The Environment and the Lung

Changing Perspectives

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The focus of public health concern and research in regard to environmental lung diseases has changed across the century. Illustrative agents include radon, indoor asbestos, environmental tobacco smoke, acidic aerosols, and oxidant gases. Tremendous progress has been made in understanding and preventing environmental lung diseases. However, we remain concerned about adverse consequences of breathing polluted outdoor and indoor air. In the persistent concerns about adverse effects of polluted air on the lung, a new emphasis is pervasive; the focus has shifted from avoiding clinical disease among highly exposed individuals to protecting the population from an unacceptable burden of risk. The technique of quantitative risk assessment has become increasingly important for characterizing the safety of environmental agents. The resulting emphasis on the final risk projection and attendant uncertainties may overly emphasize gaps in our knowledge.

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AS THE 20th century ends, we are concerned and fearful about the adverse consequences of breathing polluted air, whether outdoors or indoors, and are asking for reduction of known and potential hazards. Yet, during this century the environmental causes of many lung diseases have been identified, the pathogenetic mechanisms underlying the development of some of these diseases have been described, and control measures have been implemented with at least partial success for a number of the injurious agents. In the United States and many other developed countries, elaborate regulations and enforcement mechanisms are in place to ensure that air outdoors and in workplaces does not pose unacceptable health risks; indoor air pollution has been recently recognized as a potential threat to health as well and programs have been implemented to address some of its hazards, for example, radon and asbestos.

Despite the increasing scientific evidence and the far-reaching array of control measures, the public is still concerned about breathing the often visibly polluted air that remains in many cities and even rural locations and is learning that indoor air may be contaminated with the same chemicals that are released by industry and vehicles, and even by such invisible pollutants as radon. While regulations have controlled many of the hazards of workplaces heavily contaminated by dust and fumes, new types of manufacturing have introduced novel and uninvestigated exposures, and changing work environments have led to the emergence of new clinical problems, such as "sick-building syndrome," and concern that some cases of recognized diseases, like asthma, may be caused or exacerbated by changes in the indoor and outdoor environments.

In the persistent concerns about adverse effects of polluted air on the lung, a new emphasis is pervasive; the focus has shifted from the avoidance of clinical disease among highly exposed individuals toward the protection of the general population from an unacceptable burden of disease at much lower exposures, and an attempt to ensure that even the most susceptible persons are not adversely affected. This same emphasis extends equally to other environmental exposures and to diseases other than those affecting the lung. Quantitative risk assessment, a four-step process, has become a widely used tool for judging the safety of environmental agents, providing a framework for summarizing the evidence on health risks from toxicologic studies, controlled exposures of volunteers, and epidemiologic research with information on exposure to injurious agents (Table 1).[1] The results of risk assessment can be used to identify areas for research, to assign priorities among environmental hazards, and to select approaches for managing risks. It must be recognized, however, that quantitative risk assessment is a new methodology and that its role in regulation is still evolving.[1]

This shift in emphasis from higher exposures producing clinical disease to lower levels projected to increase population risks has raised new questions and challenges for research on environmental lung disease. Providing assurance of safety, a level of risk judged to be acceptable,[2] requires precise and confident characterization of risks, and the scope of research needs to extend

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Table 1.—The Four Steps of Risk Assessment*

Hazard identification: The determination of whether an agent is causally linked to the health effect of concern
Dose-response assessment: The determination of the relation between level of exposure and risk of the health effect
Exposure assessment: Description of the extent of human exposure
Risk characterization: Description of the human risk, including uncertainties

*Based on reference 1.

Table 2.—Selected Agents Causing Environmental Lung Disease of Current Concern and Associated Adverse Effects

Agent	Effect(s)
Acidic aerosols	Exacerbate asthma and COPD,* respiratory symptoms, reduced lung function
Asbestos	Lung cancer, mesothelioma, pleural disease
Environmental tobacco smoke	Lung cancer, respiratory infection, respiratory symptoms, reduced lung function
Nitrogen dioxide	Exacerbate asthma, respiratory infection and symptoms, reduced lung function
Photochemical pollution (ozone)	Exacerbate asthma and COPD, respiratory symptoms, reduced lung function
Radon	Lung cancer
Silica	Silicosis, lung cancer
Volatile organic compounds	Cancer, neuropsychological effects, respiratory irritation

*Chronic obstructive pulmonary disease.

beyond testing for an exposure-disease association to quantification of risk at various levels of exposure and assessment of factors that modify the exposure-disease relationship. Data from extensive animal studies and large-scale epidemiologic investigations are often required.

This study addresses the changing focus across the century of public health concern and research in regard to environmental lung diseases. We review selected agents to illustrate the shift from disease prevention in individuals to risk reduction for the whole population and the difficulty of answering the questions now raised with regard to safety for many agents. We begin by considering the broad groups of environmental agents that produce lung disease and the mechanisms of disease pathogenesis.

MECHANISMS OF LUNG INJURY BY ENVIRONMENTAL AGENTS

The environmental agents in indoor and outdoor air of greatest contemporary concern are diverse, causing both malignant and nonmalignant diseases (Table 2). Continued concern about the risks of these and other causes of environmental lung disease is justified by the myriad pollutants inhaled in the various indoor and outdoor environments where time is spent each day, the diverse mechanisms by which these pollutants cause disease, and the wide range of susceptibility to pollutants in the population. Because we inhale 10 000 to 20 000 L of air daily, doses of pollutants present even at low concentrations may become biologically significant with sustained exposure. Fortunately, the lung has physical, chemical, and immunologic defense mechanisms for clearing and detoxifying inhaled agents, although the defense systems may be overwhelmed by large pollutant doses or may not be fully effective against some pollutants.

Atmospheric pollutants are present in the form of gases, fibers, or particles. Penetration of pollutants into the lung and retention at potential sites of injury depend on the physical and chemical properties of the agents.[3] Highly water-soluble gases, such as sulfur dioxide and formaldehyde, are almost completely extracted by the upper airway of a resting subject during a brief exposure, whereas less soluble gases, such as nitrogen dioxide and ozone, penetrate to the small airways and alveoli. Pollutants in particulate form are usually found in nature as aerosols. The penetration of particles into the lung and the sites of deposition within the lung depend on the aerodynamic size of the particle. Those greater than 10 μm are effectively removed in the upper airway, whereas smaller particles penetrate and are deposited in the airways and alveoli. *Fibers* are defined arbitrarily as particles having a length at least three times the width. The handling of fibers by the respiratory tract depends on fiber width and length and susceptibility to dissolution. Exercise increases the amount of air inhaled and the proportion of oral breathing, and thereby increases the dose of inhaled pollutants.

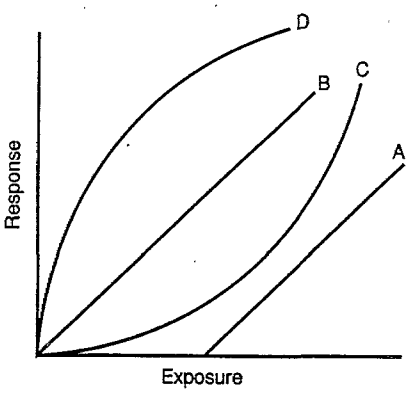
The diverse mechanisms by which inhaled gases and particles injure the lung, although not yet fully understood, can be broadly grouped as acute irritation and inflammation, chronic inflammation accompanied by a fibrotic response for some agents, immediate and cell-mediated immune responses, and carcinogenesis (Table 3). The likelihood of an adverse response to an inhaled pollutant depends on the degree of exposure to the pollutant, the site of deposition and the rate of clearance, and the individual characteristics of the exposed person that determine susceptibility. The relationship between exposure and response may have different forms, depending on the mechanisms by which the pollutant causes disease (Figure). The shape and slope of the exposure-response relationship have substantial implications for assessing the risks of environmental agents.[1] Curves having a threshold that must be exceeded to produce disease indicate that levels below the threshold are without risk; by contrast, a curve without a threshold implies that any level of exposure conveys some risk. For example, the linear no-threshold relationship, widely used to assess risks of carcinogens for regulatory purposes, is considered to be protective of public health because no level of exposure is without effect. The assumption of a linear no-threshold model for carcinogenesis remains highly controversial.[4-6] Distinguishing among the theoretical curves in the Figure cannot be readily accomplished using either animal experiments or human data, and exposure-response relationships should be assumed on the basis of biologic plausibility.[1]

ILLUSTRATIVE POLLUTANTS OF CURRENT CONCERN

This section briefly considers the currently available evidence and concerns about risk for several air pollutants, selected to be illustrative of the changing emphasis of concern across the century. The pollutants discussed include asbestos, radon, environmental tobacco smoke, acidic aerosols and sulfur dioxide, and oxidant pollutants, including ozone and nitrogen dioxide.

Radon

Radon, a naturally occurring radioactive gas in the decay series of uranium-238 that is known to cause lung cancer in underground miners, is ubiquitous in indoor environments.[7,8] The decay products of radon are themselves radioactive and release cancer-causing alpha particles, which are directly responsible for radon's carcinogenicity. The problem of cancer in underground miners was first reported over 100 years ago,[9] and radon was considered as a possible cause of the excess lung cancer in these miners by early in the century.[8] Epidemiologic studies of underground miners, initiated in the 1950s and later, soon provided convincing evidence that ra-



Examples of theoretic exposure-response relationships. Line A shows a linear exposure-response relationship with a threshold, while line B shows a linear nonthreshold relationship. Lines C and D are examples of nonlinear relationships (reprinted with permisson from reference 2).

Table 3.—Principal Mechanisms Associated With Environmental Lung Disease

Mechanism	Agents
Bronchoconstriction	Sulfur dioxide, acidic aerosols
Inflammation	Ozone, environmental tobacco smoke
Fibrosis	Asbestos, silica
Cancer	Radon, asbestos, formaldehyde, active smoking, and environmental tobacco smoke

don caused lung cancer in miners and some information on the quantitative risk of lung cancer in relation to exposure. Regulations were implemented during the 1960s and 1970s to protect miners against excess lung cancer.[10]

By the mid-1980s, it was widely recognized that radon was present in homes, sometimes reaching concentrations comparable with levels in uranium mines. To guide the development of public policy by state and federal agencies, estimates of lung cancer risk were needed across the range of concentrations measured in homes. Because epidemiologic studies directly addressing these risks could not be quickly performed, the risks found in the studies of miners were extrapolated to the general population, yielding estimates that indoor radon may cause approximately 10 000 to 20 000 lung cancer deaths annually in the United States.[8,11,12] Several sources of uncertainty have reduced confidence in the extrapolation of risks from miners to the general population.[13,14] Should the risks observed at the higher exposures in miners be extrapolated to lower exposures using a linear nonthreshold relationship? Are the quantitative risks higher or lower for the general population compared with the risks for miners? In comparison with evidence from male adult miners, predominantly cigarette smokers, what are risks of exposure for children, for women, and for never-smokers? Some have even questioned the carcinogenicity of indoor radon.[15] Reducing the uncertainties in assessing the risk of indoor radon poses a complex challenge for biomedical research. Improved understanding of carcinogenesis may lead to better support for a particular model of the relationship between exposure and lung cancer risk. Many case-control studies of indoor radon and lung cancer are now in progress with the objective of directly estimating risk due to indoor exposure, and several studies have already been reported.[8,16] However, the results of these studies are likely to be affected by difficult methodologic problems, and extremely large and unfeasible studies would be needed to fully address uncertainties and provide confident statements about risk.[17]

As we begin the 1990s, the risks of indoor radon remain extremely controversial, even though radon is an established occupational carcinogen and extensive epidemiologic data from miners provide convergent risk estimates.[8,18] The continued controversy and widespread perception of uncertainty appear to reflect the complexity of the questions that must be answered in support of policy development rather than weaknesses in the existing data. Risk assessment may highlight the gaps in scientific knowledge and, as illustrated by indoor radon and lung cancer, reduce confidence in good data by calling for answers to questions that cannot be readily answered.

Indoor Asbestos

Asbestos, a group of naturally occurring fibrous minerals, has been widely used in insulation and other materials in schools, public and commercial buildings, and residences. Man-made fibers are now widely used as a replacement for many of these applications. At the start of the century, clinical cases provided clear evidence that occupational exposure to asbestos caused asbestosis, a fibrotic disorder of the lung.[19] During the 1950s and 1960s, the results of epidemiologic studies of workers showed that occupational asbestos exposure also caused lung cancer and mesothelioma.[20] Although the information on exposures of workers in these studies was limited, quantitative relationships between estimated exposures and cancer risk were addressed in some of the studies.

Asbestos fibers can be released into the air of buildings from human activities that disturb asbestos-containing material or by maintenance activities involving asbestos-containing materials. Thus, persons potentially at risk from asbestos exposure indoors include persons handling or contacting the material during job activities or cleaning asbestos-contaminated areas, and general building occupants if they inhale contaminated air. Because of the well-documented and widely known disease risks in historical cohorts of asbestos-exposed workers, the presence of asbestos-containing material in buildings has prompted great public concern and legislative programs to reduce risks of indoor asbestos. The Asbestos Hazard Emergency Response Act requires inspection of schools for asbestos and satisfactory in-place management or, in some cases, removal. New research initiatives have been implemented to address asbestos in public and commercial buildings.

Public and private efforts for managing asbestos-containing material have been undertaken to reduce the exposures of custodial and maintenance workers and of general building occupants, including general office workers and schoolchildren. Even though concentrations of asbestos fibers in buildings are extremely low, persons in the category of general building occupants have been considered to be at risk for lung cancer and mesothelioma[21-23]; recent estimates of exposures[23,24] are somewhat lower than earlier estimates[21,22] as more data have become available on indoor concentrations. The risks for the general population can only be estimated by extrapolating from the risks in asbestos workers to the general population. Exposure-disease relationships are generalized across exposure scenarios typically differing by orders of magnitude to obtain risk projections for the general population, which are subject to great uncertainty. While increasing information is becoming available on concentrations of asbestos fibers indoors, epidemiologic studies cannot directly assess the risks of indoor asbestos for such populations as schoolchildren and office workers because of the large sample sizes needed.

Environmental Tobacco Smoke

By mid-century, a marked increase was evident in lung cancer deaths among men, and case-control studies carried out to explain the epidemic quickly provided consistent evidence that cigarette smoking was a strong

cause of lung cancer. By 1964, sufficient epidemiologic data on smoking and health were available to support a conclusion by the Advisory Committee to the Surgeon General that cigarette smoking caused lung cancer in men.[25] Further research has shown that smoking is a cause of many malignant and nonmalignant diseases.[26]

Nonsmokers inhale environmental tobacco smoke, a mixture of sidestream smoke and exhaled mainstream smoke. During the late 1960s and early 1970s, several reports suggested that exposure of children to environmental tobacco smoke by the smoking of their parents increased their risk for respiratory infections and respiratory symptoms[27,28]; in the late 1970s, adverse effects of parental smoking on lung function in children were first reported.[29] In 1981, reports of two epidemiologic studies, one in Japan and the other in Greece, indicated that never-smokers married to smokers were at increased risk for lung cancer.[30,31] Other studies with similar findings were reported during the 1980s, and by 1986 the International Agency for Research on Cancer,[32] the National Research Council,[33] and the US Surgeon General[34] had concluded that passive smoking caused lung cancer in never-smokers. In reaching their conclusions, both the International Agency for Research on Cancer and the Surgeon General's Report emphasized the biologic plausibility of the epidemiologic evidence, assuming that there is no threshold of exposure for respiratory carcinogenesis and thus any exposure conveys some risk.

In contrast to the strong and causal associations of active smoking with lung cancer, the risks of exposure to environmental tobacco smoke found in epidemiologic studies have been lower, and methodologic problems have been discussed as an alternative explanation to causality for the association.[35-36] The extent of the lung cancer risk to never-smokers caused by exposure to environmental tobacco smoke has been particularly contentious, largely because nonsmokers in public buildings and workplaces involuntarily inhale environmental tobacco smoke, and unacceptable risks for this exposure would provide a basis for limiting smoking in these locations. The lung cancer risk of exposure to environmental tobacco smoke has been primarily assessed by generalizing the exposure-response relationship from the studies of never-smokers exposed to the smoking of their spouses.[37,38] Uncertainties are evident in this approach, including the lack of information on total exposure to environmental tobacco smoke and the many assumptions inherent in deriving a general exposure-response relationship from studies of never-smokers exposed at home.

Because of the methodologic difficulties of assessing lifetime exposure to environmental tobacco smoke and precisely describing risks that are not substantially elevated, these uncertainties in assessing the lung cancer risk of environmental tobacco smoke may never be fully resolved, although they remain a subject of research. Yet, full resolution would seem unnecessary for the evolution of public policy on environmental tobacco smoke, a carcinogen with a readily controllable source. In the case of environmental tobacco smoke, it would be unfortunate if potentially irresolvable scientific uncertainties thwarted control.

Acidic Aerosols/Sulfur Dioxide

The sulfur dioxide/particulate matter type of pollution, formed primarily as a result of combustion of sulfur-containing fossil fuels, represents a widespread form of pollution in industrialized societies.[39] The large-scale mid-century pollution disasters in Donora, Pa, in 1948[40] and in London, England, in 1952[41,42] probably involved extremely high levels, by current standards, of acid aerosols and sulfur dioxide. During the London fog of 1952, an estimated excess of 4000 deaths occurred, primarily among the elderly and those with a chronic respiratory disease. A recent reexamination of London mortality data for the years 1963 through 1972 showed a correlation between daily mortality and sulfuric acid aerosol levels on the prior day.[43]

Statutory regulations promulgated in the early 1970s by the Environmental Protection Agency under the Clean Air Act resulted in significant reductions in levels of total particles and sulfur dioxide. However, local reductions in pollution were often achieved by the use of tall stacks, particularly for power plants, which resulted in the pollutants being emitted high into the atmosphere, where prolonged residence time permitted their transformation into acid species. An emerging concern about the effects of these acidic aerosols has now extended beyond environmental effects on trees and lakes to human health.

Although still limited in extent, new epidemiologic data suggest adverse effects of acidic aerosols. A consistent association was reported between hospital admissions for respiratory disease in Southern Ontario and daily levels of sulfates, ozone, and temperature.[44] The Six Cities Study, conducted by Harvard University in six eastern and midwestern US cities, demonstrated links between particle exposure and respiratory disease in children.[45] Chronic cough and bronchitis symptoms were associated with hydrogen ion concentration, a measure of acidity, rather than with sulfate levels or total levels of particles. Furthermore, controlled human studies have established remarkable sensitivity in exercising asthmatics to the bronchoconstrictor effects of sulfur dioxide[46] and acidic aerosols[47,48] at concentrations similar to those at higher outdoor levels.

Data showing that acidic aerosols are a widespread form of pollution and the emerging health evidence have led to new research in the United States and elsewhere. While the air pollution episodes earlier in the century provided clear and dramatic evidence that acidic aerosols can increase mortality, the present levels of exposure have prompted questions concerning more subtle effects on mortality and morbidity. Providing certain answers to these questions is a difficult challenge for the scientific community. Epidemiologic studies are limited by the difficulty of measuring exposure and of singling out the effect of acidic aerosols from other factors, particularly for such nonspecific health effects as increased symptoms and reduction of lung function. Controlled exposures of volunteer subjects provide information concerning short-term effects, but this approach cannot fully represent the exposures sustained in the community.

Nonetheless, the regulatory apparatus turns to the results of epidemiologic and human toxicologic research as a basis for policy. On a 5-year cycle, the Environmental Protection Agency reevaluates the "science" to either modify or support the current sulfur dioxide and particulate matter standards. Thus, acidic aerosols may be eventually listed for regulation.[49]

Oxidant Gases

Ozone and nitrogen dioxide (NO_2) are oxidant gases that contaminate outdoor air in many urban and industrial locations. Ozone is one component of the pollution mixture commonly referred to as "smog," and its concentration is used as an index of the degree of smog pollution. Indoor environments may be contaminated by oxidants from outdoor air and by NO_2 produced indoors by combustion appliances, such as gas stoves and space heaters. At high concentrations, oxidants cause extensive lung injury, including pulmonary edema and bronchopneumonia in animals and in humans[50]; however, effects at levels currently measured in outdoor and indoor air in the United States have been diffi-

cult to characterize. A better understanding of the effects of oxidant pollutants is extremely important; despite extensive control efforts, more than one half of the US population still lives in communities where the National Ambient Air Quality Standard for ozone is exceeded,[51] and many homes with gas stoves have NO_2 levels that approach the standard for outdoor air.[52] In fact, although outdoor air contamination by oxidants has been the subject of substantial research and of great regulatory concern, pollution of indoor environments by NO_2 has been recognized as the predominant determinant of personal exposure in most locations.[53]

Investigating the health effects of the oxidant pollutants requires multidisciplinary research involving toxicologic and epidemiologic approaches.[52] For example, studies show that NO_2 exposure increases the frequency and severity of respiratory tract infections in animals[54]; we are conducting research to test the hypothesis that NO_2 exposure also increases the incidence and severity of respiratory tract infections in humans. In laboratory studies, volunteer subjects are exposed to NO_2 in a chamber, cells are obtained from the respiratory tract by bronchoalveolar lavage, and the ability of the cells to kill virus is assessed. We recently reported that alveolar macrophages obtained from healthy volunteers after a 3-hour continuous exposure to 1120 $\mu g/m^3$ of NO_2 inactivated influenza virus in vitro less effectively than cells collected after air exposure.[55] In an epidemiologic study addressing this same hypothesis, over 1000 infants have been followed up from birth with prospective observation for respiratory tract illnesses and monitoring of their homes for NO_2.[56]

Persistent questions concerning the long-term effects of residence in smog-polluted locations, such as Southern California, will probably require large epidemiologic studies and further studies involving the exposure of volunteers to describe the range of susceptibility and to address the mechanisms of toxicity. While the costs of this research may be high, exposure to oxidant pollutants is widespread, and the exposures of a substantial proportion of our population may be associated with adverse effects.

CONCLUSIONS

Although we have selected a few of the contaminants that cause environmental lung disease, many other agents with a similar array of changing concerns with regard to disease risk and safety could be listed; for example, silica, the cause of silicosis, is a suspect carcinogen at contemporary occupational levels of exposure, and concern has been raised about the human carcinogenicity of man-made fibers. We suggest that the lessons to be learned from the example agents may be generalized to other pollutants.

Active cigarette smoking, occupational asbestos exposure, radon in underground mines, and high levels of acidic aerosols were remarkably strong causes of disease under the exposure conditions originally investigated. In fact, cases of disease caused by exposure to these agents were initially identified through descriptive case series rather than more formal epidemiologic investigation. The subsequent research, both epidemiologic and toxicologic, was successful in establishing causal exposure-disease associations and informative in characterizing exposure-response relationships. However, current concerns over lower concentrations of these same agents cannot be so readily answered, nor can they be answered with sufficient certainty to satisfy all interested parties, who potentially include not only the general public but also involved manufacturers, parties to litigation, environmental groups, and regulators.

The technique of quantitative risk assessment is increasingly applied to gauge the risks of environmental pollutants (Table 1). However, the frequent focus on the final risk projection—for example, stating that radon causes 10 000 to 20 000 cases of lung cancer annually in the United States—may inappropriately heighten debate over the projected numbers, even though the numbers are produced by a simplistic and mathematical representation of complex biological processes. Moreover, controversy concerning uncertainties in risk projections may detract from less ambiguous research findings. For example, radon is an established carcinogen, although any projection of the risks of indoor radon is subject to diverse uncertainties. Because malignancy fits more readily into a risk assessment framework than nonmalignant outcomes, emphasis by regulatory agencies appears to unduly weight exposures causing cancer. In using quantitative risk assessment to manage risks, the difficulties of communicating risks may further limit the capability of achieving public health goals.[57]

It should be recognized that steps can be taken to reduce risks of environmental lung disease despite the types of controversies and points of uncertainty that we have considered. For some pollutants, the individual can reduce risks. For example, prevention and cessation of smoking control the hazards of both active and passive smoking. Radon concentrations in homes can be measured inexpensively, and techniques are available for mitigating and avoiding unacceptable radon concentrations. Guidance is available for other indoor air pollutants, including asbestos. For other pollutants, only national policy and regulation can reduce risk. For example, reduction of levels of acidic aerosols or of ozone can be effected only by multifaceted regulatory strategies directed at sources.

Tremendous progress has been made across the century in understanding and preventing environmental lung diseases. The shift of our concern to morbidity at lower levels of exposure and more subtle effects on mortality parallels strong trends of declining levels for some pollutants. Certain diseases, eg, asbestosis and silicosis, are entirely preventable and the occurrence of new cases is now regarded as a sentinel event, signaling an unacceptable exposure. Toxicologic studies have provided many new insights into effects of environmental agents on the lung, although much remains to be learned about basic mechanisms of toxicity. The present emphasis on risk assessment and risk reduction, which raises many uncertainties and new questions, should not detract from these past accomplishments. The scientific community has been challenged by difficult questions, some of which may never be answered with complete certainty. Nevertheless, it is the results of research that have shifted our public health emphasis to concerns about lower and lower levels of exposure. We anticipate that research on the environment and the lung will continue to support the evolution of public policy, while raising even more difficult questions relevant to public health.

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