Chapter 1

Introduction and Summary

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INTRODUCTION

Breathing sustains life. Each day an individual inhales between 10,000 and 20,000 liters of air. In the lungs, air releases oxygen to the bloodstream and picks up carbon dioxide and other waste products, which are then exhaled. Inhaled air contains many substances—naturally occurring and anthropogenic--other than oxygen. Some of these substances can injure the lungs and impede their function.

The potential for chemicals and materials used in industry, transportation, and households to be simultaneously beneficial and toxic to human life creates a legislative and regulatory dilemma. The challenge of balancing a strong economy, one that delivers products people need and desire, with the health and safety of the populace sometimes seems to be a tremendous burden.

Technological advances add to the weight of that burden. Thousands of new, potentially toxic substances enter the market annually. Advanced instruments help scientists measure the presence of new and existing substances in minute quantities. Substances formerly unknown or undetected suddenly become worrisome as technology provides the means to predict human risks from these substances.

Governmental concern that a substance might create an adverse health effect historically focused on carcinogenicity. Most Federal legislative and regulatory efforts to prevent or minimize human exposure to toxic substances have focused on identifying and controlling carcinogens. Physicians and researchers now recognize the noncancer, toxic effects of many substances. Some of these effects, for instance teratogenicity, have become the subject of specific legislative concern. Federal regulatory attention to other types of toxic injury (e.g., to the respiratory system, the immune system, the nervous system) depends on the more general mandate to protect human health. Some observers fear that historical emphasis on carcinogenicity, combined with limited agency resources, has led to neglect of noncancer health risks-risks that may be as widespread and severe as carcinogenicity.

The Senate Committee on Environment and Public Works, and its Subcommittee on Toxic Substances, Environmental Oversight, Research and Development, asked for assistance from the Office of Technology Assessment (OTA) in evaluating technologies to identify and control noncancer health risks in the environment. The committee's interests include advances in toxicology, research and testing programs in Federal agencies, and the consequences of exposure to toxic substances. OTA has published studies on neurotoxicity and immunotoxicity (18,19).

In further response to the committee's request, this background paper describes the state-of-the-art of identifying substances that can harm human lungs when inhaled. Chapter 2 provides a primer on human lung structure and function and describes lung diseases that have been associated with inhalation of toxic substances. Chapter 3 examines the technologies and methodologies used in laboratory, clinical, and epidemiologic studies to identify substances as toxic to the lung. Chapter 4 summarizes Federal research efforts and regulations designed to reduce human exposures to these substances.

SCOPE

This study assesses whether regulators using available toxicologic and epidemiologic investigative methods can obtain health effects data sufficient to identify airborne substances as pulmonary toxicants—substances toxic to the lung—when encountered at environmentally relevant exposure levels. Several terms within this description of the scope of work require definition to delineate the boundaries of OTA's inquiry.

Regulators—Regulators are the agencies, and their employees, with responsibility, under various environ-

mental statutes, for setting standards to control human exposure to toxic substances. This study examines only Federal regulatory programs, but many States have environmental legislation and regulatory agendas that require the types of technologies and data discussed in this background paper.

Available toxicologic and epidemiologic investigative methods-This background paper reports on the technologies and methodologies applied in laboratory studies, human clinical studies, and field studies of human exposure (epidemiology) to determine whether substances exert toxic effects. As used in this study, the term laboratory studies comprises ***in vitro*** tests on cells, tissues, and fluids removed from animals and humans and ***in vivo*** tests on whole animals. The term human clinical studies refers to studies of the effects on humans of carefully controlled but purposeful exposures to potentially toxic substances; exposure to the suspected toxicant occurs in a clinical setting, hence the term. Epidemiologic studies are those in which investigators examine the effects on humans of exposures to suspected toxicants that occur without the intervention of the investigator and in a nonclinical setting, e.g., at home, in the workplace, at school, in the outdoors.

Airborne substances—Combustion, industrial processes, and other human activities can create inhalable gases and particles that may be toxic to the lungs. Technologies that enable assessment of the health effects of ***inhaled*** substances are the focus of this background paper. Substances taken orally (e.g., certain drugs) or absorbed through the skin (e.g., the pesticide paraquat) can be toxic to the human lung; some of the technologies discussed in this background paper could be used to identify their effects. However, this study limits itself to an examination of the technologies specifically applicable to investigation of the effects of airborne substances on the lung and the regulatory programs designed to control human exposure to such substances. The background paper discusses some biologic substances, e.g., organic dusts, but excludes consideration of infectious agents.

Environmentally relevant exposure levels—OTA defines "environmentally relevant exposure levels" as those that can reasonably be anticipated (under noncatastrophic circumstances) to occur in outdoor, residential, educational, commercial, and occupational environments in various regions of the United States.

This background paper describes a wide range of technologies that measure the biological effects of exposure to toxic substances-from technologies that identify minute changes in the cellular structure of the lung to technologies useful in the diagnosis of disease. Regulators use these technologies, singly or in combination, to determine not only whether a given dose of a suspected toxicant creates a measurable, biological effect but whether the measurable effect is itself adverse to respiratory health or correlates with development of an adverse condition. A definition for ***adverse*** remains a topic of considerable debate.

For example, scientists have developed several tests to detect decreases in lung function that result from exposure to toxic substances. While they agree on the technical capabilities of the tests, they disagree on the level of decreased function that should be deemed adverse for regulatory purposes. Using other tests, scientists are able to detect changes in the number of certain types of cells found in the lung following relatively low-level exposures to toxic substances. Given enough time and resources, scientists will be able to determine whether such changes reverse themselves, stabilize, or grow harmful under various types of exposure conditions. They will also learn whether those cellular changes actually impair lung function. Until those data are collected, however, regulators have insufficient evidence to deem the measurable effect adverse.

In this background paper, OTA describes the current technologies that measure the biological effects in the lung of toxic substances. The study also reports on Federal efforts to improve the technologies and regulate human exposures to substances deemed adverse. OTA makes no independent judgment concerning an appropriate definition of adverse effects or on the adequacy of current regulatory standards.

SUMMARY

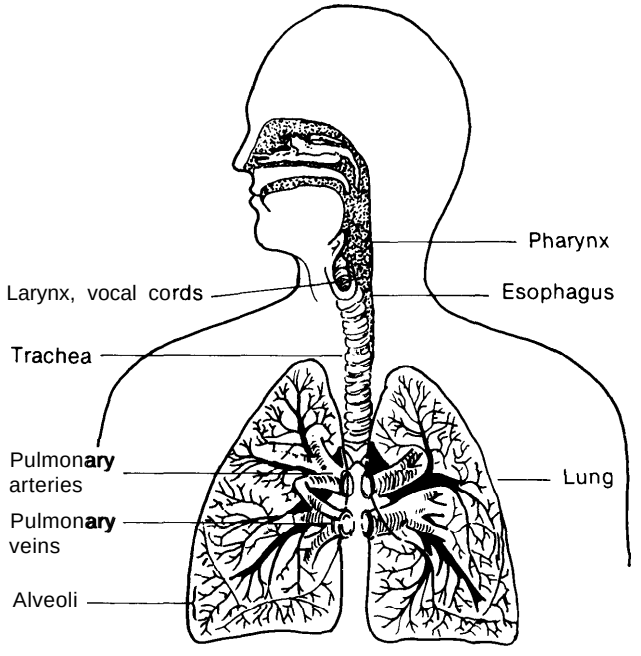
This background paper distills some of the information available about the basic and applied sciences that enable the identification and control of pulmonary toxicants. More detailed reviews of lung structure and function, lung diseases, pulmonary toxicology, and epidemiology can be found in numerous sources (1,2,5,10,11,12). The following sections summarize much of the text that appears in subsequent chapters.

Lung Structure and Function

The lung comprises two of the three distinct regions of the human respiratory tract (figure l-l). Air enters the body through the nose and mouth and passes through the ***nasopharyngeal*** region, where it is warmed and humidified. Air moves next through the ***tracheobronchial*** region (where the lung begins), which acts basically as a conducting passage. Finally air reaches the ***pulmonary,*** or ***gas exchange,*** region of the lung, where oxygen in the air is supplied to the blood, which delivers it to cells throughout the body. In turn, the blood releases a major waste product, carbon dioxide (CO_2), and other gaseous components and metabolites to air remaining in the lung, which is exhaled. The pulmonary region has a tremendous surface area—in adults about the size of a single's tennis court-which permits efficient gas exchange (oxygen for CO_2).

The respiratory system is equipped with defense mechanisms. The nasopharyngeal region can filter large particles and absorb gases with high water solubility before they reach the lung. Cells that line the tracheobronchial region secrete mucus that traps inhaled particles and reactive gases, and other cells sweep the mucus up and out of the respiratory system to the digestive system. Certain cells that reside in the pulmonary region can ingest and destroy particles that penetrate to that region. Some toxic substances can bypass or overwhelm these defense mechanisms, resulting in lung injury or disease.

Figure l-l—The Human Respiratory Tract



SOURCE: Office of Technology Assessment, 1992.

Lung Injury and Disease

Lung function suffers when resistance to airflow in the conducting airways (tracheobronchial region) increases or when a loss of healthy surface area in the pulmonary region prevents transfer of sufficient amounts of oxygen to the blood. Many agents—manmade and natural, physical and biological-can cause these basic problems, which are characteristic of several forms of disabling lung diseases (e.g., asthma, fibrosis, emphysema). Because of the limited types of pulmonary responses and the large number of agents to which individuals are exposed, the association of individual agents with specific responses has been difficult. Careful observation and experimentation over the years, however, has led to conclusions about the potential of certain toxicants to cause or exacerbate lung diseases.

Several outdoor air pollutants, e.g., sulfur dioxide, increase the breathing difficulties of high-risk groups (e.g., asthmatics). Tobacco smoke causes cancer (beyond the scope of this report), chronic bronchitis, and emphysema, and contributes to an increased incidence of respiratory disease in children of smoking parents, which may lead to chronic lung problems as they age. Occupational exposure to inhaled chemicals and fibers has yielded some of the strongest evidence linking toxic substances to lung disease.

Many tools for studying the toxicity of airborne substances have been developed in recent years, but the number of toxicants to be assessed and the amount of data required to substantiate their toxicity present a challenging task to toxicologists, epidemiologists, and regulators. Studies are under way to determine whether persistent human lung problems are correlated with exposures to many of the gases and particles encountered in everyday life.

Pulmonary Toxicology and Epidemiology

Investigators use three, complementary lines of research to assess the effects on the lung of inhaled pollutants: laboratory studies, including in vitro tests and tests in whole animals, human clinical studies, and epidemiology. Each type of study has strengths and weaknesses. In in vitro tests, scientists examine the

structure or functional capability of tissues and cells to determine the effects of toxic exposures. These studies are informative but may not give a complete picture of a toxicant's effects. In in vivo studies, scientists use animals whose respiratory systems resemble the human system and attempt to mimic expected human exposure conditions as closely as possible. Such studies are useful but are limited by the difficulty in extrapolating results from animals to humans. Clinical studies allow careful control of exposure conditions and provide human data. However, they are restricted to relatively brief exposures that will create no lasting injury and, like most animal studies, are limited to exposures to one or two substances at a time rather than the complex mixtures actually encountered in the environment. Epidemiologic studies analyze the effects created by toxicants under actual exposure conditions but are limited by imprecise measurements of exposure to the toxicant under study and by confounding factors such as smoking, preexisting disease, and unknown effects of other exposures.

Whether involving animals or humans, studies employ functional, structural, or biochemical methods of investigation. Functional assays measure the mechanics of breathing, decreases or increases in gas-exchange capacity, and the ability of the lungs to rid themselves of foreign particles, among other things. Structural studies employ the traditional techniques of pathology to gather substantial information about pulmonary toxicity. Prepared slices of excised lungs can be examined with microscopes for evidence of alterations in structure. Various regions of the excised lung can be examined for the presence of particles. Cells can be examined for injury. Advances in cellular biology in recent years contributed to some of the most important new methods of pulmonary toxicology. Toxicologists using biochemical methods can now study the cellular interactions and biochemical mechanisms of the lung using fluids recovered from lungs. In addition to biological tests on an exposed population, epidemiologists can use various databases, including mortality and morbidity statistics, hospital admissions records, and diaries of respiratory symptoms, to correlate exposure to toxicants with lung injury and disease.

In the laboratory and clinic, investigators can control the amount of the substance under study delivered to the test subject and can exclude all other exposures. The technologies used produce precise measurements of exposure but cannot reproduce the actual exposure conditions people encounter in their daily lives. Epidemiologists cannot control the dose of a toxicant received by their study subjects, but advances in stationary and personal exposure monitoring technologies have improved the accuracy of exposure measurements in epidemiologic studies. All scientists studying the effects of pulmonary toxicants must consider the fact that ***exposure***—the amount of a toxicant found in the inhalable air—frequently differs from biologically effective dose—the amount of toxicant actually retained in the lung for sufficient time to cause problems. Differences in human and animal lungs have a major impact on biologically effective dose and create many of the difficulties in extrapolating test results from animals to humans.

Integrated use of laboratory, clinical, and epidemiologic techniques often produces the best results. For instance, increased respiratory symptoms in a working population exposed to chemical fumes might suggest the need for laboratory studies of the chemical's health effects. Following the laboratory experiments, clinical studies might be performed to obtain more accurate data about harmful and harmless levels of short-term exposure in humans. Once a permissible exposure level is established for the workplace, workers could be monitored, in an epidemiologic study, to determine whether long-term exposures created effects that did not show up in the short-term studies. Pulmonary toxicologists, clinicians, and epidemiologists share the objective of identifying the health effects of airborne substances to which humans are or will likely be exposed.

AIR QUALITY

Air comprises those gases that form the atmosphere of the earth. At altitudes below 80 kilometers molecular nitrogen and oxygen dominate the mix. When water vapor is removed from the air, nitrogen and oxygen constitute 78 and 21 percent (by volume) of the air, respectively. The remaining 1 percent of this dry air consists principally of argon, but CO_2 and small quantities of neon, helium, krypton, xenon, hydrogen, methane and nitrous oxide are also found as constant components of air.

Human activities (agriculture, industry, transportation) contribute additional, variable components—pollutants—to the mix of gases called air. Level of industrialization creates most of the global variability in air pollution. For instance, wood (and other biomass) smoke may be the most common pollutant in nonindustrialized countries, while fossil fuel combustion byproducts (e.g., sulfur oxides, nitrogen oxides,

particulate matter) constitute the major air pollutants in heavily industrialized countries. Regional differences in pollutants depend on population, activity mix, geography, and climatic conditions. Within a community, air quality may differ significantly upwind and downwind of, for instance, a power plant. Family members may experience quite different pollutant exposure conditions depending on how much time they spend at work, school, or home.

In the United States, fossil fuel combustion contributes to both major types of outdoor air pollution—chemically reducing pollution and chemically oxidizing, or photochemical, pollution. Reducing type pollution is characterized by sulfur dioxide and fossil fuel smoke and by conditions of fog and cool temperatures. This type of pollution occurs mainly in the eastern part of the country, primarily in the Mid-Atlantic and Northeastern States. Oxidizing type pollution is characterized by hydrocarbons, oxides of nitrogen, and photochemical oxidants and results from the action of sunlight on polluted air masses. This pollution problem, infamous in several western U.S. cities (e.g., Los Angeles), now strikes the northeast and southeast in the summer months as well. Other types of pollutants pose seasonal problems, for instance woodsmoke in certain cities during the winter months. Toxic pollutants emitted from industrial sites or from hazardous waste sites can present highly localized air quality problems (see table l-l). Outdoor air pollution is regulated under the Clean Air Act and other environmental statutes.

Some occupations involve significant potential for exposure to airborne toxicants. These types of exposures generally are regulated under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. Health and safety regulations have reduced many of the acute exposure problems experienced by workers; experts are uncertain whether

Table l-l—The Seventeen Chemicals of the 33/50 Program, 1989

Chemicals	Total releases and transfers (pounds)	Total air releases and transfers (pounds)	Industry
Cadmium and compounds*	1,147,783	119,841	Primary metals
Chromium and compounds*	64,284,382	2,238,473	Chemicals
Lead and compounds	54,371,117	2,449,799	Primary metals
Mercury and compounds*	216,433	29,239	Chemicals
Nickel and compounds*	22,342,311	1,128,788	Primary metals
Benzene*	28,591,407	24,683,026	Primary metals
Methyl ethyl ketone*	156,992,642	127,631,835	Plastics
Methyl isobutyl ketone	38,849,703	30,682,832	Chemicals
Toluene	322,521,176	255,437,878	Chemicals
Xylenes (mixed isomers)*	185,442,035	147,486,804	Transport
Carbon tetrachloride	4,607,809	3,367,248	Chemicals
Chloroform (Trichloromethane)	27,325,508	24,268,093	Paper
Methylchloride (Dichloromethane)*	130,355,581	109,272,003	Chemicals
Tetrachloroethylene (Perchloroethylene)*	30,058,581	25,504,477	Transport
1, 1, l-Trichloroethane (Methyl chloroform)*	185,026,191	168,617,910	Transport
Trichloroethylene*	48,976,806	44,325,687	Fabricated metals
Cyanides	11,976,370	[a]	Chemicals

*EPA notes a respiratory effect.

[a]Cyanide emissions to the air have been estimated to be in excess of 44 million pounds per year. The largest single source of air emissions is vehicle exhaust, which accounts for over 90 percent of this total. This type of emission is not reported under the EPA's Toxic Release Inventory National Report.

SOURCE: U.S. Environmental Protection Agency, Office of Toxic Substances, Economics and Technology Division, *Toxics in the Community: National and Local Perspectives - The 1989 Toxics Release Inventory National Report, EPA-56014-91-014* (Washington, DC: September 1991).

current exposure limits prevent the types of persistent problems that might be associated with long-term, low-level exposures.

Most people spend most of their time indoors-at home, at school, or in the office. The primary indoor air pollutants are tobacco smoke, nitrogen dioxide, carbon monoxide, woodsmoke, biological agents (e.g., molds, animal dander), formaldehyde, various volatile organic compounds, and radon. Indoor pollutants may be generated by personal activities, such as cigarette smoking, or by things outside an individual's control, such as the geological formation on which a housesits, the source of radon. Indoor, airborne toxicants are important sources of individual exposure to toxicants that may appear in the outdoor air as well (e.g., nitrogen dioxide) and should be considered in health effects assessments. Outside of certain occupational settings, exposures to indoor, airborne toxicants remain largely unregulated.

Airborne gases and particles emanate from multiple indoor and outdoor sources, and individuals experience multiple exposures to airborne toxicants as they go about their lives. The mix of substances individuals inhale and the variety of circumstances under which they do it makes it very hard for scientists and policymakers to sort out the effects of specific substances. Some individuals are more susceptible than others to the effects of airborne toxicants, which makes it difficult for regulators to determine acceptable levels of exposure once the effects of specific substances have been determined. The technologies of air quality measurement, exposure assessment, and toxicological testing contribute to better risk assessment and better policymaking, but currently leave many uncertainties in their wake.

CONCLUSIONS

Scientists and regulators have a high degree of confidence in existing laboratory, clinical, and epidemiologic methods for studying the adverse effects of acute (short-term, high-level) exposures to existing chemicals and particles. When analyzing acute responses, scientists isolate the effects of a specific substance in

Photo credit: South Coast Air Quality Management District, El Monte, CA.

animal studies using controlled exposure conditions and then couple those test results with information (when available) about the real-life experience of exposed humans. This method enables relatively clear association between exposure to a specific substance and specific health effects, though evidence can still be equivocal. Analysis of the effects of chronic exposure is under way for many substances and data can readily be acquired from animal studies (given time and resources). However, credible human data on the effects of chronic exposure are more difficult to obtain because of extraneous factors that can affect study results (e.g., difficulties in determining the effects of previous exposures; opportunities for exposure to multiple substances). Where substances are regulated because of their pulmonary toxicity, the regulations are primarily based on health effects observed following acute exposures.

A synopsis of the attempt to set a standard for ozone that prevents adverse health effects illuminates the power and limitations of current technologies within the current regulatory framework for protection of public health. Ozone is produced when its precursors, volatile organic compounds (VOC's) and nitrogen oxides (NO_x), combine in the presence of sunlight. Current EPA regulations require States to maintain ozone concentrations in the air below 0.12 ppm. Areas where ozone in the ambient air exceeds a peak l-hour average concentration of 0.12 ppm more than 1 day per year (averaged over 3 years) are labeled nonattainment areas and are subject to legal sanctions (17).

EPA adopted the current standard for ozone exposure on the basis of evidence of the health effects of short-term exposures slightly above that level. At the time the standard was set, scientists agreed that short-term exposures to ozone caused reductions in lung function and increases in respiratory symptoms, airway reactivity, permeability, and inflammation in the general population. Asthmatics were known to suffer additional effects, including increased rates of medication usage and restricted activities (9).

The database on ozone's health effects has continued to grow since EPA set the standard for exposure in 1979. Data from human clinical studies now show that lung function decreases during exposure to 0.12 ppm (the current regulatory standard) and continues to decrease during constant exposures of 6 hours or more (4,6). Biochemical studies on lung fluids removed from individuals who were exercising during exposure to ozone above, at, and below the current regulatory standard showed lung inflammation (8,9).

The acute effects of exposure to ozone have also been the subject of epidemiologic studies. Lung function in children engaged in outdoor recreation activities decreased during exposure to ozone, and outdoor exposure caused a greater decrease than clinical exposure at the same concentration of ozone, indicating that other substances in the outdoor air potentiated the response to ozone (15,16). School children showed similar responses in another study (7).

Researchers have begun to study the effects of chronic exposure to ozone in various populations. A study of residents in the Los Angeles area showed that chronic exposure to oxidant pollution affects baseline lung function (3). Another study from the Los Angeles area, this time on the autopsied lungs of young accident victims, showed structural abnormalities in the lungs that were not expected in individuals of that age range (13). An analysis of pulmonary function data collected in a national survey showed a clear association between reduced lung function and annual average ozone concentrations in excess of 0.04 ppm (14). Based on epidemiologic research findings, a growing number of scientists believes that chronic exposure to ozone may cause premature aging of the lung, and they find support for this opinion in recent studies on rats and monkeys (9).

Scientists disagree on the health significance of the decreased lung function measured in the human clinical studies (9). EPA's Clean Air Science Advisory Committee (CASAC) split when asked to reach closure concerning a scientifically supportable upper bound for a l-hour ozone standard, with half the members accepting the current standard and half recommending a reduction in permissible exposure levels (20). CASAC noted that "resolution of the adverse health effect issue represents a blending of scientific and policy judgments." Little information on the human health effects of chronic ozone exposures has been available to regulators or their advisors, and scientists continue to urge that results from such studies be assessed cautiously. Despite strong evidence that ozone is harmful to human health at currently allowable exposure concentrations (9,21), EPA has not proposed a revision of the ozone standard.

Regulators face greater difficulties when developing supportable exposure standards for substances with

smaller health effects databases or with databases limited to results of laboratory studies (as with new substances). The difficulties lie in the technologies themselves (e.g., remaining uncertainties regarding extrapolating results from animals to humans) and in balancing competing interests (e.g., dependence on automobiles versus air pollutants' harmful effects).

None of the technologies currently in use or under development for assessing pulmonary toxicity promises to be a near term alternative to extensive (costly) studies involving animals and humans. Scientists studying the behavior of gases and particles in the lungs of various animal species and humans hold out hope for continued improvements in techniques for extrapolation from animal studies to humans. Researchers investigating the mechanisms of disease believe what they discover may enable extrapolation from study results on existing chemicals to the likely effects of new substances with similar physical properties. At present, however, there is no scientific agreement that the effects measured by new toxicologic methods are adverse-distinctly and permanently harmful—instead of changes that may evince the recuperative properties of the lung. Therefore regulators can only continue to balance the costs and benefits of different regulatory levels rather than choose a regulatory level for pulmonary toxicants that will clearly avoid adverse human health effects.

CHAPTER 1 REFERENCES

1. Amdur, M. O., Doull, J., and Klaassen, C.D. (eds.), *Casarett and Doull's Toxicology: The Basic Science of Poisons, 4th ed.* (Elms ford, NY: Pergamon Press, 1991).
2. Crystal, R. G., and West, J.B. (eds.), *The Lung: Scientific Foundations (New* York, NY: Raven Press, 1991).
3. Detels, R., Tashkin, D. P., Sayre, J. W., et al., "The UCLA Population Studies of Chronic Obstructive Respiratory Disease. 9. Lung Function Changes Associated With Chronic Exposure to Photochemical Oxidants: A Cohort Study Among Never-Smokers," *Chest* 92(4):594-603, October 1987.
4. Folinsbee, L.J., McDonnell, W. F., and Horstman, D. H., "Pulmonary Function and Symptom Responses After 6.6 Hour Exposure to 0.12 ppm Ozone With Moderate Exercise," *Journal of the Air Pollution Control Association* 38:28-35, January 1988.
5. Gardner, D.E., Crapo, J.D., and Massaro, E.J. (eds.), *Toxicology of the Lung (New* York, NY: Raven Press, 1988).
6. Horstman, D.H., Folinsbee, L.J., Ives, P.J., et al., "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," *American Review of Respiratory Disease* 142(5):1158-1163, November 1990.
7. Kinney, P.L., Ware, J. H., and Spengler, J. D., "A Critical Evaluation of Acute Ozone Epidemiology Results; *Archives of Environmental Health* 43(2):168-73, March/April 1988.
8. Koren, H. S., Devlin, R. B., Graham, D. E., et al., "Ozone-Induced Inflammation in the Lower Airways of Human Subjects," *American Review of Respiratory Disease* 139:407-415, *1989.*
9. Lippmann, M., "Health Effects of Tropospheric Ozone," *Environmental Science and Technology* 25(12):1954-1962, December 1991.
10. McClellan, R. O., and Henderson, R.F. (eds.), *Concepts in Inhalation Toxicology (New* York, NY: Hemisphere Publishing Corp., 1989).
11. National Research Council, Committee on the Epidemiology of Air Pollutants, *Epidemiology and Air Pollution* (Washington, DC: National Academy Press, 1985).
12. National Research Council, Subcommittee on Pulmonary Toxicology, *Biologic Markers in Pulmonary Toxicology* (Washington, DC: National Academy Press, 1989).
13. Sherwin, R. P., and Richters, V., "Centriacinar Region (CAR) Disease in the Lungs of Young Adults: A Preliminary Report," in *Tropospheric Ozone and the Environment* (Pittsburgh, PA: Air and Waste Management Association, 1991.)
14. Schwartz, J., 'Lung Function and Chronic Exposure to Air Pollution: A Cross-Sectional Analysis of NHANES II, " *Environment! Research* 50(2):309-321, December 1989.
15. Spektor, D.M., Lippmann, M., Lioy, P.J., et al., "Effects of Ambient Ozone on Respiratory Function in Active, Normal Children" *American Review of Respiratory Disease* 137:313-320, *1988.*
16. Spektor, D. M., Thurston, G. D., Mao, J., et al., "Effects of Single-and Multiday Ozone Exposure on Respiratory Function in Active Normal Children," *Environmental Research* 55(2):107-122, August 1991.
17. U.S. Congress, Office of Technology Assessment, *Catching Our Breath: Next Steps for Reducing Urban Ozone, OTA-O-412* (Washington, DC: U.S. Government Printing Office, July 1989).

18. U.S. Congress, Office of Technology Assessment, ***Neurotoxicity: Identifying and Controlling Poisons of the Nervous System,*** OTA-BA-436 (Washington, DC: U.S. Government Printing Office, April 1990).
19. U.S. Congress, Office of Technology Assessment, ***Identifying and Controlling Immunotoxic Substances—Background Paper, OTA- BP-*** BA-75 (Washington, DC: U.S. Government Printing Office, April 1991).
20. U.S. Environmental Protection Agency, Clean Air Scientific Advisory Committee, ***Review of the, NAAQS for Ozone,*** EPA-SAB-CASAC-89-1092 (Washington, DC: U.S. Environmental Protection Agency, 1989).
21. Van Bree, L., Lioy, P.J., Rombout, P.J., et al., "A More Stringent and Longer-Term Standard for Tropospheric Ozone: Emerging New Data on Health Effects and Potential Exposure," ***Toxicology and Applied Pharmacology*** 103(3):377-382, May 1990.