SUSCEPTIBILITY TO INHALED POLLUTANTS

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Foreword

The Conference on the Susceptibility to Inhaled Pollutants was presented 29 Sept. through 1 Oct. 1987 at Williamsburg, VA. The Conference was sponsored by The American Lung Association, The American Petroleum Institute, The Electric Power Research Institute, The Health Effects Institute, The Natural Resources Defense Council, and the U.S. Environmental Protection Agency. Mark J. Utell, The University of Rochester School of Medicine, and Robert Frank, Johns Hopkins University, served as chairmen of the conference and are editors of the resulting publication.

Contents

Preface

In the legislative history to the Clean Air Act Amendments of 1970, the Senate described how broad the protection afforded by air quality standards was to be as follows [*1*]:

> In requiring that national ambient air quality standards be established at a level necessary to protect the health of persons, the Committee recognizes that such standards will not necessarily provide for the quality of air required to protect those individuals who are otherwise dependent on a controlled internal environment such as patients in intensive care units or newborn infants in nurseries. However, the Committee emphasizes that included among those persons whose health should be protected by the ambient standard are particularly sensitive citizens such as bronchial asthmatics and emphysematics who in the normal course of daily activity are exposed to the ambient environment. In establishing an ambient standard necessary to protect the health of these persons, reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group.

The consequences of this directive are not surprising. Concern for the most sensitive or susceptible groups within the general population drives the setting of air quality standards. In turn, much of the health-research must focus on identifying sensitivity, pollutant by pollutant. At the most fundamental levels of research, there is interest in determining the mechanisms for specific forms of sensitivity.

The U.S. Environmental Protection Agency carries out the mandates of the Clean Air Act. In defining sensitivity, the Agency has stated [*2*]:

> The population at risk is a segment of a defined population exhibiting characteristics associated with significantly higher probability of developing a condition, illness, or other abnormal status. This high risk may result from either greater inherent susceptibility or from exposure situations peculiar to that group. What is meant by inherent susceptibility is a host characteristic or status that predisposes the host to a greater risk of heightened response to an external stimulus or agent.

Here, sensitivity is couched in terms of risk. It is an expensive definition, one that includes within its bounds, groups who are at risk because of exaggerated exposure as well as those who have some innate, predisposing trait. The most obvious way of exaggerating exposure is, of course, through exercise.

It is against this background of regulatory concerns and scientific interests that a conference entitled Susceptibility to Inhaled Pollutants was held in Williamsburg, VA, in Sept. 1987. The agenda, although scientific, remained cognizant of the central role of such information to standard setting, as discussed in the paper of Dr. Lippman. The sessions dealth with five major topics: markers of susceptibility; characterization of study groups and responses to exposure; exercise and regional dosimetry; and in the last two sessions, different models of

susceptibility, in particular, asthma. The book that follows is a peer-reviewed record of the conference, organized along much the same lines.

The editors wish to thank the Organizing Committee and their sponsoring agencies—the American Lung Association, American Petroleum Institute, Electric Power Research Institute, Health Effects Institute, Natural Resources Defense Council, and U.S. Environmental Protection Agency—for their support of the workshop on which this book is based.

References

[1] Senate Committee on Public Works: A Legislative History of The Clean Air Amendments of 1970, Serial No. 93-18, 93rd Congress, 2nd Session, 411, 1974.
[2] U.S. EPA Air Quality Criteria for Lead. Chapter 13, Page 11, 1977.

Joseph D. Brain[1]

The Susceptible Individual: An Overview

REFERENCE: Brain, J. D., **"The Susceptible Individual: An Overview,"** *Susceptibility to Inhaled Pollutants, ASTM STP 1024,* M. J. Utell and R. Frank, Eds., American Society for Testing and Materials, Philadelphia, 1989, pp. 3–5.

ABSTRACT: Understanding and describing variations in responsiveness to inhaled toxins among individuals is a challenging intellectual task as well as as essential step in the regulatory process. Both altered exposure-dose relationships and dose-response relationships can contribute to the process. Better assessment of the degree of susceptibility and the number and geographical distribution of more responsive individuals is urgently needed. Only then can we design and implement strategies to protect all individuals.

KEY WORDS: air pollution, susceptibility, respiratory tract, variability

This Special Technical Publication (STP) focuses on familiar questions frequently asked, which I would like to address in this general overview. For millennia, humans have wondered why only some individuals become sick or die when all are exposed to a common poison or contagion. To what extent does the distribution and severity of disease reflect divine providence, guilt, and chance, or are some individuals predisposed to disease? If some are more susceptible, what are the responsible mechanisms? How much more susceptible are they? Are they 10% more vulnerable or is their risk of getting a disease when exposed to the same concentration of a toxin ten times greater? Does an increase in individual risk relate to higher doses of toxins at critical sites in the body, or do other biological mechanisms such as the potency of repair mechanisms and differences in metabolism increase vulnerability? These questions are now being addressed and slowly answered. A recently published book summarizes the area in relation to inhaled pollutants [*1*].

For most of the criteria pollutants now regulated by the Environmental Protection Agency, the question of susceptible populations looms large. Are children exposed to oxides of nitrogen or to ozone more affected than adults? Because of their greater activity and because of developing lungs, children may be more susceptible. A publication by the World Health Organization [*2*] has addressed the question of children's susceptibility to chemicals and has emphasized that different considerations apply. The summary of the report is, "The infant and young child have different structural and functional characteristics from those of the older child and adult. These represent stages in normal growth and development and may affect their vulnerability when exposed to chemicals."

Even the unborn child is frequently designated as a susceptible individual. During the first trimester, embryos are known to be particularly susceptible to teratogenic agents because that is the crucial period of organogenesis. What about the fetus of a mother who smokes and also lives at high altitude? Is such a fetus, which already has a higher level of carboxy-

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hemoglobin and lower phosphorus oxides (PO_2s) more susceptible to carbon monoxide released from cars and trucks? The Environmental Protection Agency has also considered the fetus and the child as being more susceptible to lead, another criteria pollutant.

The airways of asthmatics are more responsive to a variety of stimuli. Therefore, these people may have lower thresholds to a specific concentration of pollutant gases or particles than healthy, nonasthmatic subjects. For example, a recent paper by Mohsenin [*3*] reported that asthmatics, but not normals, develop heightened airway reactivity after exposure to 0.5 ppm nitrogen dioxide.

When considering the effects of carbon monoxide, there is concern for individuals with advanced cardiovascular disease. Will increased carbon monoxide levels in urban centers decrease the time to the onset of angina or make the pain more severe in patients with compromised coronary blood flow? Several clinical studies recently carried out by the Environmental Protection Agency and the Health Effects Institute address this question. Their outcome will be of relevance to the carbon monoxide (CO) standard. Other familiar examples of increased susceptibility by the elderly and sick are the well-known air pollution episodes in Donora, PA (October 30, 1948); London, England (December 5–12, 1952); and the Meuse Valley in Belgium many decades ago. In these extreme situations, thousands of individuals with preexisting heart and lung disease were affected the most and were most likely to die.

Enhanced susceptibility to a given concentration of a toxic material in inspired air may reflect either variations in innate responsiveness or simply altered exposure-dose relationships. Many published papers clearly demonstrate that many variables influence the amount and distribution of retained particles in the respiratory tract even when their concentrations in the air are constant. For example, changes in breathing pattern caused the deposition fraction (collection efficiency) to range from 1 to 42% and the sites of particle deposition to change [*4*]. Although all individuals in a given city or building breathe the same air, we should not assume that the resulting doses at critical sites in the body are equivalent. For example, breathing by mouth and the increase in ventilation caused by exercise will markedly increase the pulmonary dose of large particles and soluble gases to the airways. Activity level, age, smoking, preexisting disease, and other factors are all known to influence exposure-dose relations.

Even if the dose of the agent or one of its key metabolites to the sensitive target was equal among individuals, would their responses be identical? The capacity for response to the agent would still vary. For example, the tendency of airways to constrict is greater in asthmatics than in normal individuals even when both groups experience the same dose of a bronchoconstrictor drug. In other individuals, genetic determinants may influence the circulating levels of antiproteases or antioxidants in the blood, which protect against inflammatory responses caused by some inhaled gases. Genetic factors may even regulate the velocity of mucus transport in the trachea [*5*]. A major purpose of this meeting is to identify and quantify those factors that modify exposure-dose relations as well as subsequent dose-response relations.

We cannot adequately describe the range of susceptibility among individuals by simply identifying them as fetuses, asthmatics, or smokers. We need to find better ways to carefully characterize each individual. This goal demands a new kind of statistics. Variability is no stranger to biological processes; expectations of variability are always fulfilled in the real world as well as in controlled laboratory environments. Yet most statistical techniques emphasize measures of central tendency and their variability. Few of us focus on extremes when analyzing and reporting our data. We need to emphasize and understand the tails of the bell shaped curve as well as the center. We need to develop techniques to determine the extent to which the variations inevitably seen reflect random measurement error in contrast with true and reproducible differences in response. We also need to encourage investigators to present data on all the animal or human subjects evaluated in each study.

There is still the tendency for many scientists to eliminate subjects whose responses are extreme compared to the group mean. In fact, we need to devote special attention to these individuals whose responses are unusual. Are the same individuals always less responsive or more responsive to a given toxin? Quantifying their responses is essential in identifying safe levels. Moreover, the mechanisms responsible for their unusual response may give important clues to the mechanisms of injury.

Another key issue is not only to identify and characterize susceptible individuals, but also to measure how many there are. Where do they live, and what is the degree of their heightened or diminished responsiveness? Definitions are important. If a scientist tells us that asthmatics are more responsive to a particular material, objectively defining the kind of asthmatic being studied is essential. Are we studying the top 10% of a curve describing airway reactivity in the population, the top 1%, or the top 0.1%? Because of ethical constraints with experimental exposures in humans, the most responsive individuals are rarely studied.

Finally, realizing that susceptible individuals are not exotic, improbable species is essential. The individuals who make up susceptible groups change with time. All of us have been or will become more susceptible to one substance or another as we pass from the cradle to the grave. Most of us will suffer periodically from trauma and infectious disease. These conditions may alter our response to some toxic materials. Other aspects of life-style that alter exposure-dose relations are also widely distributed. Work, exercise, smoking, and certain aspects of diet are common variables that affect responsiveness. Increasing age is another universal factor that makes individuals more vulnerable to the harmful effects of inhaled particles and gases. There is a progressive loss of cardiopulmonary function and cancer becomes increasingly likely. The history of catastrophic pollution episodes such as those that occurred in London during the 1950s make abundantly clear that elderly individuals who suffer from chronic diseases, especially those of the cardiopulmonary system, are more severely affected by air pollution than young healthy individuals. Furthermore, demographic projections indicate that the number of elderly people living in cities and thus exposed to urban air pollution will continue to increase in the United States during this century.

Conclusion

There is a growing awareness in regulatory agencies, the Congress of the United States, and especially among the public that individuals do vary in their susceptibility, and that these differences must be measured and expressed in environmental and occupational policy. A better understanding of these issues will permit us to design better experiments to elucidate and quantify variations in susceptibility as well as to improve statistical methods needed to analyze the results. I believe this information will in turn improve our ability to protect all individuals.

References

[1] *Variations in Susceptibility to Inhaled Pollutants—Identification, Mechanisms, and Policy Implications*, J. D., Brain, B. D., Beck, A. J., Warren, and R. A., Shaikh, Eds., The Johns Hopkins Press, Baltimore, 1988.

[2] "Environmental Health Criteria 59: Principles for Evaluating Health Risks from Chemicals During Infancy and Early Childhood: The Need for a Special Approach," World Health Organization, Geneva, 1986.

[3] Mohsenin, V., "Airway Responses to Nitrogen Dioxide in Asthmatic Subjects," *Journal of Toxicology and Environmental Health*, Vol. 22, 1987, pp. 371–380.

[4] Valberg, P. A., Brain, J. D., Sneddon, S. L., and LeMott, S. R., "Breathing Patterns Influence Aerosol Deposition Sites in Exercised Dog Lungs. *Journal of Applied Physiology: Respiratory and Environmental Exercise Physiology*, Vol. 53, 1982, pp. 824–837.

[5] Brownstein, D. G., "Tracheal Mucociliary Transport in Laboratory Mice: Evidence for Genetic Polymorphism," *Exp. Lung Research*, Vol. 13, 1987, pp. 185–191.

Morton Lippmann[1]

The Influence of Responses in Susceptible Populations in Establishing Standards for Ambient Air Pollutants

REFERENCE: Lippmann, M., **"The Influence of Responses in Susceptible Populations in Establishing Standards for Ambient Air Pollutants,"** *Susceptibility to Inhaled Pollutants, ASTM STP 1024*, M. J. Utell and R. Frank, Eds., American Society for Testing and Materials, Philadelphia, 1989, pp. 6–20.

ABSTRACT: This paper reviews the ways in which pollutant-related responses among especially susceptible population groups affect the establishment of primary (health related) National Ambient Air Quality Standards (NAAQSs). It includes the Environmental Protection Agency's (EPA's) interpretation of its statutory authority for addressing such considerations in standard setting; definitions of terms such as adverse effects, adequate margin of safety, and sensitive population groups; and a summary of the actions taken in setting standards for the six criteria pollutants, carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter (PM), sulfur dioxide (SO_2), ozone (O_3), and lead (Pb). In each case, the NAAQSs have been selected to provide protection against either known or hypothetical responses among one or more susceptible subpopulations, such as angina in cardiovascular patients exposed to CO, bronchoconstriction in exercising asthmatics exposed to SO_2, and neurobehavioral responses in preschool children exposed to Pb.

KEY WORDS: susceptible population responses, ambient air pollutants, ambient air standards, adequate margin of safety, adverse health effects, carbon monoxide, nitrogen dioxide, particulate matter, sulfur dioxide, ozone, lead

The current National Ambient Air Quality Standards (NAAQSs) have been based primarily on responses in susceptible segments of the population, and such responses have continued to be a major focus in considering revisions of NAAQSs. The specific wording and legislative history of the Clean Air Act (CAA) of 1970 provides the basis for thorough consideration of responses in such groups in establishing NAAQSs. This paper reviews the pertinent parts of the CAA, its legislative history, and the subsequent interpretations and implementations as they apply to identifying and considering susceptible populations in the setting of NAAQSs. It is based largely on knowledge gained as a participant (1980 to 1987) in the public reviews by the Environmental Protection Agency's (EPA's) Clean Air Scientific Advisory Committee (CASAC) of Criteria Documents (CDs) and Staff Papers (SPs) for the so-called criteria pollutants, that is, carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter (PM), sulfur dioxide (SO_2), ozone (O_3), and lead (Pb). The NAAQSs for these pollutants specify the concentration limits for ambient air in terms of specific averaging times and the frequency of permissable exceedances. The other EPA air stan-

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dards—those for the so-called hazardous air pollutants—are known as National Emission Standards for Hazardous Air Pollutants (NESHAPs). As of this writing, there are NESHAPs for nine pollutants, and an "intent to regulate" decision made for ten others [*1*]. NESHAPs are based primarily on the application of specific source control technologies, and will not be reviewed here.

The legal and administrative basis for the establishment and revision of NAAQSs by EPA was summarized by the Office of General Counsel in January 1981 in a working draft. While this draft never became a formal EPA document, its contents have in practice been consistently applied in the NAAQS process, and I will summarize those parts of it which pertain to the role of susceptible populations in setting NAAQSs. I will also summarize the consideration given to susceptible populations in setting NAAQSs for each criteria pollutant. For this latter summation, I have drawn heavily on a paper presented by Grant and Jordan [*2*] at the 1985 Annual Meeting of the Air Pollution Control Association.

Definitions

Primary Standards

Primary standards "shall be ambient air quality standards the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health" (Section 109 (b) (1), CAA of 1970). They are uniform, nationwide standards, applicable every place in the country, and are to be attained within three years from the date on which state implementation plans are approved (Section 110 (1) (2) (A), CAA of 1970). This definition necessitates, in turn, a definition of an adequate margin of safety.

Adequate Margin of Safety

Congress specified that the primary NAAQS include an "adequate margin of safety" to protect against effects that have not yet been uncovered by research and effects whose medical significance is a matter of disagreement. The requirement for a margin of safety underscores that the primary NAAQSs are not simply intended to protect against health effects that are known to be clearly harmful; Congress authorized the EPA Administrator to exercise judgment in setting NAAQSs precisely to permit action in the face of uncertainty.

Sensitive Population Groups

Congress did not intend that only healthy persons be protected by the NAAQSs. At the same time, the standards were not intended to protect those dependent on a controlled internal environment, such as persons in intensive care units. Instead, Congress emphasized 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" (*Legislative History of Clean Air Act Amendments of 1970*). The standard is statutorily sufficient whenever there is "an absence of adverse effect on the health of a statistically related sample of persons in sensitive groups from exposure to the ambient air." Congress defined a statistically related sample as "the number of persons necessary to test in order to detect a deviation in the health of any person within such sensitive group which is attributable to the condition of the ambient air." For this discussion, it will be assumed that "sensitive" groups are functionally equivalent to "susceptible" groups.

The ways in which these guidelines have been applied in the NAAQS revision process will be described later in this paper for each of the criteria pollutants.

The application of the definition of the protection of particularly sensitive citizens from an adverse effect requires, in turn, a definition of "adverse effect."

Adverse Effects

The primary standards are not intended to protect against all identifiable effects, but only those judged by the Administrator to be "adverse." However, because the primary NAAQS were intended by Congress to be precautionary and preventive, the Administrator is not free to define as adverse only those effects that are clearly harmful or for which there is a medical consensus about the degree of harm. Rather, the Administrator must evaluate reasonable medical concerns and theory in deciding which effects are significant enough to be considered adverse.

The health effects Congress was concerned about at the time the 1970 amendments were enacted ranged from cancer, metabolic and respiratory diseases, and impairment of mental processes, to "headaches, dizziness, nausea . . ." (*Legislative History*). To put the health effects intended to be protected against by the NAAQS in some perspective, Congress elsewhere directed that if a pollutant is found to result in an increase in "serious irreversible, or incapacitating reversible, illness," it would qualify for regulation as a hazardous pollutant under Section 112 of the 1970 CAA.

A more specific outline of the EPA's thinking on adverse effects has been presented by Padgett and Richmond [*3*] of the Office of Air Quality Planning and Standards (OAQPS).

> The scientific literature is the key to the identification of adverse health effects, but frequently the literature is not sufficient to clearly establish whether an observed effect is in fact adverse or at what level of exposure the effect occurs. For example, many air pollutants cause a temporary degradation in lung function. When this degradation is sufficiently high, there is little doubt that the resulting effect on human health is adverse. However, there is considerable disagreement among scientists as to how much degradation one must experience before this effect should be considered adverse. Likewise, the literature indicates that some air pollutants cause physiological or symptomatic responses, such as running noses or coughs. In these cases, EPA must assess the potential that these symptomatic effects are indicators of other more serious health effects. Often there is no scientific consensus as to the implication of such effects but the scientific and medical communities clearly are the most qualified to offer guidance concerning the medical significance of these effects . . . However, at the margin where effects are often subtle and reasonable scientists disagree about their importance, the Administrator must ultimately judge which effects should be regarded as "adverse" for standard-setting purposes.

In 1985, The American Thoracic Society (ATS) published guidelines as to what constitutes an adverse respiratory health effect, with special reference to epidemiologic studies of air pollution [*4*]. Some parts which pertain directly to respiratory function effects follow:

> Not all changes (e.g., physiologic) are necessarily adverse. This is illustrated by the reaction of carbon monoxide with hemoglobin. There is a continuum of detectable response (carboxyhemoglobin formation) at increasing levels of carbon monoxide exposure. The Environmental Protection Agency (EPA) has decided, for the present, that concentrations of carboxyhemoglobin in the blood above 2.5% produce medically significant adverse effects and are not acceptable, whereas concentrations below 2.5% are associated with trivial effects and are acceptable . . .
>
> Considering the degree of reversible effects that can be tolerated by an individual or by population groups leads to the question, "What percentage irreversible change in pulmonary function should be considered adverse?" The measurements have a certain amount of variability that must be taken into account. The degree of variability will also depend on whether comparisons of population groups are on a cross-sectional basis, or whether each person is used as his or her own control in a prospective study. Thus, the percentage change that indicates an adverse effect can vary from group to group and situation to situation.

> The rate at which a functional attribute, such as FEV_1 or FVC, increases or decreases with growth or aging can also be used to assess whether an effect is adverse or not. A statistically significant increased rate of decline of pulmonary function with aging should be considered adverse. Identification of such trends requires repeated examinations over a period of years to define the trend adequately, and to avoid cohort effects that might bias a cross-sectional study. Similarly, with children, failure to maintain their predicted lung-growth curve should also be considered to be adverse. These effects should be associated with air pollution concentrations to be relevant.

While this guidance from ATS helps place things in perspective, it fails to provide concrete criteria on acceptable functional changes in relation to setting NAAQSs. In the absence of authoritative guidance, the process of setting NAAQSs has evolved in recent years through the preparation and reviews of criteria documents, staff papers, and *Federal Register* proposals and promulgations. The EPA staff and CASAC have agreed *ad hoc* on a number of specific judgements concerning adverse effects. For example, an increase in the frequency of episodes of angina, more frequent provocation of asthmatic attacks, and increased incidence of respiratory tract infections have been judged adverse effects. There also has been consensus on adverse effects that do not occur as discrete events, such as reduced average IQs in children in proportion to lead exposure.

Decrements in the average level of a respiratory function index fall into the latter category. While it is agreed that the effects are adverse at some magnitude, there have been clear differences of opinion on what the threshold of adversity ought to be. The 1979 O_3 NAAQS promulgation (44 FR 8207) indicated that the EPA's summation of experts' judgements led to a 5 to 15% decrease in function as range of the boundary. On the basis of this criterion, the current O_3 NAAQS has essentially no margin of safety. Based on a study of respiratory function in 91 summer camp children, Spektor et al. [5] reported that the mean FEV_1 decrement at the current O_3 NAAQs was 7.7%, while the decrement in the upper decile of the population was $\geq$19%. The corresponding responses for FVC were 4.9 and 14%, for midmaximal expiratory flow (MMEF), 11 and 33%, and for peak expiratory flow rate (PEFR), 17 and 42%.

The World Health Organization-European Region (WHO-Euro) has recently prepared Air Quality Guidelines [6]. In their guidelines for SO_2 and particulate matter, they judged that effects of health concern, in terms of changes in FEV_1 in children, began at 180 $\mu g/m^3$ of total suspended particulate matter (TSP) in association with SO_2. This was based on an FEV_1/TSP response of 0.39 $mL/\mu g/m^3$. Thus their level of concern arose at an average decrement of 70 mL, or ~3%.

Consideration of Responses in Susceptible Populations for the Criteria Pollutants

Basis for 1985 CO NAAQS

The evidence cited as the basis of the original (1971) NAAQS for CO regarding the impairment of the ability to discriminate time intervals could not be replicated. Therefore, this evidence could not be used for standard-setting in the revisions required by the 1977 CAA.

New evidence of health effects from CO exposure published since 1971 was evaluated in the revised Criteria Document for CO (EPA-600/8-79-022) and in a 1979 OAQPS Staff Paper (SP). In assessing new CO research, the EPA identified cardiovascular system effects as one of several types of effects attributed to CO. The EPA stated that aggravation of angina pectoris by CO [7,8] is an adverse health effect for at least two major reasons. First, the angina reflects hypoxia, which may also result in cardiovascular damage that is un-

quantifiable using present technology. Second, aggravation of angina may be the first in a series of progressively more serious symptoms that accompany cardiovascular disease. The EPA concluded that CO exposures resulting in carboxyhemoglobin (COHb) levels of 2.7 to 2.9% were linked to adverse health effects in some portion of the estimated five to seven million persons with angina pectoris in the U.S. population, making such persons the "susceptible population."

The revised Criteria Document (CD) was published on 18 August 1980 with the *Federal Register* notice of proposed rulemaking (45 FR 55066). As a result of the review and revision of criteria, the EPA proposed to retain the existing primary 8-h standard at 9 ppm and to lower the primary 1-h standard to 25 ppm.

No further actions were taken with respect to the revision of the CO NAAQS until developments in early 1983 caused the EPA to question the validity of some of the research cited in 1979. The EPA assessed the impact on the CO standards of the reduced data base, as evaluated in an Addendum to the 1979 CO Criteria Document (EPA-600/8-83-033F) and CO staff paper (EPA-450/5-83-004), both of which were reviewed in draft by CASAC in September, 1983. Based on this review, EPA staff concluded that cardiovascular patients must be protected from ambient CO. The CASAC supported the Staff Paper recommendations that the 8-h standard be set within the range of 9 to 12 ppm and the 1-h standard be set within the range of 25 to 35 ppm. The original, 1971 CO NAAQS of 9 ppm for 8 h and 35 ppm for 1 h was reaffirmed in September, 1985.

Basis for Lead NAAQS

On 5 October 1978, the EPA published in the *Federal Register* (43 FR 46246) a NAAQS for lead at a level of 1.5 μg lead per cubic meter of air (μg Pb/m^3), averaged over a calendar quarter.

In establishing the level of the primary standard, the EPA determined that young children (aged one to five years) should be regarded as a group within the general population that is particularly sensitive to lead exposure. The lead NAAQS is based on preventing most (99.5%) children in the United States from exceeding a blood lead level of 30 μg per deciliter of blood (μg Pb/dL). The selection of 30 μg/dL as a "maximum safe" blood lead level was the same as the selection in 1978 made by the Centers for Disease Control of the Public Health Service (and endorsed by the American Academy of Pediatrics) as reflecting undue pediatric exposure to lead.

Based on data used to determine the maximum safe blood lead level for an individual child, the EPA took into account variations in individual susceptibilities and lead exposures in determining a maximum safe geometric mean blood lead level for the sensitive population as a whole. Given a log normal population distribution of blood lead with a geometric standard deviation of 1.3, the maximum safe geometric mean blood lead level for young children was determined to be 15 μg Pb/dL to keep 99.5% of the pediatric population below the level of 30 μg Pb/dL.

The EPA further calculated, based on then-available epidemiological data, that out of the target population mean blood lead level of 15 μg Pb/dL, 12 μg Pb/dL should be attributed to "nonair" lead sources unaffected by a lead NAAQS (43 FR 46246). That left a contribution of 3 μg Pb/dL to blood lead levels from air sources. Studies of changes in blood lead levels with different air lead levels were then used to estimate an "air-lead to blood-lead ratio" of 1:2. This means that a continuous exposure to 1.5 μg Pb/m^3 air would be expected to increase a child's blood lead level by 3 μg Pb/dL. Thus, a level of 1.5 $\mu g/m^3$ was selected for the lead NAAQS.

Since promulgation of the NAAQS for lead in 1979, considerable improvements have occurred in the lead data base. Included among major issues and important findings evaluated in the June, 1986 Pb CD are that

1. Demographic covariates influence lead exposure in U.S. populations, and blood lead levels tend to be higher among urban nonwhite children in lower-income families.
2. Children's blood lead levels are affected by the relationships between absorbed lead and external lead exposure, either directly through inhalation, or indirectly via soil, dust, or the food chain.
3. Studies utilizing analyses of stable lead isotope ratios to determine sources (e.g., gasoline, paint, soil, dust, food) of lead in blood indicate that air lead, either absorbed directly via inhalation or indirectly via ingestion, contributes significantly to total human body burdens of lead.
4. Health effects associated with low-level lead exposures of children include small, but significant, deficits in IQ, school performance, and social behavior. These have been associated with children with blood lead levels as low, and possibly lower, than the 40 μg/dL threshold level for hemoglobin decrements. Other types of neurotoxic effects, such as altered electrophysiological brain wave patterns in children (as well as altered peripheral nerve conduction velocities in adults), have also been reported at lower levels. The medical significance of these findings remain to be fully defined. They are, however, generally consistent with low-level, lead-induced alterations in several neurotransmitter systems and in neural subcellular functions, such as mitochondrial respiration and protein synthesis. Disruption of vitamin-D metabolism and other indications of widespread impacts of lead-induced interference with synthesis of heme in many organ systems have also been found at blood lead levels that range well below 30 μg/dL.
5. Health effects associated with exposures of adults include lead-induced blood pressure increases. In light of the emerging evidence on the relationship between hypertension and blood lead range levels of ≥30 to 40 μg/dL to ≤10 to 15 μg/dL, white males aged 40 to 59 have been identified as yet another subpopulation potentially at risk. This subpopulation accompanies other traditionally accepted groups at risk: preschool-aged children (age six and below) and pregnant women (owing to the risk to the fetus).

CASAC's closure letter of 29 August 1986 on the Pb CD concluded that the blood lead level at which adverse health effects are recognized as beginning to appear has fallen rather sharply since 1977, when the previous Air Quality Criteria Document for Lead was published. This clearly has implications for the level of the standard and for the appropriate margin of safety to be considered when the NAAQS for Lead is revised. For example, the onset of detectable heme synthesis impairment in children may occur at blood lead levels starting around 10 to 15 μg/dL. Along with indications of increasing degrees of interference in pyrimidine and vitamin-D metabolism, as well as alterations in central nervous system activity at these same levels, this may be biomedically adverse.

In addition, the emerging data on the effects of perinatal exposure to low levels of lead on physical and neurobehavioral development appears to indicate that fetal exposure to lead at levels as low as 15 μg/dL can have undesirable effects on infant mental development, the length of gestation, and possibly other aspects of growth and development.

The EPA has not completed a final version of its Staff Paper for Pb. In a letter of 29 August 1986 to the Assistant Administrator for Air and Radiation, CASAC recommended