American Thoracic Society

What Constitutes an Adverse Health Effect of Air Pollution?

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1999

PURPOSE OF THE STATEMENT

As the twentieth century ends, the health effects of outdoor air pollution remain a public health concern in developing and developed countries alike. In the United States, the principal pollutants monitored for regulatory purposes (carbon monoxide, nitrogen dioxide, sulfur dioxide, particles, ozone, and lead; see Table 1) show general trends of declining concentrations, although ozone pollution now affects many regions of the country besides southern California (1). Yet, even at levels of air pollution now measured in many cities of the United States, associations between air pollution levels and health indicators are being demonstrated at concentrations around those set by standards of the U.S. Environmental Protection Agency (2, 3). In many countries of the developing world, concentrations of air pollutants are rising with industrialization and the increasing numbers of motor vehicles (4, 5). Extremely large and densely populated urban areas, often referred to as "megacities," have the potential to generate unprecedented air quality problems.

There are common principles to air quality management throughout the world. Public health protection unifies all approaches, whether based on voluntary guidelines, mandated standards for concentrations, or source control. The intent is to limit or to avoid any impact of air pollution on the public's health. Air quality management is thus based on a scientific foundation built from the epidemiologic, toxicologic, and clinical evidence on health effects of air pollution. In interpreting this evidence for public health protection, there is a need to identify those effects that are considered "adverse" and to separate them from those effects not considered adverse.

The American Thoracic Society has previously provided guidance on the distinction between adverse and nonadverse health effects of air pollution in its 1985 statement, "Guidelines as to What Constitutes an Adverse Respiratory Health Effect" (6). Definitions of adverse effects have also been offered by the World Health Organization (7–10), but the guidance of the American Thoracic Society has received particular emphasis in the United States. Preparation of the original statement was intended to coincide with consideration of the passage of an amended Clean Air Act and to provide a framework for interpreting scientific evidence relevant to the mandate of the act. In particular, the Clean Air Act requires that the Administrator of the Environmental Protection Agency promulgate, for certain pollutants, standards that will be sufficient to protect against adverse effects of the air pollutants on health. The act is silent on the definition of "adverse effect" and, at the time of the 1985 statement, there was considerable controversy around the interpretation of this language as revision of the act was being considered. Recognizing the need of policy makers for expert guidance, the American Thoracic Society released the 1985 statement, which to date constitutes the sole set of recommendations on this issue from an expert panel convened by a health organization.

The American Thoracic Society has revised the 1985 statement because new scientific findings, published since the original statement, have again raised questions as to the boundary between adverse and nonadverse in considering health effects of air pollution. These new findings reflect improved sensitivity of research approaches and the application of biomarkers that can detect even subtle perturbations of biologic systems by air pollutants. Epidemiologic research designs have been refined and large sample sizes and increasingly accurate methods for exposure assessment have increased the sensitivity of epidemiologic data for detecting evidence of effects. New statistical approaches and advances in software and hardware have facilitated analyses of large databases of mortality and morbidity information. The design of clinical studies-including controlled exposures of volunteers-has also advanced and biologic specimens may be obtained after exposure, for example, by fiberoptic bronchoscopy, to identify changes in levels of markers of injury. Toxicologic studies have also gained in sophistication through incorporation of more sensitive indicators of effect and the careful tracing of the relationship between exposure and biologically relevant doses to target sites, which may now be considered at a molecular level.

New dimensions have been added to the array of outcome measures. Medical outcomes research now recognizes that patient well-being should be broadly conceptualized and measured rigorously, in addition to considering the biological process of the disease itself. As a result, health-related quality of life, the perception of well-being, is now considered a necessary component of outcomes research. Validated instruments have been developed to assess the impact of health-related symptoms and impairment on functional status and quality of life (11-14). The formalization of the concept of environmental justice acknowledges that the effects of specific pollutants cannot be evaluated in isolation without giving consideration to the overlapping exposures of populations, often minority group members of low socioeconomic status, who live in neighborhoods that are heavily exposed to multiple environmental contaminants (15).

This new statement, like the 1985 statement, is intended to provide guidance to policy makers and others who interpret the scientific evidence on the health effects of air pollution for the purpose of risk management. The statement does not offer strict rules or numerical criteria, but rather proposes principles to be used in weighing the evidence and setting boundaries between adverse and nonadverse health effects. Even if the technical tools were available for scaling the consequences of air pollution on the multiple relevant axes, the placement of dividing lines should be a societal judgment and consequently

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TABLE 1

U.S. NATIONAL AMBIENT AIR QUALITY STANDARDS*

Pollutant	NAAQS Concentration (ppm)	NAAQS Concentration ($\mu g/m^3$)	Standard Type
Particulate matter ≥ 10 Pm (PM_{10})			
24-h average		150	Primary and secondary
Annual arithmetic mean		50	Primary and secondary
Particulate matter ≥ 2.5 μm ($PM_{2.5}$)			
24-h average		65	Primary and secondary
Annual arithmetic mean		15	Primary and secondary
Ozone (O_3)			
24-h average	0.12	235	Primary and secondary
Annual arithmetic mean	0.08	157	Primary and secondary
Sulfur dioxide (SO_2)			
24-h average	0.14	365	Primary
Annual arithmetic mean	0.03	80	Primary
3-h average	0.50	1,300	Secondary
Nitrogen dioxide (NO_2)			
Annual arithmetic mean	0.053	100	Primary and secondary
Carbon monoxide (CO)			
1-h average	35	40	Primary
8-h average	9	10	Primary
Lead (Pb)			
Quarterly average		1.5	Primary and secondary

* For detailed information on scientific bases and policy considerations underlying decisions establishing the NAAQS listed here, see the AQCDs, staff papers, and NAAQS Promulgation notices cited in text. Such information can also be obtained from several internet websites (e.g., http://www.epa.giv/airs/criteria.html; http://www.epa.gov/oar/oaqps/publicat.html; and http://www.epa.gov/ncea/biblio.htm).

TABLE 2

ADVERSE RESPIRATORY HEALTH EFFECTS

A. Increased mortality (*Increased* as used here and subsequently means significantly [$p < 0.05$] increased above that recorded in some standard, comparable population. In selected situation, $p < 0.1$ may be appropriate)
B. Increased incidence of cancer
C. Increased frequency of symptomatic asthmatic attacks
D. Increased incidence of lower respiratory tract infections
E. Increased exacerbations of disease in persons with chronic cardiopulmonary or other disease that could be reflected in a variety of ways
   1. Less able to cope with daily activities (i.e., shortness of breath or increased anginal episodes)
   2. Increased hospitalization, both frequency and duration
   3. Increased emergency ward or physician visits
   4. Increased pulmonary medication
   5. Decreased pulmonary function
F. Reduction in FEV_1 or FVC associated with clinical symptoms
   1. Chronic reduction in FEV, or FVC associated with clinical symptoms
   2. A significant increase in number of persons with FEV_1 below normal limits: chronically reduced FEV, is a 'predictor of increased risk of mortality. Transient or reversible reductions that are not associated with an asthmatic attack appear to be less important. It should be emphasized that a small but significant reduction in a population mean FEV, or $FEV_{.75}$ is probably medically significant, as such a difference may indicate an increase in the number of persons witn respiratory impairment in the population. In other words, a small part of the population may manifest a marked change that is medically significant to them, but when diluted with the rest of the population the change appears to be small
   3 An increased rate of decline in pulmonary function (FEV,) relative to the predicted value in adults with increasing age or failure of children to maintain their predicted FEV, growth curve. Such data must be standardized for sex, race, height, and other demographic and anthropometric factors
G. Increased prevalence of wheezing in the chest apart from colds, or of wheezing most days or nights. (The significance of wheezing with colds needs more study and evaluation.)
H. Increased prevalence or incidence of chest tightness
I. Increased prevalence or incidence of cough/phlegm production requiring medical attention
I. Increased incidence of acute upper respiratory infections that interfere with normal activity
K. Acute upper respiratory tract infections that do not interfere with normal activity
L. Eye, nose, and throat irritation that may interfere with normal activity (i.e., driving a car) if severe
M. Odors

this committee does not propose specific boundaries for separating adverse from nonadverse effects.

OVERVIEW OF THE 1985 STATEMENT

The 1985 statement of the American Thoracic Society was directed at respiratory health effects of air pollution and emphasized the interpretation of the epidemiologic evidence. The statement recognized the spectrum of responses to air pollution, which begins with exposure and evidence of exposure and ends at death. This spectrum has been characterized as a pyramid, based in the most common consequence-exposure-and having mortality, the least common and most severe consequence, at its tip. The statement included a table that lists adverse respiratory health effects, seemingly in order of declining severity (Table 2). The 1985 statement hinged the distinction between adverse and nonadverse effects on medical considerations. The committee recognized that the boundary is further influenced by societal considerations: "Where one draws the line to categorize it as an adverse health effect or an action level between pathophysiologic or physiologic change is probably best left to the individual or the community."

The committee's definition of adverse respiratory health effects was ". medically significant physiologic or pathologic changes generally evidenced by one or more of the following: (*1*) interference with the normal activity of the affected person or persons, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury, and/or (5) progressive respiratory dysfunction." The committee noted that all changes are not adverse, citing the example of carboxyhemoglobin. The level of carboxyhemoglobin, beyond that from endogenous production, is indicative of exposure but it is not predictive of adverse effects until reaching threshold levels, depending on the effect and the susceptibility of the exposed person. The statement recognized that a distinction should be drawn between effects to individuals and effects to populations and that populations are heterogeneous in their susceptibility. The comment was offered that a change in a population could be "medically significant" for that group. The statement also provides guidance on interpretation of'reversible effects and on interpreting irreversible effects. In acknowledging that research would continue to address uncertainties, the committee recommended that the guidelines should be periodically reviewed and updated.

METHODOLOGY FOR DEVELOPING THIS STATEMENT

Following the recommendation of the committee that authored the 1985 statement, the Environmental and Occupational Health Assembly of the American Thoracic Society recognized a need to reconvene a group to review and revise the prior statement. The statement had been used for more than a decade and new investigative approaches were being used to identify effects of air pollution that were not considered by the first committee. In addition, societal perspectives had shifted since the early 1980s and a forma1 concern for the impact of air

pollution on specific groups had been expressed through the environmental justice movement.

To revise the statement, a multidisciplinary committee was convened in 1997 that included expertise in pulmonary medicine, public health, epidemiology, both clinical and animal toxicology, biochemistry, and cellular and molecular biology. This committee conducted several planning meetings and consulted experts in environmental economics and in ethics. In addition, a multidisciplinary workshop was convened to gain input from the range of groups potentially interested in the statement and its application. The committee's approach was discussed at a symposium held at the 1999 Annual Meeting of the American Thoracic Society. After further revisions, the statement was reviewed and submitted to the Board of the American Thoracic Society.

BACKGROUND ON THE CLEAN AIR ACT

The preparation of the original statement was largely motivated by potential ambiguity in interpreting the language of the Clean Air Act, which addresses adverse effects of air pollution without providing clear guidance as to the distinction between adverse and nonadverse effects. In addition, questions regarding this distinction arise repeatedly in interpreting the findings of research studies, whether observational or experimental. Consequently, the 1985 statement has had broader application than just the interpretation of evidence on air pollution and health for the purpose of promulgating air quality regulations. Nonetheless, the committee found the legislative history of the Clean Air Act to be relevant to its charge.

The first national legislation on air pollution, the Air Pollution Control Act, was passed in the mid-1950s; the original Clean Air Act was passed in 1963 and last revised in 1990. The act is lengthy and complex in its provisions; most relevant to considerations in defining an adverse health effect are Sections 108 (Air Quality Criteria and Control Techniques), 109 (National Ambient Air Quality Standards), and 112 (Hazardous Air Pollutants). National Ambient Air Quality Standards (NAAQS) are set individually for six prevalent pollutants (Table 1), often referred to as "criteria pollutants." They are so designated because of the requirement for comprehensively reviewing relevant information in a criteria document. The primary NAAQS are to be set at a level that protects the public health with an adequate margin of safety, regardless of economic or technical feasibility of attainment. The secondary standards are concerned with welfare and environmental consequences.

The hazardous air pollutants, as defined in Section 112, are not covered under Sections 108 and 109 as criteria pollutants. In 1990, the Congress offered a list of 189 such pollutants and a process for listing and delisting substances. The 1990 Clean Air Act states: "The Administrator shall periodically review [and revise] the list [of 189 hazardous air pollutants] by. adding pollutants which present, or may present, through inhalation or other routes of exposure, a threat of adverse human health effects (including, but not limited to substances which are known to be, or may reasonably be anticipated to be, carcinogenic, mutagenic, teratogenic, neurotoxic, which cause reproductive dysfunction, or which are acutely or chronically toxic). ." Section 112(f)(2) further directs the Environmental Protection Agency to assess whether the emissions standards for the listed hazardous air pollutants required under other subsections "provide an ample margin of safety to protect public health" and if not, then the agency is to develop standards that will address the "remaining risk."

The historical record provides an indication of the intent of the Congress in framing the language of the Clean Air Act with regard to protection of the public's health. Research now shows that the most highly susceptible individuals may respond to common exposures that are often at or close to natural background pollutant levels.

With regard to sensitivity, the 1970 Clean Air Act recognized that some persons were so ill as to need controlled environments, e.g., persons in intensive care units or newborn infants in nurseries; the act stated that the standards might not necessarily protect such individuals. It further stated, however, that the standards should protect "particularly sensitive citizens such as bronchial asthmatics and emphysematics who in the normal course of daily activity are exposed to the ambient environment." The act further suggested that the adequacy of any standard could be tested in a statistically representative sample of sensitive individuals. The hearing record on the 1970 act is informative. Dr. Hon T. Middleton (Commissioner, National Air Pollution Control Administration, Department of Health, Education, and Welfare) addressed the Senate Subcommittee on Air and Water Pollution of the Committee on Public Works on May 27, 1970. He testified that the intent of any national air quality standard is to be "protective of health in all places" and set at a level below which effects have not been observed. Dr. Middleton recognized the difficulty of finding a demarcation point of exposure below which there is no effect and he noted that there may be subtle effects and evolving scientific understanding.

Further difficulties in the language of the Clean Air Act were later noted in ***A Legislative History of the Clean Air Act Amendments of 1977: A Continuation of the Clean Air Act Amendments of 1970.*** This document noted the difficulty of applying the margin of safety and the erosion of margins of safety by advancing scientific knowledge. The document also commented on the implicit assumption of a safe threshold in the language of the act and the implausibility of this assumption. The report questioned whether the NAAQS (I) protect against genetic mutations, birth defects, and cancer, (2) take sufficient account of the consequences of long-term low-level exposures or short-term peaks, and (3) sufficiently consider synergism among pollutants and the formation of secondary pollutants, e.g., sulfates, with their own toxicity. These considerations remain relevant more than 20 years later.

This selective review of the historical record indicates that Congress intended that the NAAQS would afford health protection not only to the general population but to subgroups with enhanced susceptibility to air pollution, including people with asthma and people with chronic obstructive lung disease. Nevertheless, it is also clear that some exquisitely susceptible individuals might remain outside the ambit of protection of the NAAQS. A margin of safety was to be provided but quantitative specification was not offered. The evolutionary nature of the supporting scientific evidence was repetitively acknowledged and the need to distinguish adverse from nonadverse effects was at least implicitly recognized. The current language of Section 112 explicitly acknowledges the possibility of shifting understanding of risks of specific hazardous air pollutants.

GENERAL CONSIDERATIONS

In preparing the statement, the committee identified several general considerations that are relevant to interpreting evidence on the health effects of air pollution. Each of these considerations and the committee's judgment as to their proper weighting are detailed below.

Population Health versus Individual Risk

The effects of air pollution can be viewed in the complementary contexts of the increment of an individual's risk for disease—the clinician's measure of impact-and of the additional risk incurred by a population, which is the public health perspectivc (16). Both perspectives arc relevant to interpreting research findings on air pollution and to regulations that are protective of the public's health. Any risk incurred by an exposed individual beyond some boundary, determined by the individual or on a societal basis, could be deemed unacceptable. For example. prolonged exposure to a respiratory carcinogen could result in an individual-level incremental risk of exposure of 10^{-4}, more than two orders of magnitude lower than the baseline lifetime individual risk in the United States. Nevertheless, among an exposed population of IO', the estimated number of cancer cases that might result from such an exposure would number 10^{3}, illustrating that minute individual risks may be significant from the standpoint of population exposures.

Exposure could also enhance risk for a population to an unacceptable degree, perhaps without shifting the risks of any particular individuals to an unacceptable level. Figure 1 illustrates the distinction. In Figure l A, the population's distribution of exposure shifts toward a higher level and some members of the population cross the boundary to an unacceptable risk. In Figure lB, the shift affects the position of the population distribution, but no individuals move to an unacceptable level of risk. Effects on persons with asthma are illustrative. A population of children with asthma could have a distribution of lung function such that no individual child has a level associated with significant impairment. Exposure to air pollution could shift the distribution toward lower levels without bringing any individual child to a level that is associated with clinically relevant consequences. Individuals within the population would, however, have diminished reserve function and are at potentially increased risk if affected by another agent, e.g., a viral infection. Assuming that the relationship between the risk factor and the disease is causal, the committee considered that such a shift in the risk factor distribution, and hence the risk profile of the exposed population. should be considered adverse, even in the absence of the immediate occurrence of frank illness.

Ethics and Equity

The past decade has brought increasing concern over the ethics of heterogeneous, inequitable distributions of environmental and occupational exposures (IS). Within the United States, some groups receive disproportionate exposures to environmental agents that arc injurious to health; the environmental justice movement seeks to redress these inequities. The exposures of concern originate in breathing polluted outdoor air, living in substandard housing with indoor air pollution problems, including exposures to certain bioacrosols and combustion products, and working in jobs with occupational respiratory risks. Groups encompassed by this movement in the United States include various racial and ethnic minority populations. particularly those living within urban areas, and the socioeconomically disadvantaged. In the developing world, such exposures can occur at substantially higher levels and may, in some instances, extend to a majority of a given nation's population. Limited access to care and medications may enhance susceptibility to pollution.

The concept of environmental equity had not been formally voiced when the 1985 statement was written. The present committee viewed inequities of exposure as potentially representing a form of susceptibility to air pollution. In other words, individuals within the target groups may be at increased risk of experiencing adverse effects from a given level of ambient air pollution because their baseline risk level may have been raised by other exposures. Moreover, in some instances there may be genetic and nutritional factors enhancing susceptibility as well. It should be noted, however, that there are other exposure scenarios and other subpopulations with increased baseline risks that are not formally included within the environmental justice movement. The heterogeneity of populations needs full acknowledgment, whether it reflects disproportionate noxious exposures or other factors. Observing that there have been few investigations of the effects of other exposures, genetics, or nutrition on susceptibility to air pollution-related effects, either in the United States or internationally, the committee issued a call for additional research in these areas.

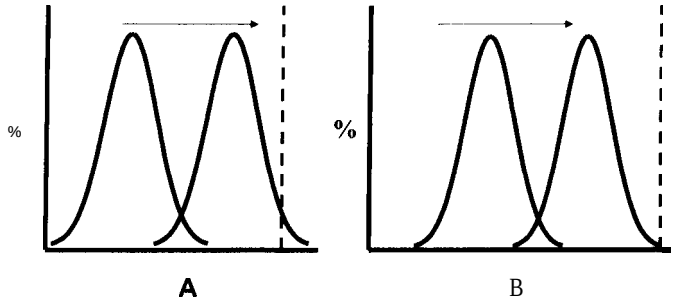

Figure 7. Hypothetical distributions **of exposure for two populations, *A* and *B*. (See text for explanation.)**

Economic Costs

Adverse health effects of air pollution incur costs, including direct costs of providing treatment for illness and indirect costs of lost work time and productivity. Cost-benefit analysis provides an estimate of the balancing of the costs of controls against the benefits; cost effectiveness analysis provides an indication of the level of control accomplished in relation to costs. Cost-benefit and cost-effectiveness analysis are assumption-laden tools now being used for policy-making purposes. Cost estimates depend on the valuation given to illness, lost work time and productivity, and even to lost life. It has been proposed that cost-benefit analysis may facilitate the process of deciding whether a given air pollution-related health impact should be considered adverse. The legislative history of the Clean Air Act explicitly excludes consideration of economic factors in setting ambient air quality standards or in developing emissions standards for hazardous air pollutants. In the context of air quality regulation, cost-benefit analysis is a multistep process involving the articulation of value judgments regarding potential costs (expenditures of public and private resources to reduce pollutant emissions and exposures) versus benefits (avoidance of specified adverse health impacts in a designated population). Benefits, in theory, should be quantified as the willingness of beneficiaries to pay to avoid the adverse impact. In practice, quantification of such health impacts from exposure to air pollution is often based on direct costs related to medical treatment and indirect costs such as school absenteeism, lost work time, decreased productivity, and, at the extreme, person-years of life lost. Valuations of a given effect may vary internationally, as differences in population age distributions, comorbidity, nutritional status, and other circumstances can affect this process. Ideally, cost–bene-

fit analysis should make explicit the value judgments underlying these assessments, highlighting distinctions among alternative pollution control strategies to achieve specific air quality standards. Willingness of individuals to pay to avoid adverse health effects is also estimated from responses to contingent valuation surveys and from market data concerning choices about employment that carries health risks.

Nevertheless, the committee concurred that the specification of which health effects should be considered adverse must precede the application of cost-benefit analysis for evaluation of air pollution control strategies. That is, once a given outcome is designated as adverse, this information can be used as input to cost-benefit analysis. Estimates of costs associated with a given health outcome. while useful from a public policy perspective, cannot be translated into any clinical or biological framework to distinguish adverse from nonadverse effects. Therefore, the committee concluded that however valuable this economists' tool may be for regulatory decision-making, cost-benefit analysis lay outside the scope of this position paper and, indeed, the expertise of the American Thoracic Society.

Susceptibility

The issue of susceptibility has been recognized throughout the history of our initiatives to regulate outdoor air pollution. Susceptibility, broadly defined, may include extrinsic factors, including the profile of exposures to other pollutants, for example, in the workplace or at home, and intrinsic factors, for example, genotype. The size of the population of individuals susceptible to indoor air pollution is large, potentially including infants and the elderly, persons with chronic heart and lung diseases, and the immunocompromised. Persons with multiple deleterious exposures may also be considered as having heightened susceptibility, particularly if the combined effects of the agents are synergistic. Even with the populations considered as susceptible there is a distribution of the degree of susceptibility. For example, levels of nonspecific airway responsiveness in persons with asthma span several orders of magnitude.

The current explosive growth in knowledge of the genetic basis of lung disease, including responses to environmental agents, will provide increasing insights into the mechanistic basis of susceptibility and provide markers of risk status. We already have evidence of between-person variation in the pulmonary function response to ozone and interstrain variation in the pulmonary effects of environmental exposures, including criteria pollutants, in rodent species. As we develop the capacity to more precisely identify those at risk, we may find it increasingly challenging to assure protection for all individuals against adverse health effects.

The present committee agreed with the principle espoused in the Clean Air Act: that regulations should extend protection to include those with enhanced susceptibility to air pollution, recognizing that some highly susceptible individuals may still respond to low-level exposures. Research now shows that some highly susceptible individuals may respond to common exposures that are often unavoidable. Furthermore, by definition, susceptible individuals cannot have the same margin of safety as the nonsusceptible groups within the population.

Heterogeneity of Perspectives

In society there is an extraordinary range of views on environmental issues and tolerance of risk. Looking more globally to other developed countries and to the developing countries, the range of perspectives is even broader. The committee acknowledges that any defined boundaries for distinguishing adverse health effects may not be embraced by all groups. This heterogeneity and the possibility that some may reject the committee's proposal challenged the committee to recommend in principle that control measures should maximize public health benefits while assuring equity.

DIMENSIONS OF ADVERSE EFFECTS

Biomarkers

Biomarkers are indicators of exposure, effect, or susceptibility that are measured in biologic materials, such as blood or bronchoalveolar lavage fluid. The concept of biomarkers has been formalized since the 1985 statement (17) and since then. a continuously increasing number of candidate indicators of exposure, effect, and susceptibility have been developed and applied in laboratory studies of humans and animals and in both occupational and environmental population studies. The progressive refinement of techniques in the field of cellular and molecular biology, and the burgeoning understanding of the complex chemical intracellular and cell-to-cell signaling pathways collectively termed "cytokines" (18), have rapidly expanded the spectrum of candidate markers of effects. It is now possible to detect very early, or initiating phases of responses at the molecular level, such as the production of mRNA for cytokines. Similarly, the progressive development of genetic assays and understanding of the human genome have provided numerous candidate markers of both effects and susceptibility (19).

Biomarkers relevant to air pollution have been measured in blood, exhaled air, urine, sputum, and in bronchoalveolar lavage fluids and tissue specimens collected by bronchoscopy. Bronchoalveolar lavage fluids, for example, are now frequently analyzed for cell numbers and types, cytokines (e.g., several interleukins and tumor necrosis factor α), enzymes (e.g., lactate dehydrogenasc and β-glucoronidase), fibronectin, protein, arachidonic acid metabolites, and reactive oxygen species. Because many of the epithelial cell types of the nasopharyngeal region are similar to epithelia and responses in the trachea, bronchi, and bronchioles, responses of nasal cells have been examined as potential biomarkers for their ability to predict parallel responses in lung airways, which are more difficult to sample.

Biomarkers have been extensively applied in toxicologic studies of air pollution, both in animals and in clinical studies involving exposures of human volunteers. The biomarkcrs are examined for their ability to provide evidence of "biologically effective" doses, including the earliest phases of homeostatic responses, the occurrence of injury, outcomes that are intermediate between injury and disease, and the presence of established disease processes. Genetic markers of susceptibility have begun to be applied to the respiratory system, and this application will undoubtedly expand rapidly. A frequent goal of biomarker development is the ability to readily measure changes that precede and predict continued or progressive events leading to clinical effects and disease (Figure 2).

To date, although biomarkers have proved informative about homeostatic adjustments to exposure and the mechanisms of injury and disease, lack of validation against previously established measures of effect. such as clinical status or even physiologic impairment, remains an important weakness. We do not know if elevations of biomarkers during short-term experimental exposures signal risk for ongoing injury and clinical effects or simply indicate transient responses that can provide insights into mechanisms of injury. The utility of some older biomarkers is well established, such as the relationships among carboxyhemoglobin. exposure to carbon monoxide,

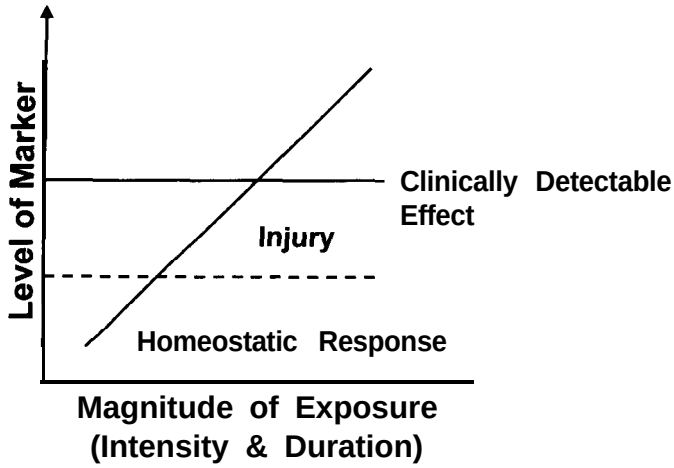

figure 2. Schema for considering biomarkers of response.

impairment of oxygen-carrying capacity, and the risk for angina in the presence of ischemic heart disease. However, the interpretative value for the majority of the many promising new cytokine and genetic biomarkers remains to be established. Not only is it difficult to assess the value of many biomarkers for distinguishing between physiological, homeostatic responses and injury, but it is also difficult to judge the value of changes during short-term exposures for predicting ongoing injury or risk for longer-term clinical effects.

The committee concluded that the continued development of biomarkers is an important need because of their considerable potential not only for detecting the adverse effects of air pollution exposure, but also for aiding the determination of the types and levels of response that should be considered adverse. We often do not know in a parallel, iterative manner, whether the exploration and validation of biomarkers will unquestionably advance our understanding of the mechanisms of homeostatic and injury responses. At this time, however, few of the rapidly growing list of candidate biomarkers have been validated to such an extent that their responses can be used with confidence to define the point at which a response should be equated to an adverse effect warranting preventive measures. Thus, we presently have only a very modest ability to translate evidence from biomarkers directly into a taxonomy of adverse health effects. Consequently, the committee cautions that not all changes in biomarkers related to air pollution should be considered as indicative of injury that represents an adverse effect.

Quality of Life

Health, in its broadest definition, includes not only the absence of disease but the attainment of well-being. Since the preparation of the 198.5 statement, the National Institutes of Health, the Centers of Disease Control, the Food and Drug Administration, and the World Health Organization have broadened their perspective of health to incorporate the concept of health-related quality of life as a valid and important health outcome. Health-related quality of life (HRQL) refers to the individual's perception of well-being, and includes such factors as self-care functioning, mental health, pain, and sense of overall well-being. Decreased health-related quality of life is widely accepted to be an adverse health effect. For this reason, measurable negative effects of air pollution on quality of life, whether for persons with chronic respiratory conditions or the population in general, were consequently considered by this committee to be adverse health effects. Air pollution exposure can adversely affect several domains of quality of life including physical functioning (particularly for persons with respiratory or cardiovascular conditions) and general well-being. Stinging, watery eyes resulting from air pollution not only reflect a chronic physical symptom but may decrease overall quality of life. Outdoor air pollution and odors have been associated with psychiatric symptoms, including anxiety and depression. Increased levels of some air pollutants have been reported to be associated with an increase in psychiatric admissions. The potential effects of air pollution and respiratory symptoms on different domains of quality of life are illustrated in Figure 3.

Measurement of the impact of air pollution on health-related quality of life can be accomplished either by measuring specific domains that may be influenced by air quality (e.g., anxiety, functional status), or by using specific quality of life instruments designed to measure multiple health-related domains (e.g., MOS-SF-36, St. George's Respiratory Questionnaire). The cost-benefits of improved air quality on health-related quality of life could also be measured by the use of quality of life measures that employ utility rating scales. The effects of air pollution of a magnitude considered to be clinically significant with these instruments should be regarded as adverse in interpreting evidence on the health effects of air pollution, regardless of the affected dimension. Additional research is needed to develop an information base for interpreting data from new and more sensitive instruments directed specifically at air pollution.

Physiological impact

The 198.5 statement acknowledged a distinction between reversible and irreversible effects. Healthy persons may sustain transient reductions in pulmonary function associated with air pollution exposure, e.g., reduction of the forced vital capacity (FVC) with exercise at times of higher levels of ozone pollution. However, the committee recommends that a small, transient loss of lung function, by itself, should not automatically be designated as adverse. In drawing the distinction between adverse and nonadverse reversible effects, this committee recommended that reversible loss of lung function in combination with the presence of symptoms should be considered as adverse. This recommendation is consistent with the 1985 statement. The Environmental Protection Agency has also needed to address the interpretation of such data. The Envi-

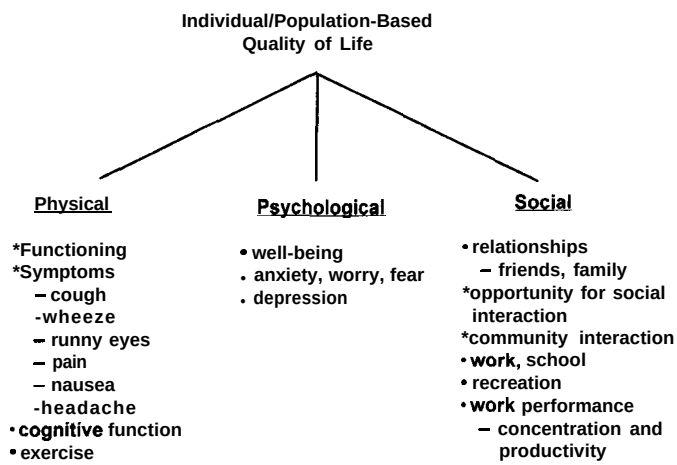

Figure 3. Quality of life domains vulnerable to the adverse health/respiratory effects of air pollution.

ronmental Protection Agency, in its 1989 review of ozone (20), offered a graded classification of lung function changes in persons with asthma. Reduction of the forced expiratory volume in 1 s (FEV_1) was graded as mild, moderate, or severe for reductions of less than 10%, 10–20%, and more than 20%, respectively. This classification has not been validated for acceptability or against other measures.

There is also epidemiologic evidence that air pollution may adversely affect lung growth or accelerate the age-related decline of lung function. Epidemiologic studies are limited in their power to detect such permanent effects and any evidence of association between air pollution exposure and permanent loss of function is indicative of an adverse effect at the population level. Some individuals may sustain clinically relevant, permanent losses of lung function. This committee considered that any detectable level of permanent lung function loss attributable to air pollution exposure should be considered as adverse.

Symptoms

Air pollution exposure can evoke symptoms in persons without underlying chronic heart or lung conditions and also provoke or increase symptom rates in persons with asthma and chronic obstructive lung disease. The Environmental Protection Agency also offered a scale for cough and pain on taking a deep breath in its 1989 ozone review (20). "Infrequent cough" was classified as "None/Normal."

Do all levels of increased symptom occurrence constitute an adverse health effect? The committee judged that air pollution-related symptoms associated with diminished quality of life or with a change in clinical status should be considered as adverse at the individual level. Characterizing the degree of symptomatology associated with diminished quality of life is an appropriate focus for research and a topic that could be investigated using new approaches for assessing quality of life. A change in clinical status can be appropriately set in a medical framework as one requiring medical care or a change in medication. At the population level, any detectable increment in symptom frequency should be considered as constituting an adverse health effect.

Clinical Outcomes

A wide range of clinical outcome measures has been considered in relation to air pollution, including population-level effects, such as increases in numbers of emergency room visits for asthma or hospitalizations for pneumonia, and individual-level effects, such as increased need for bronchodilator therapy. The present committee shared the view of the previous group: detectable effects of air pollution on clinical measures should be considered adverse.

At the population level, the magnitude of the detectable air pollution effect will depend on the extent of the data available for evaluation and methodological aspects of the data, including the degree of error affecting exposure and outcome variables. With large databases, seemingly modest effects may be detectable. However, the committee recommends that no level of effect of air pollution on population-level clinical indicators can be considered acceptable.

Mortality

Following the development of new approaches for the analysis of time-series data, extensive analyses have now been reported on the relationship between daily mortality counts and levels of air pollution on the same or prior days. Several prospective cohort studies have also addressed the effect of longer-term indicators of air pollution exposure on mortality, controlling for relevant individual factors, including age, sex, cigarette smoking, and occupational exposures, among others. Cross-sectional studies-comparing mortality across locations having different levels of air pollution while controlling for a variety of potential confounding factors-have also been conducted. The air pollution-associated mortality findings figured prominently in the recent revision of the U.S. NAAQS for particulate matter.

Associations between air pollution levels and daily mortality counts have been interpreted by some as reflecting the impact of air pollution on a pool of frail individuals with severe underlying heart or lung disease. One explanation for the day-to-day associations attributes them to a brief advancement of the time of death for extremely frail individuals who would have been expected to die soon even in the absence of an air pollution-related insult (21). Work has shown, however, that while this phenomenon of advancement, referred to as mortality displacement, may occur, it cannot provide a full explanation of the associations repeatedly found between daily fluctuations of air pollution and mortality (22, J. Schwartz, "Harvesting and long term exposure effects in the relationship between air pollution and mortality" [1999, unpublished manuscript]). In addition, some mortality time-series studies have found effects across all age strata, not just among the elderly or the very young, suggesting potentially substantial effects on person-years of life lost. Finally, studies of long-term exposures have shown a gradient of mortality risk from cardiopulmonary disease as well as differences in life expectancy across cities with different long-term pollution levels. Thus, although we still have little insight into the extent to which mortality displacement occurs, the evidentiary ensemble from several types of study designs consistently shows that air pollution can shorten the life span to an unacceptable degree.

Risk Assessment

Since the publication of the 1985 statement, quantitative risk assessment has emerged as a key tool for summarizing information on risks to health from environmental agents. Quantitative risk assessment offers a framework for organizing information on risks within its four elements: hazard identification, exposure assessment, dose-response assessment, and risk characterization. The findings of a risk assessment, encompassed in the risk characterization component, may include an overall assessment of impact, a description of the distribution of risk in the population, and an evaluation of risk for susceptible persons within the population. Quantitative risk assessment has been a cornerstone in evaluating risks of environmental carcinogens and we anticipate increasing application to non-carcinogenic health effects of environmental agents, including air pollution.

In interpreting the findings of risk assessments, guidance can be found in precedents offered by key interpretations of regulatory requirements, including the Supreme Court's decision on the benzene standard proposed by the Occupational Safety and Health Administration, and in pollutant-specific regulatory actions. Risks may be couched as the numbers of attributable events in the population and also as the level of risk incurred by individual members of the population.

The committee recognized the rising use and potential utility of quantitative risk assessment in characterizing the health effects of air pollution. However, the committee noted that the results of quantitative risk assessment can often be sensitive to assumptions regarding the distribution and magnitude of exposure, the choice of an appropriate dose-response relationship, and other input decisions. Judgments on acceptability of risk are societal and made through complex regulatory

processes involving extensive public input. The committee did not consider that its mandate extended to offering specific guidance on acceptable risk levels for populations or individuals, nor is risk assessment an appropriate basis for determining what constitutes an adverse effect.

CONCLUSIONS

Since the preparation of the 1985 statement of the American Thoracic Society, there have been tremendous advances in the scientific methods used to investigate the health effects of air pollution. These advances range from the molecular to the behavioral levels of inquiry. As a result, this statement covers topics that are new since the 1985 statement. Yet, this committee, like the 1985 group, was confronted by a lack of formal research or investigation on the very topic of this statement: the boundary between adverse and nonadverse effects. Consequently, the committee needed to exercise its collective judgment on matters that should be based in some broader, societal decision-making **process. Its recommendations are summarized below.**

- ***Biomarkers.*** Few of the rapidly growing list of candidate biomarkers have been validated sufficiently that their responses can be used with confidence to define the point at which a response should be equated to an adverse effect warranting preventive measures. The committee cautions that not all changes in biomarkers related to air pollution should be considered as indicative of injury that represents an adverse effect.
- ***Quality of life.*** Decreased health-related quality of life is widely accepted as an adverse health effect. For this reason, measurable negative effects of air pollution on quality of life, whether for persons with chronic respiratory conditions or for the population in general, were consequently considered to be adverse by this committee.
- ***Physiological impact.*** The committee recommends that a small, transient loss of lung function, by itself. should not automatically be designated as adverse. In drawing the distinction between adverse and nonadverse reversible effects, this committee recommended that reversible loss of lung function in combination with the presence of symptoms should be considered adverse. This committee considered that any detectable level of permanent lung function loss attributable to air pollution exposure should be considered adverse.
- ***Symptoms.*** The committee judged that air pollution-related symptoms associated with diminished quality of life or with a change in clinical status should be considered adverse at the individual level.
- ***Clinical outcomes.*** The present committee shared the view of the previous group: detectable effects of air pollution on clinical measures should be considered as adverse.
- ***Mortality.*** This committee agreed with the conclusion articulated by the 1985 group that any effect on mortality should be judged as adverse. In addition, we are now faced with the challenge of interpreting the findings of time-series studies of effects on short time frames. In interpreting this type of evidence, consideration needs to be given to the extent of life-shortening underlying the association.
- ***Population health versus individual risk.*** Assuming that the relationship between the risk factor and the disease is causal, the committee considered that such a shift in the risk factor distribution, and hence the risk profile of the exposed population, should be considered adverse, even in the absence of the immediate occurrence of frank illness.

This statement was prepared by an ad-hoc committee of the Assembly on Environmental and Occupational Health. Members of the committee are:

JON SAMET, M.D., ***Co-chair***
SONIA BUIST, **M.D.**, ***Co-chair***
REBECCA BASCOM, M.D.
JOE GARCIA, **M.D.**
MICHAEL LIPSETT, M.D.
JOE MAUDERLY, D.V.M.
DAVID MANNINO, **M.D.**
CYNTHIA RAND, **Ph.D.**
ISABELLE ROMIEU, M.D.
MARK UTELL, **M.D.**
GREGORY WAGNER, **M.D.**

Workshop Participants
DAVID V. BATES, M.D.
MELVIN L. BILLINGSLEY, **Ph.D.**
MICHAEL GELOBTER, M.D.
BENJAMI F. HOBBS, **Ph.D.**
STEPHEN KLEENBERGER, **Ph.D.**
NANCY KLINE LEIDY, **Ph.D., R.N.**
STEPHANIE LONDON, **M.D., Dr.P.H.**
WILLIAM F. MCDONNELL, M.D., Ph.D.
DIETER SCHWELA, **M.D.**
JAMES C. WILEY, **M.D.**

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