	Concentration of exposure	Effect	Reference	Comment
SO _x NO _x		Infant deaths	36	
		Respiratory tract symptoms	40,56	
		Asthma exacerbations	41	
		Reduced lung function growth	42	
		Lymphoma (especially Hodgkin's) incidence	46	Proximity to traffic as proxy for exposure during pregnancy
PM ₁₀	>250 ppb	Enhanced allergen response	43,57	
		Infant deaths, principally from respiratory illness	35,36,37,51	
Diesel exhaust particulate		Sudden infant death syndrome	35	
		Leukemia and central nervous system tumors	45	Proximity to traffic as proxy for exposure
		Lymphoma (especially Hodgkin's) incidence	46	Proximity to traffic as proxy for exposure during pregnancy
O ₃	Traffic density >20,000 vehicles/d	Childhood leukemia	61	Traffic density as proxy for exposure
	Various	Respiratory or asthma hospitalizations	25,26,28	
		School absences for respiratory tract illness (63% increase per 20-ppb increase in ozone)	31	
	>110 ppb	37% increase in emergency department visits for asthma	27	
		Development of asthma (3-fold increase among high ambient ozone, high outdoor activity group)	34	
	>120 ppm	Decreased FEV ₁ among asthmatic subjects with aeroallergen exposure	32	
		Wheezing incidence (35% increase per 50-ppb increase)	24	
		Increased allergen reactivity	32,50	
		Increased need for rescue medications	24,29	
		Increased respiratory infections, decreased peak flow	30	
WTC dust	Near the WTC within 3 wk after 9 AM on 9/11/01	Small for gestational age	48	Exposure during pregnancy
	Within 2 miles of WTC	Decreased weight and reduced length at birth	63	Exposure during pregnancy
		Shorter gestation duration and smaller head circumference at birth	63	First trimester of pregnancy on 9/11/01

SO_x, Sulfur oxides; NO_x, nitrous oxides; PM₁₀, particulate matter ≤10 μm in diameter; WTC, World Trade Center.

At an asthma camp in rural Connecticut conducted in the early 1990s, the number of asthma exacerbations in children requiring physician-prescribed rescue medication increased in direct proportion to the ambient O₃ level, as shown in Fig 1.²⁹ In a study in Paris in which 82 asthmatic children were followed for 3 months and had every exacerbation of asthma evaluated by a physician, O₃ levels

were shown to be associated with an increase in the occurrence of asthma attacks, respiratory infections, and reductions in peak flow rate.³⁰ In the ongoing Southern California Children's study, exposure to O₃ was also associated with increased school absences for respiratory illness among both asthmatic and nonasthmatic children, although children with asthma might have been more at

risk.³¹ These epidemiologic associations have also been confirmed by controlled human exposures to O₃, which have shown not only diminished lung function but also an increased reactivity to allergens after exposure to O₃.^{32,50}

One well-documented event that has provided tangible evidence of the health benefits of reducing O₃ emissions was the observation of reduced hospital admissions for children with asthma in Atlanta, Georgia during the 1996 Summer Olympics that resulted after a reduction in the levels of this pollutant from city-wide traffic control measures.³³

A graphic representation of the types of health benefits that are estimated to be associated with O₃ reductions is depicted in Fig 2, which shows the pyramid of benefits that have been estimated to be achievable in New York City when the 1997 O₃ standards are fully achieved in that city. Although there are about 8 million persons in New York City, there are a total of some 122 million persons throughout the United States who now live in areas exceeding the US Environmental Protection Agency's (EPA's) new O₃ standard and will therefore also benefit from that revised standard. Thus, the New York City hospital admissions and mortality effects are best viewed as an indicator of a much broader spectrum of potentially avoidable adverse health effects being experienced by the public today as a result of air pollution exposures.

One important new study suggests that long-term O₃ exposure can increase the chances that children will have asthma. Although acute exposure to O₃ and other outdoor air pollutants clearly exacerbates asthma acutely, the chronic effects of air pollution have been less studied, and air pollution is not generally thought to induce new cases of asthma. However, children exercising outside receive greater doses of outdoor pollutants to the lung than those who do not and thus would be more susceptible to any chronic effects of air pollution. The California Children's Health Study carefully tested the hypothesis that air pollution can cause asthma by investigating the relation between newly diagnosed asthma and team sports in a cohort of children exposed to different concentrations of air pollutants. The relative risk of asthma development in children playing 3 or more sports in the 6 more polluted communities was 3.3 (95% CI, 1.9-5.8) compared with children in these areas playing no sports. Sports had no effect in areas of low O₃ concentration areas (relative risk, 0.8; 95% CI, 0.4-1.6), but time spent outside was associated with a higher incidence of asthma in areas of high O₃ (relative risk, 1.4; 95% CI, 1.0-2.1). Exposure to pollutants other than O₃ did not alter the effect of team sports.³⁴ This study needs to be replicated elsewhere, but it does suggest that higher long-term exposure to air pollution might well cause the induction of asthma.

PM

PM is a general term that refers to a mixture of solid particles or liquid droplets of varying chemical composition and physical properties suspended in the air. Deposition in the respiratory tract varies with particle size. Combustion and secondary particles are usually very

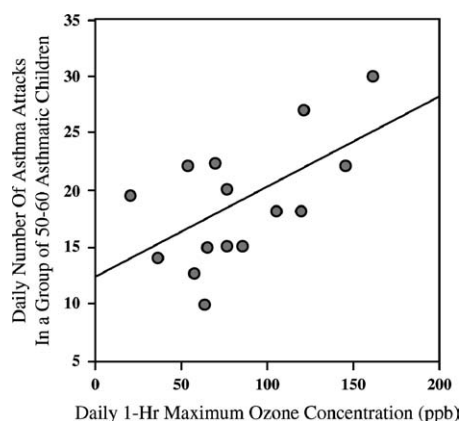


FIG 1. Asthma exacerbations increase as O₃ pollution exposures increase. Reprinted with permission from Thurston G, Lippmann M, Scott MB, Fine JM. Summertime haze air pollution and children with asthma. Reprinted with permission from: Thurston G, Lippmann M, Scott MB, Fine JM. Summertime haze air pollution and children with asthma. *Am J Respir Crit Care Med* 1997;155:654-60.

small (<1 μm in diameter) and are present in children because of their frequent mouth breathing, and these particles are especially of concern because they usually contain more toxic compounds and can penetrate deeper into the lung than the larger PM generated by natural processes (eg, windblown soil particles). Particles larger than 10 μm in diameter do not typically pass beyond the larynx, but because of their frequent mouth-breathing behavior, these particles can more often deposit in the respiratory tract of children. PM₁₀ is composed of both fine and coarse particles; coarse particles in the PM₁₀ are 2.5 to 10 μm in diameter and can include dust generated from the breakdown of rocks, soil, and dust. Fine particles, including those that are formed in the atmosphere from gaseous pollutants, are less than 2.5 μm in diameter (PM_{2.5}) and result from the combustion of fuels used in motor vehicle, power plant, and industrial operations, as well as the combustion of wood (eg, in wood-burning stoves) and other organic material. Sulfates are a major component of the water-soluble fraction of suspended PM containing the sulfate ion, including but not limited to strong acids and sulfate salts. Sulfates also contribute to acid rain and can often be seen in the air as a milky white summertime haze that impairs visibility, especially in the Eastern United States, downwind of coal-fired power plants in the Midwest that emit a large portion of the nation's sulfur oxide emissions and their resultant secondary sulfates.

PM₁₀ exposure has been increasingly associated with infant respiratory illness and infant death in recent studies across the globe. Woodruff et al³⁵ found an association with infant deaths in the United States, even when they excluded neonatal deaths. This excess risk seemed to be principally from respiratory illness, although sudden infant death syndrome rates were also increased. Bobak and Leon³⁶ also found a similarly significant association between infant death rates and particle and SO₂ concentration in the Czech Republic. Other studies have

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

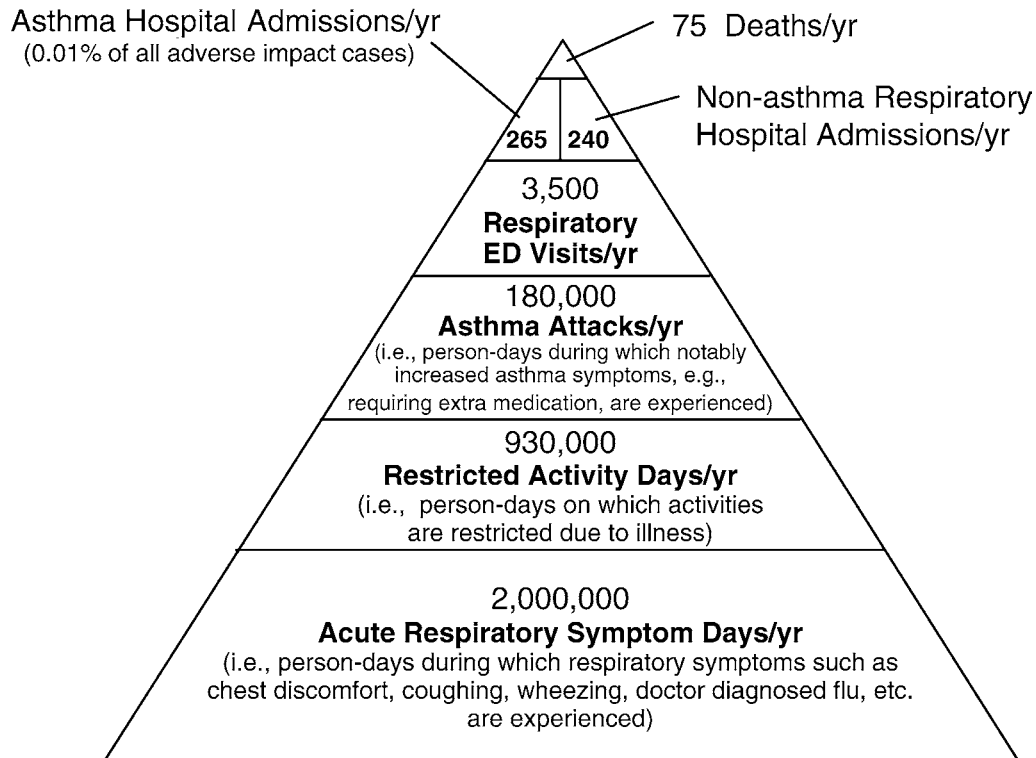


FIG 2. Estimated number of acute adverse health effects avoided by meeting the 1997 US EPA Ozone Ambient Air Quality standard. Reprinted with permission from the prepared statement of Dr George D. Thurston from Clean Air Act: ozone and Particulate matter standards. Hearings before the Subcommittee on Clean Air, Wetlands, Private Property and Nuclear Safety of the Committee on Environment and Public Works, US Senate. Washington (DC): US GPO; 1997. p. 124.

associated day-to-day changes in air pollution with day-to-day changes in infant deaths in Mexico City³⁷ and Sao Paulo.⁵¹

Lead

Although paint and soil generally are the most common sources of lead exposure for children,⁵¹⁻⁵⁵ industrial operations, such as smelters and battery manufacturers, emit potentially harmful amounts of lead.³⁸ Before the removal of lead from gasoline used in motor vehicles, airborne lead was an important source of lead exposure. However, in the absence of controls on automotive emissions and the volume of traffic in parts of the developing world, the use of leaded gasoline in some major cities still poses serious risks to children's health from these mobile sources of exposure.³⁹

NO_x

Diesel- and gasoline-powered vehicular engines and coal- and oil-fired power plants are the main sources of ambient NO_x emissions, which typically result from the fixation of nitrogen in the air during high-temperature combustion. The available epidemiologic studies are often

difficult to interpret because of the high degree of co-variation between NO₂ and other outdoor air pollutants. However, they suggest a possible synergistic role by NO₂ with other air pollutants in mediating lower respiratory tract illnesses among children.

Studies in London and Japan have associated increased ambient NO₂ with risks of respiratory tract symptoms,^{40,56} whereas in Santa Clara, California, NO₂ levels were associated with childhood asthma exacerbations.⁴¹ In a fourth-grade cohort of southern California children, exposure to NO₂ was associated with reduced lung function growth.⁴² Controlled-exposure studies of persons with asthma have found that 30-minute exposures to NO₂ can enhance the allergic response after subsequent challenge with allergens. Enhancement was seen at concentrations as low as 0.26 ppm, a level experienced in some American communities on a short-term basis, despite compliance with current federal regulations.^{43,57}

Other diesel exhaust pollution

As a result of fuel evaporation and tailpipe exhaust emissions, motor vehicles contribute a complex mixture of CO, PM_{2.5}, NO_x, hydrocarbons, and O₃ formation in

outdoor air. The US EPA and the International Agency for Research on Cancer have concluded that there is considerable evidence of an association between exposure to diesel exhaust and an increased risk of lung cancer.^{58,59}

Because of the complex nature of diesel exhaust composition, researchers have often used proximity to traffic as a proxy for diesel exhaust exposure. Epidemiologic research carried out in the Netherlands, United Kingdom, and Italy have associated increased frequency of wheezing, chronic productive cough, and asthma hospitalizations with residence near areas of high traffic density, particularly truck traffic. Diesel exhaust might also enhance allergic and inflammatory responses to antigens and might facilitate development of new allergies.^{44,60}

Epidemiologic relationships of diesel exhaust to childhood cancer have been more difficult to discern. A small study in Sweden found an association between proximity to traffic and leukemia as well as central nervous system tumors.⁴⁵ A Danish study found associations of doubling of the concentration of benzene and NO₂ during pregnancy with 25% and 51% increases in lymphoma (especially Hodgkin's lymphoma) incidence, but increases in leukemia, central nervous system tumors, and all selected cancers combined were not found.⁴⁶ A Colorado study found associations with childhood cancers and childhood leukemia, especially with areas of highest traffic density category with more than 20,000 vehicles per day.⁶¹

Most of the nation's school bus fleets run on diesel fuel, and many of these fleets contain a significant number of buses that are 15 years of age or older and are much more polluting than diesel buses manufactured today. A recent study of diesel pollution exposures in school buses found that children riding inside of a diesel-powered school bus might be exposed to as much as 4 times the level of diesel exhaust as someone riding in a car ahead of it. In fact, the study notes that these exposures pose more than 20 times the cancer risk level considered significant under federal law. These results suggest that diesel exhaust on school buses could add to respiratory problems among sensitive children, such as asthmatic subjects.⁶²

Pollutants associated with the World Trade Center disaster

The destruction of the World Trade Center (WTC) on September 11, 2001, released vast amounts of toxic materials into the air of New York City. These materials included chrysotile asbestos, highly basic PM, polycyclic aromatic hydrocarbons, volatile organic compounds, lead, dioxins, and furans. In general, airborne levels were highest on September 11th and in the first days and weeks thereafter, but PM from the WTC fires remained in the air until December, when all the fires were finally extinguished. Pediatricians advised parents and children in lower Manhattan to stay indoors and minimize outdoor exercise in the weeks after September 11th. New cases of asthma and exacerbations of existing cases have been reported in children exposed to air pollution since September 11th. The long-term consequences, particularly of exposure to potential carcinogens, will be ascertained

with more certainty only through prospective follow-up study.⁴⁷ Nonetheless, this episode has also proved once again the unique fetal vulnerability to outdoor air pollutants. Exposures of pregnant women to toxic drugs and smoke released to the environment by the attacks on the WTC on September 11, 2001, were associated with a doubling in the number of babies who were small for gestational age.⁴⁸

A second WTC study found that women who lived within 2 miles of the WTC delivered infants with significantly lower weight (−149 g) and reduced length (−0.8 cm).⁶³ Only part of these reductions was due to shortening of gestation duration. Mothers in the first trimester of pregnancy on September 11th delivered infants with statistically significantly shorter gestation duration (−3.6 days) and a smaller head circumference (−0.48 cm) compared with women at later stages of pregnancy, regardless of the distance of their residences or work sites from the WTC. The observed adverse effects of these WTC studies suggest an effect of air pollutants, stress, or both related to the WTC disaster on mothers and their infants.

Other air pollutants

More than 80,000 new synthetic chemicals have been developed and disseminated in the United States over the past 50 years. Portions of many of these chemicals are released into the air. Children are at special risk of exposure to the 2800 high-volume chemicals that are produced in quantities greater than 1 million pounds per year.⁶⁴ Fewer than half of these high-volume chemicals have been tested for their potential toxicity, and fewer still have been tested for their possible developmental toxicity to fetuses, infants, and children.^{65,66}

Some of these air pollutants deposit into soil and water and biologically accumulate in human subjects. Mercury, for example, is emitted in its elemental form by coal-fired electric power-generation facilities and other industrial activities and is subsequently transformed within aquatic microorganisms into methylmercury, which bioaccumulates in the marine and aquatic food chains and reaches very high concentrations in predatory fish, such as swordfish, tuna, king mackerel, and shark. Exposure to this potent fetal neurotoxicant results principally from consumption by pregnant women of fish and seafood contaminated by anthropogenic and natural mercury.⁶⁷ A recent study has estimated that between 316,588 and 637,233 US children each year suffer loss of IQ resulting from methylmercury toxicity, costing the United States \$8.7 billion (in 2000 dollars; range, \$2.2–43.8 billion) in lost economic productivity.^{67a}

A group of 188 pollutants has been labeled by the EPA as a group as hazardous air pollutants, “toxic air contaminants,” or “air toxics.”⁶⁸ This grouping includes chemicals known or suspected to cause serious health effects, including cancer, birth defects, and respiratory tract and neurologic illness, such as polycyclic aromatic hydrocarbons, acrolein, and benzene; hexane and toluene; hexavalent chromium; perchloroethylene; diesel exhaust;

and persistent organic pollutants, such as polychlorinated biphenyls. The EPA has identified 33 of these air toxics as posing the greatest population-wide concern, and is focusing its effort to collect air-monitoring data on these chemicals.⁶⁹

The special vulnerability of the fetus

Low-level chronic exposures to outdoor air pollutants have also been associated with an array of disquieting adverse effects on fetal development. Prenatal exposure of populations to prevailing levels of air pollution is associated with early fetal loss,⁷⁰ preterm delivery,⁷¹⁻⁷³ and lower birth weight.⁷⁴⁻⁸⁰ Causality has not been proved, but these associations merit prudent avoidance of exposures and additional study. Further support for the causative association between outdoor air pollution and adverse effects on fetal development is provided by the mounting evidence for the effect of environmental tobacco smoke, which is rich in PM, on low birth weight.⁸¹

MOLECULAR MECHANISMS OF AIR POLLUTION TOXICITY

Exposure to outdoor air pollutants has been proven to induce molecular processes that could cause adverse fetal and perinatal outcomes. In one study, volunteers exposed to diesel particles for 1 hour had increases in peripheral white blood cell counts, as well as increased vascular cellular adhesion molecule 1 and intercellular adhesion molecule 1 levels in the lung epithelium. Increases in levels of C-reactive protein, an acute-phase inflammatory marker, have been associated with air pollution exposure in adults. O₃ is a highly reactive gas associated with oxidative stress in many studies.⁸²⁻⁸⁵ O₃ exposure has also been shown to be fetotoxic in an animal model.⁸⁶

The variety of outdoor air pollutants and their ability to act synergistically, especially in mixtures of varying composition, confound the identification of one specific mechanism of air pollution toxicity. Instead, many plausible pathways exist. O₃ and PM can cause pulmonary inflammation directly and might deplete intracellular glutathione, leading to accumulation of oxidized glutathione and a decrease in the glutathione/oxidized glutathione ratio. This oxidative stress can initiate proinflammatory cytokine, chemokine, and adhesion receptor expression.⁸⁷ CO competitively inhibits oxygen transport by complexing with hemoglobin to form carboxyhemoglobin. Other pollutants might covalently modify enzymes, disrupt immune response to pollutants and allergens, and facilitate coagulation.⁸⁸ Pollutants such as diesel exhaust particulates might synergize with allergen in the human upper respiratory mucosa to enhance allergen-specific IgE production by initiating a T_H2 cytokine environment.⁸⁹

CLINICAL IMPLICATIONS

During the past 15 years, the incidence of asthma and the prevalence of severe asthma have increased in many

countries, despite the availability of improved medications. A recent careful survey of schoolchildren in Hartford, Connecticut found that 19% had asthma.⁹⁰ Some evidence suggests that air pollution might have contributed to the increasing prevalence of asthma.^{91,92} Regardless of the role of air pollution as a contributing factor to the prevalence of asthma, the study by Gent et al²⁴ and others like it indicate that the increasing numbers of children with asthma represent an expanding pool of children at risk for respiratory symptom aggravation caused by air pollution and by O₃ in particular.

Accumulating evidence of the relation between asthma and air pollution seems to have had little effect. For example, the National Asthma Education and Prevention Program Task Force's "Report on the cost effectiveness, quality of care, and financing of asthma care" failed to mention air pollution as a factor in patient admissions for asthma.⁹³ It seems that current data from epidemiologic and toxicological studies have not yet been translated into a general understanding and emphasis by physicians caring for patients with asthma. Because there is no skin test for air pollution exposure, it all too often goes unrecognized as an important factor in the causation of asthma exacerbations. Some children might be influenced by one pollen and others by yet another, but all those with asthma can have their lung inflammation worsened by air pollution exposures, thereby increasing the likelihood of an acute exacerbation by all those with asthma.

Although physicians no doubt recognize that they cannot do much about modern urban air pollution on an individual level, they can make recommendations to patients with asthma to help them avoid the potentially adverse effects of air pollution. Patients and parents of children with asthma should be aware of the ozone alert forecast, which is widely publicized in news reports and listed in the United States on the Internet (<http://www.epa.gov/airnow>). Patients with asthma should stay indoors on high-pollution days because indoor O₃ levels are much lower than outdoor levels and because the O₃ level is reduced by contact with air conditioner filters, walls, and draperies. However, some O₃ does get indoors (and children have a natural wish to exercise outdoors), and exposure to other triggers of asthma (eg, dust mites) might be increased by staying indoors. Patients with asthma also should avoid strenuous outdoor exercise on high-pollution days. The treatment of symptoms and the use of medication should be based on the usual clinical indications, although some patients might benefit by having their anti-inflammatory asthma medications increased on high-pollution days.

Recent air pollution studies also indicate that the preventive use of asthma medications might reduce these acute adverse effects of air pollution on those with asthma. In epidemiologic studies the association between particle air pollution and respiratory symptoms appears to be stronger among nonmedicated than medicated children with asthma.^{94,95} In studies with controlled chamber exposures, medication use attenuates the effects of SO₂ exposure on respiratory outcomes in volunteers with asthma.⁹⁶⁻⁹⁸

KEY STEPS FOR PREVENTION OF EXPOSURE

Infants and children are among the most susceptible to the important and diverse health effects of outdoor air pollution and provide a compelling need to move forward on efforts to ensure clean air for all. Currently, levels of O₃ and PM air pollution remain unhealthy in many parts of the United States, and the current National Ambient Air Quality Standards might not protect the public adequately. The findings of Gent et al²⁴ suggest that asthmatic children who use maintenance medication were particularly vulnerable to O₃, even at pollution levels of less than present US EPA air quality standards. PM might contribute to premature mortality and hospital admissions at levels well below those allowed by the current US PM_{2.5} and PM₁₀ standards as well.

Of the many triggers of asthma in the environment, air pollution is one of the few that can be legislated and regulated. Therefore, policy makers and regulatory agencies governing air quality necessarily have an important responsibility in ensuring that greater efforts are made to clean the air by reducing the emissions that lead to O₃ formation, thereby helping to improve the health of adults and children with asthma. The American Academy of Pediatrics' recently released policy statement, "Ambient air pollution: health hazards to children," recommends that National Ambient Air Quality Standards for PM₁₀, PM_{2.5}, O₃, and NO₂ be revised in light of recent studies that suggest that children are not adequately protected by current regulations.⁹⁹

In many cases, preventive measures can be implemented cheaply, with relatively small costs to industry. Indeed, the benefit/cost ratio of air pollution control in the United States has been shown to be very favorable.¹⁰⁰ For example, sulfate particles can readily be reduced by removing sulfur oxide emissions by using scrubbers on power plants (their largest source) at a cost that is less than 1% of the current price of electricity. NO_x reduction, a major component of an O₃ reduction strategy, can also be retrofitted onto power plants.¹⁰¹ Society is clearly willing to pay for interventions that can reduce childhood morbidity; this is proven by the demand for mattress covers and indoor air filters to lower allergen exposures.

As noted by the recent policy statement by the American Academy of Pediatrics,⁹⁹ important action can be also taken by physicians to reduce the exposures and effects of air pollution in our children. For example, because most of the nation's school buses use diesel fuel, reductions in school bus idling and the retrofit of emissions control devices on diesel buses can provide children with important reductions in exposures, but most school systems have been slow to implement such prudent steps. Physicians can do much to protect children, not only by educating their patients about proper asthma management, but also by educating their local policy makers about the need for cleaner air and of the need to replace old diesel buses, retrofit older buses with pollution-reducing

devices, or both, and limit school bus idling wherever children congregate.

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