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Ozone, Air Pollution, and Respiratory Health

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Of the outdoor air pollutants regulated by the Clean Air Act of 1970 (and recently revised in 1990), ozone has been the one pollutant most difficult to control within the federal standards. The known human health effects are all on the respiratory system. At concentrations of ozone which occur during summer air-pollution episodes in many urban metropolitan areas of the United States, a portion of the healthy population is likely to experience symptoms and reversible effects on lung function, particularly if exercising heavily outdoors. More prolonged increase in airway responsiveness and the presence of inflammatory cells and mediators in the airway lining fluid may also result from these naturally occurring exposures. Serial exposures to peak levels of ozone on several consecutive days are more characteristic of pollution episodes in the Northeast United States and may be associated with recurrent symptoms. No "high-risk" or more sensitive group has been found, in contrast to the case of sulfur dioxide, to which asthmatics are more susceptible than normals. The occurrence of multiple exposure episodes within a single year over many years in some areas of California has led to studies looking for chronic effects of ozone exposure on the lung. To date, no conclusive studies have been reported, although further work is under way. Much of what we know about the effects of this gas on the lung are based on controlled exposures to pure gas within an environmental exposure laboratory. Interactions between substances which commonly co-occur in air-pollution episodes are also under investigation.

INTRODUCTION

Ozone occurs naturally in high concentrations in the upper stratosphere, where it shields the earth's surface from ultraviolet radiation. This ozone layer is believed to affect the incidence of ultraviolet light-induced epithelial malignancies and cataracts. Ozone can be found in trace concentrations throughout the atmosphere, even in the absence of industrialized society, produced by the mixing of stratospheric ozone with air at ground level and by the interaction of biogenic hydrocarbons with solar ultraviolet radiation. Concentrations of ozone from these sources have not produced human health effects.

Ozone at higher concentrations in outdoor air is recognized as one of the most important air pollutants by the National Ambient Air Quality Standards. Episodic elevations in the concentration of ozone have been measured since the 1950s as a component of urban air pollution. During these summer events, oxides of nitrogen from internal combustion engines and hydrocarbons from these and other man-made sources react to form ozone [1]. The simultaneous occurrence of high concentrations

Abbreviation: ppb: parts per billion

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of emission precursors, strong sunlight, elevated ambient air temperature, and meteorologic air stasis are necessary to produce these ozone air-pollution episodes. Such episodes frequently occur in combination with elevations in the levels of other pollutants, including aerosols of sulfuric and nitric acid, which may potentiate the effects of ozone. In urban population centers, large numbers of people are sporadically exposed to concentrations of this mixture in amounts sufficient to produce reversible mild symptomatic and functional respiratory effects. These elevations in ozone concentrations last up to several hours per day and sometimes recur over several consecutive days. Air masses containing elevated levels of ozone may occasionally move hundreds of miles from their locations of origin, carrying the gas to rural areas [2]. A substantial minority of the United States population lives in metropolitan areas, where the ozone concentration on one or more occasions during each summer reaches the threshold for symptoms and reversible lung function responses in the more sensitive individuals [3]. Ozone is also used in community water purification and may be a short-lived by-product of many industrial processes. Inhalation of concentrations of ozone much higher than those which occur in outdoor air-pollution episodes can occur in a variety of occupations, most notably in arc welding [4].

Because it is less water-soluble than other similarly irritant gases, such as chlorine or sulfur dioxide, ozone penetrates more effectively through the bronchial tree to the gas exchange surfaces of the alveoli. Ozone is a far more potent oxidant than oxygen and is highly reactive when in contact with cell membranes, rapidly becoming dissipated in the process. The small (2 mm) conducting airways of the respiratory system are the first tissues of the lungs to show morphologic changes when ozone is inhaled chronically [5], and little is absorbed systemically. The human respiratory system is currently the only organ known to be affected by inhalation of ozone at concentrations found in the outdoor environment. Ozone at low concentrations also has important effects on some food crops, leading to growth retardation. Forests and populations of small animals can also be adversely affected.

SHORT-TERM EFFECTS

Inhaled ozone is irritating to the respiratory system even in extremely dilute concentrations. In studies of exposure of healthy individuals exercising intermittently for two hours, a threshold effect can be seen when the concentration of ozone in air approaches 120 parts ozone per billion molecules of air [6,7], as compared, for example, with the usual 200 million parts oxygen per billion molecules of air. Measurements of ozone in the air of the 90 largest U.S. metropolitan statistical areas in 1988 showed that the Environmental Protection Agency standard (of 120 parts per billion for the second highest annual one-hour peak level) was exceeded in 65 of these 90 areas, representing approximately 40 percent of the national population (Fig. 1; Table 1). While all residents of a metropolitan area reporting an elevated one-hour average ozone level are not exposed to that concentration, elevations in the concentration of ozone characteristically extend over a wide area surrounding the point of measurement [3]. A Pollutants Standard Index widely used in the United States characterizes overall air quality on a dimensionless scale of 10 to 500, where 100 corresponds to 120 parts per billion (ppb) ozone, and 300 corresponds to 400 parts per billion ozone.

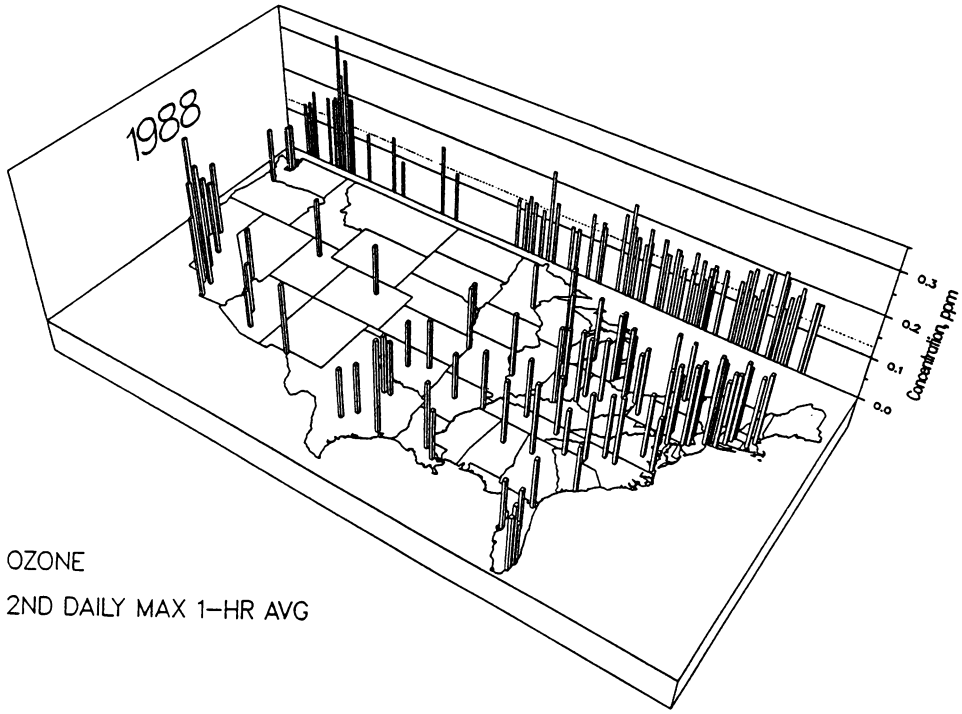

FIG. 1. Maximum outdoor ozone concentration measured in the 90 largest metropolitan areas of the continental United States for the year 1988 (most recent available data). Values shown are the second highest annual one-hour average ozone concentration for that metropolitan area (second highest values rather than highest are reported, according to Environmental Protection Agency reporting requirements). Projections of levels on the graph indicate the concentration of ozone in parts per million. The dashed line represents the National Ambient Air Quality Standard of 0.12 parts per million (120 parts per billion).

Sixty-five of the 90 largest metropolitan areas did not meet the standard in 1988. The highest levels were measured in California, the Texas Gulf Coast, the Northeast Corridor, and other heavily populated regions. (*Source:* United States Environmental Protection Agency, Office of Air Quality Planning and Standards, EPA-450/4-90-002, March 1990.)

In some locations in California, ozone levels have, on rare occasions in the past, reached 400 parts per billion, a level at which the majority of healthy individuals will experience some symptoms and lung function changes after exercising vigorously for a period of two hours.

Most of the experimental studies of human health effects of ozone have been performed in carefully controlled environmental exposure chambers where ozone alone is introduced into clean air. Recent data indicate that sequential exposures to ozone and other components of summer urban haze in asthmatic adolescents cause larger acute decrements in lung function than would occur with exposure to ozone alone [22].

Table 2 summarizes acute respiratory system effects of breathing ozone. At the threshold of measurable response, subjects begin to notice a feeling of chest tightness, discomfort on deep inspiration, and dry cough. These effects may be seen within a few minutes of first exposure. Although it may not be noticeable to the individual, the pattern of breathing also becomes more rapid and shallow. Ozone stimulates irritant receptors in the lung, which activate a neural path ending in the

TABLE 1
Second Highest Annual One-Hour Ozone Concentration Measured in the 90 Largest Continental United States Metropolitan Statistical Areas in 1988 (Adapted from [3])[a]

Metropolitan Statistical Area	1987 Population	Ozone (ppm)
Akron, OH	647,000	0.17
Albany—Schnectady—Troy, NY	846,000	0.13
Allentown—Bethelehem, PA—NJ	666,000	0.16
Anaheim—Santa Ana, CA	2,219,000	0.24
Atlanta, GA	2,657,000	0.17
Austin, TX	738,000	0.12
Bakersfield, CA	505,000	0.17
Baltimore, MD	2,303,000	0.19
Baton Rouge, LA	538,000	0.16
Bergen—Passaic, NJ	1,294,000	0.19
Birmingham, AL	917,000	0.15
Boston, MA	2,842,000	0.17
Buffalo, NY	958,000	0.15
Charleston, SC	502,000	0.11
Charlotte—Gastonia—Rock Hill, NC—SC	1,091,000	0.16
Chicago,IL	6,119,000	0.22
Cincinnati, OH—KY—IN	1,438,000	0.17
Cleveland, OH	1,851,000	0.14
Dallas, TX	2,456,000	0.13
Dayton—Springfield, OH	939,000	0.14
Denver, CO	1,645,000	0.12
Detroit, MI	4,362,000	0.16
El Paso, TX	573,000	0.17
Fort Lauderdale—Hollywood—Pompano, FL	1,163,000	0.15
Fort Worth—Arlington, TX	1,269,000	0.14
Fresno, CA	597,000	0.17
Gary—Hammond, IN	604,000	0.17
Grand Rapids, MI	657,000	0.15
Greensboro—Winston Salem—High Point, NC	916,000	0.15
Greenville—Spartanburg, SC	612,000	0.11
Harrisburg—Lebanon—Carlisle, PA	584,000	0.14
Hartford, CT	784,000	0.19
Houston, TX	3,228,999	0.22
Indianapolis, IN	1,229,000	0.14
Jacksonville, FL	878,000	0.12
Jersey City, NJ	547,000	0.20
Kansas City, MO—KS	1,546,000	0.15
Knoxville, TN	594,000	0.14
Lake County, IL	494,000	0.16
Las Vegas, NV	600,000	0.12
Little Rock—North Little Rock, AR	512,000	0.11
Los Angeles—Long Beach, CA	8,505,000	0.33
Louisville, KY	967,000	0.18
Memphis, TN—AR—MS	972,000	0.14
Miami—Hialeah, FL	1,791,000	0.13
Middlesex—Somerset—Hunterdon, NJ	966,000	0.21
Milwaukee, WI	1,389,000	0.19
Minneapolis—St. Paul, MN—WI	2,336,000	0.11
Mobile, AL	438,000	0.11
Monmouth—Ocean, NJ	957,000	No data
Nashville, TN	956,000	0.14

TABLE 1—*Continued*

Metropolitan Statistical Area	1987 Population	Ozone (ppm)
Nassau—Suffolk, NY	2,631,000	0.16
New Haven—Meriden, CT	519,000	0.17
New Orleans, LA	1,321,000	0.12
New York, NY	8,529,000	0.18
Newark, NJ	1,891,000	0.18
Norfolk—Virginia Beach—Newport News, VA	1,346,000	0.13
Oakland, CA	1,968,000	0.14
Oklahoma City, OK	975,000	0.11
Omaha, NE—IA	972,000	0.10
Orlando, FL	935,000	0.06
Oxnard—Ventura, CA	628,000	0.18
Philadelphia, PA—NJ	4,866,000	0.20
Phoenix, AZ	1,960,000	0.12
Pittsburgh, PA	2,105,000	0.16
Portland, OR—WA	1,168,000	0.13
Providence, RI	643,000	0.17
Raleigh—Durham, NC	665,000	0.16
Richmond—Petersburg, VA	825,000	0.15
Riverside—San Bernardino, CA	2,119,000	0.28
Rochester, NY	979,000	0.14
St. Louis, MO—IL	2,458,000	0.15
Salt Lake City—Ogden, UT	1,055,000	0.14
San Antonio, TX	1,307,000	0.12
San Diego, CA	2,286,000	0.19
San Francisco, CA	1,590,000	0.11
San Jose, CA	1,415,000	0.12
Scranton—Wilkes Barre, PA	731,000	0.15
Seattle, WA	1,796,000	0.11
Springfield, MA	517,000	0.17
Syracuse, NY	647,000	0.12
Tacoma, WA	545,000	0.04
Tampa—St. Petersburg—Clearwater, FL	1,965,000	0.12
Toledo, OH	611,000	0.16
Tucson, AZ	619,000	0.017
Tulsa, OK	733,000	0.017
Washington, DC—MD—VA	3,646,000	0.18
West Palm Beach—Boca Raton—Delray, FL	790,000	0.10
Wiilmington, DE—NJ—MD	559,000	0.19
Youngstown—Warren, OH	503,000	0.12

[a]Metropolitan statistical areas correspond to those shown in Fig. 1.
ppm: Parts per million

muscles of inspiration, restricting the maximal inspiratory volume that can be taken [8].

Resistance to expiratory airflow is mildly increased, indicating bronchoconstriction, and the permeability of the bronchial epithelium is transiently increased [9]. These effects become progressively greater over a six-hour exposure period [10]. At ozone concentrations which sometimes occur during air-pollution episodes, an increase in the transport of mucus along the pulmonary airways (reflecting increased activity of the tracheobronchial mucociliary system) and more rapid clearance of

TABLE 2
Short-Term Human Respiratory Responses to Breathing Oxone at Concentrations Which May Occur During Air-Pollution Episodes

1. Respiratory symptoms [5]
2. More rapid, shallow breathing during exercise [5]
3. Decreased maximal inspiratory capacity [8]
4. Increased specific airway resistance (SRaw) [5]
5. Increased mucociliary transport [11]
6. Airway hyper-responsiveness to non-immunologic stimuli (e.g., methacholine challenge) [13]
7. Increased numbers of inflammatory cells in alveolar lining fluid [12]
8. Increased respiratory epithelial permeability [9]

particulate matter from the lungs occur [11]. Normal subjects exposed during intermittent exercise to a concentration of ozone approaching the highest levels measured in the United States (400 parts per billion) have increased numbers of polymorphonuclear cells and levels of neutrophil elastase in the alveolar lining fluid which are potentially capable of producing damage to the airway [12].

These effects of a single, short-term exposure are short-lived, usually reversing spontaneously within minutes to hours. Mild increases in airway responsiveness (bronchial hyperreactivity) to non-immunologic stimuli, as measured by the methacholine challenge test, also may occur as a more persistent effect of a single short-term exposure to ozone. This response to breathing ozone is in some ways similar to, but of much smaller magnitude than, the persistent airway hyperresponsiveness seen in clinical asthmatics. Its duration is limited to from several hours to several days after a single exposure [13].

Normal subjects breathing ozone will respond at lower concentrations when exercising vigorously than when at rest because the effect of a given concentration of ozone is proportional to the minute ventilation (volume of air breathed per minute).

Since the concentration of ozone during the worst air-pollution episodes is near the threshold of human responses, the individuals most likely to be symptomatic during such an episode are those who exercise vigorously for a prolonged period of time in the high-concentration areas. Minute ventilation rises proportionally to the level of exercise, so those who engage in prolonged, sustained, or intermittent outdoor activity (e.g., heavy outdoor work, athletics, bicycling) are most likely to experience symptoms. Conversely, sedentary individuals are relatively "protected" from the symptomatic effects of ambient ozone.

Exposure to ozone is usually highest in the midday and early afternoon of hot summer days, with a drop in air concentrations toward evening, although many exceptions to this pattern occur. In the northeastern United States, summertime ozone episodes sometimes occur as six- to eight-hour plateaus rather than brief, one-hour "peak" elevations. The average maximal lung function changes under such conditions are small (generally less than a 10 percent decline) and are rapidly reversed when exposure ends. Under carefully selected circumstances in which active normal children's and adults' lung function is monitored repeatedly over a period of weeks in relation to outdoor ozone levels, correlations between higher ozone and very slight, reversible decrements in lung function have been detected at levels below the National Ambient Air Quality Standard of 120 ppb [14,15,16]. When conditions lead to a sustained elevation of ozone concentration above 80 ppb on a

single summer day in the northeastern United States, the creation of a reservoir of ozone above the ground level makes it probable that ozone will be elevated for one or more subsequent days [17]. Where repeated exposures occur over a period of days, a prior day's exposure may enhance the degree of reversible decrement in lung function seen on the second day [18], but, with multiple repeated exposures over a period of several days, the respiratory system adapts with progressively smaller drops in lung capacity and airflow. In animals challenged similarly on multiple days, however, the degree of pulmonary inflammatory response is not attenuated with serial exposure [19].

VARIATION IN SUSCEPTIBILITY

Among healthy individuals, marked variability exists in susceptibility to these effects of ozone exposure. After exercising for one-half hour while breathing 400 parts per billion ozone, some individuals show no symptoms and little change in pulmonary function, while others are overcome by paroxysmal cough and may experience a 20 percent or more reduction in spirometric lung function. Yet, among such healthy people, there are no available clinical indicators to predict which will be more and which will be less susceptible to ozone. The degree of inflammatory response of the lungs to inhaled ozone in experimental animals has been shown to be, at least in part, under genetic control. Resistant and susceptible strains of mice have an elevenfold difference in responsiveness to the same inhaled ozone exposure [20]. Initial efforts to identify more susceptible subgroups within the general population (such as children, the elderly, or asthmatics) have not detected any group at markedly higher risk of greater effects from two-hour exposures patterned after typical urban air quality alert "peaks."

These studies have compared the frequency and severity of symptoms and the percentage decline from baseline pulmonary function in these different groups under similar exposure conditions (usually two hours' intermittent exercise in a controlled human environmental exposure chamber with 400 parts per billion ozone). When comparing groups of more than 100 individual volunteers from the general population, no important differences were found in comparing children to young adults and to healthy adults over age 65; when comparing men with women; when comparing blacks with whites; when comparing asthmatic with non-asthmatic children and adults; and when comparing adults with mild chronic obstructive pulmonary disease with healthy adults. These studies were cross-sectional in design. Cohort studies looking for changes in susceptibility with aging have not been performed. Typically, the concentration of ozone in indoor air is only about one-half that of outdoor air during episodes of ozone elevation. This fact, and the relation of symptoms to elevated minute ventilation, have formed the basis for a frequently made recommendation that patients with clinically significant respiratory disease avoid vigorous outdoor activity during air-pollution "alerts." The efficacy of such restrictions on the prevention of symptoms or any other measure of health status in those with pre-existing respiratory disease is, however, unproven.

Effects of ozone alone on respiratory morbidity under present-day exposure conditions in North America have not been unequivocally demonstrated. In a region of 5.9 million inhabitants in southern Ontario, a correlation has been detected between hospital admissions for all respiratory conditions and summer air-pollution episodes during which air levels of sulfates and ozone as well as air temperature are

elevated [21]. Of the mixture of substances comprising these "summer acid haze" episodes, increasing data point to acid sulfate aerosols as having the major effects on respiratory health.

CHRONIC OZONE EXPOSURE

Lifelong residents of urban areas in which frequent elevations of ozone levels occur may be repeatedly exposed to concentrations sufficient to produce a measurable pulmonary function response on a number of occasions each summer over a lifetime. Whether repeated reversible pulmonary responses to ozone or the accumulated chronic exposure to ozone alone produce any chronic effects on the respiratory system has not been established. Some, but not all, of the studies comparing pulmonary function in large populations residing in high-exposure areas to populations in areas with low ozone and other air pollution have detected small differences. Such studies have so far been unable to attribute the differences measured firmly to ozone exposure, as opposed to the many other factors which might affect lung function. Other comparisons of respiratory health between exposed and non-exposed populations have not demonstrated marked differences. If such a chronic effect of exposure does exist, these studies in the aggregate suggest it would probably be very small in terms of the health effect to the average individual. It is not known whether there are subgroups in the population at markedly higher risk for chronic effects of ozone on the respiratory system. Epidemiologic investigations currently in progress should provide answers to these and other important questions in the coming years.

CONCLUSIONS

Because of the gradual growth in the United States population and in the use of technologies which contribute to ozone generation, the number of individuals exposed to ambient ozone is increasing with time, in spite of success in reducing the peak environmental concentrations. Residents of some urban areas in other countries may currently be exposed to peak concentrations higher than those currently measured in the United States, and to much more frequent elevations at levels comparable to those in the United States. In addition to its importance for potential human health effects, ozone appears to be an important air pollutant in relation to environmental effects on crops and the growth and development of certain trees. Equally or more important than ozone for human respiratory effects may be acidic aerosols in combination with airborne suspended particulates, although less is known about the health effects of this form of environmental exposure. As current research moves from the study of short-term effects to further examination of the potential for long-term and irreversible effects, more may be learned about interactions between ozone exposure and other respiratory toxins such as cigarette smoke, acidic aerosols, and occupational inhalation exposures.

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