

To Print: Click your browser's PRINT button.

NOTE: To view the article with Web enhancements, go to:

<http://www.medscape.com/viewarticle/417594>

The Pulmonary Effects of Ozone and Particle Air Pollution

Patrick L. Kinney, Sc.D., Columbia School of Public Health, Division of Environmental Health Sciences, New York, New York

Semin Respir Crit Care Med 20(6):601-607, 1999. © 1999 Thieme Medical Publishers

Abstract and Introduction

Abstract

Over the past three decades, considerable progress has been made in controlling levels of several outdoor air pollutants with well-established effects on human health (e.g., sulfur dioxide, carbon monoxide, and lead). However, concern remains about the potential human health impacts of two air pollutants, ozone (O_3) and fine particulate matter ($PM_{2.5}$), for which much less progress has been made. Both O_3 and $PM_{2.5}$ derive largely from fossil fuel combustion, and both have been shown to have human health effects at levels frequently observed in outdoor air. In the case of O_3 , controlled chamber experiments have shown that brief, ambient-level exposures cause acute, reversible drops in lung volumes, increases in nonspecific bronchial responsiveness, and pulmonary inflammation. Epidemiology studies have confirmed many of these findings and further have demonstrated associations with asthma exacerbations, emergency room visits, hospital admissions, and deaths. Populations most at risk include children and adults who are active outdoors, especially those with asthma. $PM_{2.5}$ is a heterogeneous mixture of suspended solid and liquid particles with widely varying diameters and compositions. The evidence for health effects of $PM_{2.5}$ derives largely from epidemiological studies that have reported associations with both acute and chronic mortality in urban areas. Other effects associated with ambient particulate matter include increases in hospitalizations and respiratory symptoms and decreases in lung function. Populations at greatest risk of $PM_{2.5}$ effects include the elderly and those with preexisting cardiopulmonary disease. Important questions remain regarding PM health effects, including the nature of the PM component(s) responsible, the biological mechanism(s) involved, and the host factors that promote greater susceptibility; these are currently areas of active research.

Introduction

Major air pollution episodes earlier this century provided clear evidence of the adverse human health consequences of elevated outdoor air pollution concentrations. For example, striking increases in daily mortality and hospitalizations were observed in London during and following the famous fog episode of December, 1952. Especially affected were the old and the sick.^[1] It has been estimated that 4000 premature deaths occurred in London as a result of the episode. Public concern regarding the human health effects of outdoor air pollution, motivated in part by episodes like that one, led eventually to the development of air quality regulations. In the United States, this effort culminated in the federal Clean Air Act of 1970, which created the U.S. Environmental Protection Agency (U.S. EPA), and established for the first time nationwide standards for outdoor air quality.

In 1971, the U.S. EPA established the first National Ambient Air Quality Standards (NAAQS) for "criteria pollutants," a small set of ubiquitous outdoor air pollutants with well-established human health effects. The current criteria pollutants are O_3 , $PM_{2.5}$, PM_{10} , lead, carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). The current NAAQS are summarized in Table 1.

Over the past three decades, considerable success has been achieved in reducing outdoor concentrations of several criteria pollutants, including SO_2 , CO, and lead. On the other hand, much less progress has been made for O_3 and for the smaller-size fractions of particulate matter, such as those with aerodynamic diameters under $2.5 \mu m$ ($PM_{2.5}$).

Considerable scientific evidence has accumulated suggesting that present-day concentrations of O_3 , PM_{10} , and $PM_{2.5}$ pose significant health risks to the public. In the case of O_3 , evidence for pulmonary health effects derives from a large and varied body of scientific literature, both epidemiological and experimental. Although important uncertainties remain, a rather complete understanding now exists of the basic features of O_3 toxicity. For PM_{10} and $PM_{2.5}$, a much less complete understanding exists regarding health effects. The majority of evidence for adverse impacts of particulate matter derives from epidemiology studies.

The present article summarizes key features of our current understanding of the pulmonary health effects associated with

contemporary levels of O₃ and PM_{2.5}. Areas of uncertainty are highlighted. Clinical implications are noted.

Patterns of O₃ and PM_{2.5} Exposures

In order to place into better context the health effects evidence discussed in the next section, it is useful to review patterns of human exposures to O₃ and PM_{2.5}. Exposure patterns have implications for interventions, both clinical and environmental, to reduce exposure-related health risks.

O₃ is a strong oxidant gas that occurs naturally in the stratosphere (i.e., 30 to 50 km altitude) but is an unwelcome pollutant in the troposphere (the lowest 10 km of the atmosphere). Tropospheric O₃ is a secondary pollutant (i.e., not directly emitted to a substantial degree) that results from complex chemical reactions involving nitrogen oxides, reactive hydrocarbons, and sunlight. In populated areas, the primary sources of O₃ precursor pollutant emissions are motor vehicles and the fuel supply system that supports them. Because of the importance of solar radiation and temperature in O₃ photochemistry, significant concentrations of O₃ appear only in the warmer months, in other words, May through October. Further, O₃ production occurs only during daylight hours, resulting in a characteristic midday concentration peak in urban areas. However, O₃ concentrations often remain elevated late into the evening, especially in regions downwind of major urban areas. As a result, residents of downwind regions, such as the Connecticut coastline, typically experience longer periods of elevated O₃ levels than do urban dwellers, such as those living in New York City. Because of its reactive nature, O₃ only partially penetrates indoors, with indoor-outdoor ratios ranging from 0.1 to 0.8, depending on the degree of natural ventilation (penetration is greatest when open windows are used for ventilation).

Until 1997, the national ambient air quality standard for O₃ was a 1-hour concentration of 120 ppb, not to be exceeded more than 1 day per year. In 1997, in light of new data on the cumulative effects of O₃ on lung function and inflammation, the U.S. EPA revised the ozone standard to an 8-hour concentration of 80 ppb.

Data on spatial and temporal variations in O₃ concentrations are available from a nationwide network of more than 700 air monitoring sites that have been operating since the late 1970s. These data reveal frequent excursions above the 8-hour standard of 80 ppb in a large number of metropolitan regions, with the highest and most frequent peaks occurring in the Los Angeles area and the northeastern coastal states. Year to year variations in O₃ concentrations are driven primarily by interannual meteorologic variations; only modest reductions in 8-hour average O₃ concentrations have occurred over the past 20 years.

PM_{2.5} represents the mass concentration of air-borne particles with aerodynamic diameters smaller than 2.5 μm. PM_{2.5} particles vary widely in size, composition, and origin. Some are emitted directly by fossil fuel combustion, such as fly ash and soot from coal and diesel fuel combustion. Others form as secondary pollutants by chemical reactions in the atmosphere that convert gases emitted by fossil fuel combustion, such as sulfur dioxide, to particles, such as acid sulfates. Although all particles less than 2.5 μm diameter are capable upon inhalation of reaching the deepest portions of the lung, particles less than 0.1 μm diameter have a higher likelihood of depositing in the deep lung, because of their high diffusion coefficients.^[2] However, because particle mass increases as the third power of diameter, large-diameter particles tend to dominate measurements of PM_{2.5}, which are reported in units of micrograms of particles per cubic meter of air. Important chemical components of PM_{2.5} include sulfates, nitrates, elemental carbon, organic molecules, and a variety of trace elements.^[2]

Outdoor PM_{2.5} particles penetrate readily to the indoor environment.^[3] Unlike O₃, significant indoor sources of PM_{2.5} exist, the most prominent being smoking and cooking.

In response to new epidemiological studies reporting increased mortality risks associated with living in cities with elevated PM_{2.5} concentrations, the first national ambient air quality standards for PM_{2.5} were promulgated in 1997 by the EPA. Two standards were set: an annual average standard of 15 μg/m³ and a 24-hour standard of 65 μg/m³. Limited data are available documenting spatial and temporal variations in PM_{2.5} concentrations. Pope and colleagues⁴ reported annual average PM_{2.5} concentrations in 1980 ranging from 9.0 to 3.5 μg/m³ (mean = 18.2 μg/m³) across 50 metropolitan areas in the United States based on EPA data. A similar range across six U.S. cities was reported by Dockery and colleagues.^[5] Control efforts specifically directed at PM_{2.5} concentrations have only recently begun. Previous regulatory control efforts were focused primarily on the larger-diameter particles that dominate total suspended particulate (TSP) matter and, to a lesser extent, PM₁₀ measurements. Technically, it is far more difficult to control emissions of particles less than 2.5 μm than it is to control larger, "coarse" particles. This is because coarse particles have sufficient mass to be easily collected by physical methods that exploit inertial impaction (i.e., the inability of massive particles to follow convoluted air streams without hitting solid surfaces), just as occurs in the human upper respiratory system.

Strengths and Limitations of Experimental and Epidemiology Studies

Broadly speaking, scientific evidence on the human health effects of air pollution is derived from two classes of studies: controlled experiments and epidemiology studies. Most experimental studies of air pollution involve controlled exposures, in other words, where

exposure level and duration is fixed and where other experimental conditions, such as temperature and relative humidity, are held constant. The best experimental studies compare health outcomes observed following pollution exposure with health outcomes measured following clean air exposure, where both the subjects and the experimenters are blinded as to the exposure conditions. Results of such studies can be used to make inferences regarding cause and effect relationships. In addition, experimental studies enable the testing of single pollutants in isolation, yielding results that are usually more directly useful for standard setting. However, individual pollutants rarely occur in isolation in outdoor air, and the testing of environmentally relevant pollutant mixtures in chamber studies presents considerable technical challenges. In addition, logistical constraints limit the range of exposure times that can be tested in human experimental studies.

Epidemiology studies involve observation, measurement, and analysis of exposure and health data collected in human populations exposed to air pollution in the real world. Studies may evaluate health and exposure differentials over time (time-series studies) or across space (cross-sectional studies). Time-series studies usually address short-term, or acute, exposure and health relationships, whereas cross-sectional studies usually address long-term, or chronic, exposure and health relationships. The most directly interpretable epidemiological results are produced from studies in which measurements of exposure, health, and covariates (e.g., smoking) are available on individual subjects. Though time consuming and relatively expensive, such studies make possible direct inferences regarding individual health risks associated with air pollution, controlling for potential confounding variables. More difficult to interpret are findings from observational (also called ecological) studies, in which exposure, outcome, and covariate data are available only at the aggregate level for groups under study, such as studies correlating mortality rates and mean air pollution levels across a number of metropolitan areas. Results observed at the aggregate level may or may not reflect risks at the individual level.

Although epidemiology studies offer the advantage of real-world exposure conditions, health effects of individual pollutants are often difficult to disentangle because of the high degree of correlation among different pollutants. Further, in contrast to experimental studies, individual epidemiology studies can only demonstrate statistical associations between adverse health outcomes and air pollution exposures. They cannot, by themselves, prove that such associations represent cause and effect relationships.

Human Pulmonary Effects of O₃

The acute pulmonary effects of ambient-level O₃ exposures have been demonstrated extensively in human and animal chamber studies as well as in epidemiology studies. Chronic pulmonary effects have been demonstrated in long-term animal studies and are also suggested in recent epidemiology studies. However, more studies are needed to better understand chronic pulmonary effects of O₃.

O₃ is a strong oxidant gas that, upon inhalation, deposits throughout the respiratory system. Epithelial cells lining the respiratory bronchioles and alveoli are especially vulnerable to oxidant damage, both because the delivered dose of O₃ is greatest in the deep lung and because these cells lack a protective mucous layer. Acute O₃-induced lung injury is characterized by epithelial cell destruction, pulmonary edema, and inflammation.^[6]

Human chamber studies have shown that brief O₃ exposures at or above 80 ppb cause reversible drops in lung volumes, increases in nonspecific bronchial responsiveness, and pulmonary inflammation.^[6-8] There is a broad distribution of responsiveness across human subjects for all of these effects, with some individuals exhibiting responses several-fold higher than the population mean response, and others showing no response. It appears that the effects of O₃ occur via at least two pathways, one involving irritation of airway sensory nerve receptors, the other involving pulmonary inflammation.

Epidemiology studies involving repeated measures across days have also demonstrated the acute effects of low-level O₃ exposures on lung function in children and adults.^[9-11] A combined analysis of data from six summer camp studies reported an average drop in afternoon FEV₁ of about 3% for an increase in ambient O₃ concentration of 120 ppb.^[12] A recent study of 19 adults exposed to O₃ while exercising outdoors in New York City reported bronchoalveolar lavage (BAL) findings that were consistent with persistent O₃-induced inflammation.^[13] Levels of lactate dehydrogenase, a marker of cell membrane damage, were significantly elevated in summer season lavage samples as compared with winter season samples in the same individuals.

Epidemiology studies also have reported acute associations between O₃ and daily asthma exacerbations, emergency room visits, hospital admissions, and deaths.^[14-16] Hospital admissions for respiratory illnesses increased up to 35% in association with 100 ppb increases in daily maximum 1-hour O₃ concentrations. Because temporal correlations often exist between O₃ and other pollutants and temperature, it is not clear whether associations of these kinds represent effects of O₃ alone or O₃ in combination with other environmental factors. However, these studies suggest that asthmatics may be especially vulnerable to O₃-induced pulmonary effects. The known effects of O₃ on acute pulmonary inflammation suggests a plausible role in exacerbation of asthma.

Concern exists about possible chronic pulmonary effects of O₃ in humans associated with long-term exposures. Repeated inflammation over many years might result in tissue damage, remodeling, and fibrotic changes in the deep lung such as those observed in long-term rat and nonhuman primate studies.^[6] In monkeys, in which distal airway structure is similar to that in humans, significant distal airway remodeling has been observed with daily 8-hour exposures to 150 ppb O₃ over 6 or 90 days.^[17] Recent

epidemiology studies have reported decreases in lung function in young adults who have lived for long periods in areas with high ambient O₃ concentrations.^[18,19] Associations appear most pronounced for measures of small airways function such as forced expiratory flow, mid-expiratory phase (FEF 25%-75%), consistent with a hypothesis of small airway narrowing secondary to chronic pulmonary inflammation. It is not clear whether these epi-demiological findings are due to O₃ exposure alone or O₃ in combination with other copollutants.

The chronic pulmonary effects of long-term O₃ exposures are in greatest need of further research. Epidemiology studies are needed that incorporate relevant measures of small airway function or pathology, or both, and accurately characterize long-term O₃ exposures using available or special-purpose ambient monitoring data, along with data on exposures to other potentially important air pollutants, such as PM_{2.5}. The possibility that the effects of O₃ are augmented by PM_{2.5} or other copollutants should be explored.

Human Pulmonary Effects of Particulate Matter

The evidence for health effects of particulate matter derives largely from epidemiological studies reporting associations with both acute and chronic mortality in urban areas. The role played by pulmonary toxicity, as distinct from cardiovascular or systemic effects, in these findings is not yet known. A smaller body of evidence suggests associations between elevated ambient particulate matter and increases in hospitalizations and respiratory symptoms and decreases in lung function. Because of data limitations, only a handful of epidemiology studies have yet examined the effects of PM_{2.5} specifically. Major areas of uncertainty include the nature of the PM component(s) responsible for adverse health effects, the biological mechanism(s) involved, and the host factors that promote greater susceptibility. A large number of recent time series observational studies have reported small, statistically significant associations between particulate matter (i.e., TSP, PM₁₀) and daily mortality, suggesting that the mortality effects seen in episodes earlier this century persist at lower contemporary levels of particle exposure, at least among the most vulnerable members of society, such as the elderly and those with preexisting cardiopulmonary disease.^[20-23] Cause-specific analyses usually have observed larger relative effects for deaths attributed to respiratory, and to a lesser extent cardiovascular, causes than for other causes of death. Quantitative results from studies of this kind have been remarkably consistent, suggesting a 5 to 10% increase in total daily deaths associated with increases of 100 µg/m³ in daily average PM₁₀ concentrations.^[24]

Results from time-series studies appear to confirm the existence of small acute impacts of PM on daily mortality at contemporary ambient concentrations. However, several important uncertainties cloud the interpretation of these findings, including the identity of the population subgroups that are most at risk, the unique impact of PM as distinct from other copollutants,^[22,23] the PM subcomponent that is most important, the impact on life expectancy of these findings, and the pathophysiological mechanism(s) responsible.^[25] These are all areas of active research.

A more limited body of epidemiological evidence is available showing acute pulmonary effects of daily PM exposures.^[26] Observational time-series studies similar to those addressing acute mortality have reported acutely increased hospitalizations or emergency room visits for respiratory complaints in association with PM_{2.5} or sulfate particles, or both.^[14,15,27] Repeated-measures studies in small co-horts of subjects have reported small but statistically significant declines in FEV₁ and increases in lower respiratory symptoms associated with ambient PM₁₀ and sulfate concentrations.^[28,29] As a group, findings from these studies of pulmonary effects reinforce the plausibility of the acute mortality results noted earlier and suggest a possible role of acute pulmonary irritation in the mechanistic pathway leading to mortality in susceptible individuals.

Epidemiology studies correlating mortality rates and PM concentrations across metropolitan areas represent the oldest and most extensive evidence for chronic PM effects.^[30,31] However, interpretation of early cross-sectional observational studies was seriously hindered by uncertainties regarding potential confounding by cigarette smoking, occupational exposures, and other factors.^[31]

Confirmatory results have emerged recently from two large prospective cohort studies that, based on individual questionnaire data on smoking and other risk factors, were able to control for major potential confounders at the individual level in the analyses.^[4,5] These two recent studies are also important because they analyzed multiple, alternative PM measures, including PM_{2.5}. In a cohort of 8111 white adults, Dockery and colleagues^[5] reported a linear exposure response of mortality risk versus average PM_{2.5} concentrations across six U.S. cities, controlling for smoking and other risk factors. The risk of death was increased by 26% for an exposure difference of 18.6 µg/m³ across cities. This mortality risk was similar to that associated with 25 pack-years of cigarette smoking. Pope and colleagues^[4] reported similar findings from a prospective follow-up of 552,138 adults from 151 metropolitan areas. For a subset of 50 locations where PM_{2.5} data were available, the risk of death was increased by 17% for an exposure difference of 24.5 µg/m³ across metropolitan areas.

Of particular interest are comparative results from a secondary analysis in which data from the same metropolitan areas was analyzed in a purely observational way (i.e., using adjusted mortality rates for each city computed from aggregate data), with no control for cigarette smoking rates. The PM_{2.5} mortality risk estimated in this observational analysis was consistent with that found in the cohort analysis, suggesting that confounding in observational studies may not be as severe a problem as was once feared.

Viewed in total, the epidemiological evidence for increased acute and chronic mortality risks associated with ambient PM is quite strong. Epidemiological evidence implicating PM_{2.5} specifically is rather limited at present. However, plausibility arguments based on pulmonary penetration and deposition, as well as the known concentration of toxic chemical species in the fine particle fraction, argue for adoption of a working hypothesis that PM_{2.5}, or a subcomponent of PM_{2.5}, is likely to be the correct metric of PM-related mortality risk. The evidence linking low-level PM exposures to clinically significant pulmonary function effects remains weak at present. Especially lacking are controlled chamber experiment studies demonstrating pulmonary toxicity in response to environmentally relevant PM_{2.5} concentrations. Studies now underway in several laboratories are attempting to fill this gap, as well as to understand the mechanisms underlying acute mortality risk in susceptible populations. Chamber studies exposing animals or humans to concentrated ambient aerosols appear promising but will require careful interpretation because of differences in the degree of concentration for fine particles of different diameters.^[32,33]

Relevance to Clinical Practice

Current scientific knowledge regarding human health effects of air pollution raises concerns about potential health risks faced by Americans because of continued exposures to O₃ and PM_{2.5}, especially among the young, the old, and those with compromised respiratory health such as asthmatics. As we celebrate the progress that has been achieved over the past 30 years in improving air quality in the United States, we must also recognize clearly the need for continued efforts to reduce ambient levels of O₃ and PM_{2.5}. Given the difficulties experienced to date in reducing levels of these pollutants, future progress is likely to require more aggressive and technically innovative approaches. Continued support from the clinical and public health communities for governmental action to address these problems will provide a critical foundation for success. In addition, regulatory control efforts will be most effective and efficient to the extent that they can profit from the best available science the biomedical and engineering communities can provide.

From the perspective of clinicians concerned about health risks faced by individual patients from exposures to outdoor air pollution, the implications of the available scientific knowledge base are less clear. Given what is known about the acute pulmonary effects of O₃, it is reasonable for clinicians to advise patients of all ages with compromised respiratory status to curtail outdoor activity on days of elevated O₃ concentrations. In urban areas and the regions downwind of them, high O₃ concentrations are most common in the afternoon hours on hot sunny days in summer. In many cases, O₃ alert days are announced in the media. Clinicians can play a key role in raising patient awareness about the potential impacts of ambient O₃.

Much of the evidence for health effects of particulate matter is based on studies reporting small statistical associations linking population risk with population exposure. While such findings are useful in risk assessments and policy decisions at the population level, their relevance to clinical evaluation of individual risk remains very uncertain. It is hoped that ongoing research will begin to illuminate mechanisms and susceptibility factors for PM_{2.5} toxicity. Such information, in conjunction with publicly accessible real-time PM_{2.5} monitoring data, may make it possible to develop specific treatment or avoidance recommendations for susceptible individuals. A new nationwide network of PM_{2.5} monitoring stations that is being established in 1999 will be helpful in this regard.

Summary

Among the criteria air pollutants, two pollutants related to fossil fuel combustion, O₃ and PM_{2.5}, possess the greatest body of scientific evidence for human health effects at current ambient concentrations. Controlled chamber experiments have shown that brief, ambient-level O₃ exposures cause acute, reversible drops in lung volumes, increases in nonspecific bronchial responsiveness, and pulmonary inflammation. Epidemiology studies have confirmed many of these findings and further have demonstrated associations with asthma exacerbations, emergency room visits, hospital admissions, and deaths. Populations most at risk include children and adults who are active outdoors, especially those with asthma. PM_{2.5} is a heterogeneous mixture of suspended solid and liquid particles with widely varying diameters and composition. The evidence for health effects of particulate matter derives largely from epidemiological studies, which have reported associations with both acute and chronic mortality in urban areas. Other effects associated with ambient particulate matter include increases in hospitalizations and respiratory symptoms and decreases in lung function. Populations at greatest risk of PM effects include the elderly and those with preexisting cardiopulmonary disease. Important questions remain regarding PM health effects, including the nature of the PM component(s) responsible, the biological mechanism(s) involved, and the host factors that promote greater susceptibility; these are areas of active research.

Tables

Table 1. Current Primary National Ambient Air Quality Standards for Criteria Pollutants

Pollutant	Standard	Averaging Time	Year Last Revised

Ozone	80 ppb	3-year average of the annual 4th highest 8-hour concentration	1997
PM _{2.5}	15 µg/m ³	annual	1997
	65 µg/m ³	24 hours	
PM ₁₀	50 µg/m ³	annual	1987
	150 µg/m ³	24 hours	
Lead	1.5 µg/m ³	quarterly	1978
Carbon monoxide	9 ppm	8 hours	1994
	35 ppm	1 hour	
Nitrogen dioxide	53 ppb	annual	1995
Sulfur dioxide	30 ppb	annual	1996
	140 ppb	24 hours	

References

1. Logan WPD. Mortality in London fog incident, 1952. *Lancet* 1953;264:336-338
2. Spengler J, Wilson R. Emissions, dispersion, and concentration of particles. In Wilson R, Spengler JD, eds. *Particles in Our Air: Concentrations and Health Effects*. Harvard School of Public Health, 1996; 000-000
3. Ozkaynak H, Spengler J. The role of outdoor particulate matter in assessing total human exposure. In Wilson R, Spengler JD, eds. *Particles in Our Air: Concentrations and Health Effects*. Harvard School of Public Health, Cambridge, MA: Harvard University Press 1996; 41-62
4. Pope CA III, Thun MJ, Namboodiri MM, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 1995;151:669-674
5. Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993;329:1753-1759
6. U.S. Environmental Protection Agency. *Air Quality Criteria for Ozone and Related Photochemical Oxidants*. EPA/600/P-93/004cF, Washington, D.C.: USEPA Office of Research; July, 1996
7. Horstman DH, Folinsbee LJ, Ives PJ, Abdul-Salaam S, McDonnell WF. Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. *Am Rev Respir Dis* 1990;142:1158-1163
8. Devlin RB, McDonnell WF, Mann R, et al. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 1991;4:72-81
9. Kinney PL, Ware JH, Spengler JD, et al. Short-term pulmonary function change in association with ozone levels. *Am Rev Respir Dis* 1989;139:56-61
10. Spektor DM, Thurston GD, Mao J, et al. Effects of single- and multi-day ozone exposures on respiratory function in active normal children. *Environ Res* 1991;55:107-122
11. Hoek G, Fischer P, Brunekreef B, et al. Acute effects of ambient ozone on pulmonary function of children in the Netherlands. *Am Rev Respir Dis* 1993;147:111-117
12. Kinney PL, Thurston GD, Raizenne M. The effects of ambient ozone on lung function in children: A reanalysis of six summer camp studies. *Environ Health Perspect* 1996;104:170-174
13. Kinney PL, Nilsen DM, Lippmann M, et al. Biomarkers of lung inflammation in recreational joggers exposed to ozone. *Am J Respir Crit Care Med* 1996;154:1430-1435
14. Thurston GD, Ito K, Kinney PL, Lippmann M. A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: Results for 1988 and 1989 summers. *J Expo Anal Environ Epidemiol* 1992;2:429-450
15. Burnett RT, Dales RE, Raizenne ME, et al. Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. *Environ Res* 1994;65:172-194
16. Kinney PL, Ozkaynak H. Associations of daily mortality and air pollution in Los Angeles county. *Environ Res* 1991;54:99-120
17. Harkema JR, Plopper CG, Hyde DM, et al. Response of macaque bronchial epithelium to ambient concentrations of ozone. *Am J Pathol* 1993;143:857-866
18. Kuenzli N, Lurmann F, Segal M, et al. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen -- results of a pilot study. *Environ Res* 1997;72:8-23
19. Galizia A, Kinney PL. Long-term residence in areas of high ozone: Associations with respiratory health in a nationwide sample of non-smoking young adults. *Environ Health Perspect* 1999;107:675-679
20. Pope CA III, Schwartz J, Ransom MR. Daily mortality and PM₁₀ pollution in Utah valley. *Arch Environ Health* 1992;47:211-217
21. Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. *Am J Epidemiol* 1993;137:1136-1147
22. Kinney PL, Ito K, Thurston GD. A sensitivity analysis of mortality/PM₁₀ associations in Los Angeles. *Inhal Tox* 1995;7:59-69
23. Katsouyanni K, Touloumi G, Spix C, et al. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12

- European cities: Results from time series data from the APHEA project. *Br Med J* 1997;314:1658-1663
24. U.S. Environmental Protection Agency. Air Quality Criteria for Particulate Matter. EPA/600/P-95/001aF, Washington, DC.:USEPA Office of Research; April, 1996
 25. Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. *Lancet* 1995;345:176-178
 26. Dockery DW, Pope CA III. Acute respiratory effects of particulate air pollution. *Annu Rev Public Health* 1994;15:107-132
 27. Schwartz J. Air pollution and hospital admissions for the elderly in Birmingham, Alabama. *Am J Epidemiol* 1994;139:589-598
 28. Hoek G, Brunedreef B. Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. *Arch Environ Health* 1993;48:328-335
 29. Pope CA III, Kanner RE. Acute effects of PM₁₀ pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;147:1336-1340
 30. Lave LB, Seskin EP. Air pollution and human health. *Science* 1970;169:723-733
 31. Evans JS, Tosteson T, Kinney PL. Cross-sectional mortality studies and air pollution risk assessment. *Environ Internat* 1984;10:55-83
 32. Sioutas C, Koutrakis P, Ferguson ST, Burton RM. Development and evaluation of a prototype ambient particle concentrator for inhalation exposure studies. *Inhal Tox* 1995;7:633-644
-