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December 30, 1983

Honorable William D. Ruckelshaus
Administrator
U.S. Environmental Protection
Agency
401 M St. SW
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

The Clean Air Scientific Advisory Committee (CASAC) of the Science Advisory Board has completed its assessment of research needed to support the development of National Ambient Air Quality Standards (NAAQS). The Committee reviewed the existing data base for four of the criteria pollutants--carbon monoxide, nitrogen oxides, particulate matter and sulfur oxides--as a means of addressing your request of September 1 that the Agency and the Committee work to improve research planning efforts geared to fulfilling regulatory information requirements.

The Committee has approached the issue of research needs assessment with several key assumptions and perspectives in mind. These include:

- the enforcement of ambient air quality standards imposes large compliance costs upon private industry; in addition, the Clean Air Act requires that you set the standards at a level that protects public health with an adequate margin of safety. It is therefore imperative that such standards be based upon a scientific data base that identifies and resolves the critical issues of public health and welfare for decision-makers. The Committee feels compelled to point out to you, the Office of Management of Budget (OMB) and to the Congress that large gaps exist in our understanding of these pollutants which have already resulted and will continue to result in extended controversy regarding the appropriate level of control of criteria pollutants. Given the magnitude of the compliance costs and the importance of public health protection, the EPA research program for ambient pollutants can only be characterized as an underfunded series of efforts to support the Agency's mission for setting NAAQS. Simply stated, the research program does not meet decision-makers' current information needs. The Committee has attempted to define research priorities, including epidemiology and personal exposure assessment, to assist you in the development of scientific data bases for standard setting.

● it is the responsibility of the Environmental Protection Agency (EPA) to conduct or sponsor research to resolve critical research questions related to setting ambient air standards. It is a fallacy to assume that other agencies of the Federal government will carry out research, such as epidemiology, that will systematically address EPA's direct information needs for setting specific standards. It is also clear that the Congress has recognized this need for such information and the important link between research and regulatory decision-making by its authorization of EPA's ambient air research program.

● historically, many EPA and OMB program managers have viewed the short-term technical assessment and the longer term components of EPA research as pursuing incompatible or unrelated objectives. In reality, both elements can serve to support the Agency's fundamental mission in the ambient standards program: to identify, assess and abate the risk posed by ambient air pollutants to the public health and welfare. Viewed in this context, the strategic mission of the ambient air research program, in both the current fiscal year as well as over a longer time frame, is to develop and advance the technical basis for risk assessment.

The enclosed report is the first of a series of periodic CASAC reviews that will address research needs for the development of ambient air quality standards. In this particular review emphasis has been placed on identifying research most directly related to the development of the primary health-based standards. Due to time constraints much less attention has been placed on the many important research issues associated with atmospheric processes and welfare effects. These issues will continue to be of concern to CASAC and will be reviewed in a future report.

The benefits of this CASAC review process include providing advice to insure that orderly and adequate progress is being made in the research program directed by the Office of Research and Development (ORD) and providing guidance for your adjustment, as necessary, of the research planning process and the statement of research goals to take into account any new information or changing regulatory requirements. It is also the Committee's understanding from ORD program managers that future air quality criteria documents will include a research needs assessment that will be reviewed by CASAC as part of the criteria document. The Committee sees a major advantage in this approach because the document will include guidance on research needs at the same time there is the most thorough review of the scientific data base and the strongest focus on regulatory information requirements.

The Committee is pleased to respond to your request for advice on criteria pollutant research needs as a way to ensure that the setting of NAAQS is based upon the best possible scientific evidence. I would be pleased to brief you on the content of CASAC's conclusions and recommendations contained in the enclosed report.

Sincerely,

Morton Lippmann, Chairman
Clean Air Scientific
Advisory Committee

Enclosure

cc: Mr. Alvin Alm
Mr. Joseph Cannon
Mr. David Gibbons
Dr. Bernard Goldstein
Mr. Fred Khedouri
Dr. Terry F. Yosie

RESEARCH NEEDS ASSESSMENT

FOR

SETTING NATIONAL AMBIENT AIR QUALITY STANDARDS

A Report of the Clean Air Scientific Advisory Committee

Science Advisory Board

U.S. Environmental Protection Agency

December 1983

NOTICE

This report has been written as part of the activities of the Environmental Protection Agency's Congressionally established Science Advisory Board, a public group providing advice on scientific issues. The Board is structured to provide a balanced, independent, expert assessment of scientific matters it reviews, and hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency nor of other agencies in the Executive Branch of the Federal government.

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I. EXECUTIVE SUMMARY

This is the first of a series of reports by the Clean Air Scientific Advisory Committee (CASAC) of the Science Advisory Board to review the U.S. Environmental Protection Agency's (EPA) research needs for the development and support of National Ambient Air Quality Standards (NAAQS). The report was prepared at the direct request of EPA Administrator William D. Ruckelshaus, who solicited CASAC to advise him on research needs associated with strengthening the scientific basis for setting NAAQS. The Committee met over a three month period to review EPA's assessment of its information needs, the scope of the research effort and its adequacy to policy questions.

The Committee is keenly aware that EPA's research program must be directed in a manner that addresses and resolves critical issues that confront policy makers during the standards setting process. In this sense EPA's inhouse and extramural research efforts are significantly different from those of other Federal research agencies, notably the National Institutes of Health and the National Science Foundation, which are not directly responsible for providing technical support for a regulatory program.

EPA's research efforts, to be successful, must encompass not only the support of regulatory programs under development in the next six months to a year but must include a research component to stimulate advances in the environmental sciences. The latter task involves a time commitment of several years, but it is geared to the same end as research carried out over a shorter time frame. In reality, both elements serve to support EPA's fundamental mission for setting ambient air quality standards: to identify, assess and abate the risk of criteria pollutants to the public health and welfare. Viewed in this context, the strategic mission of EPA's ambient air pollutant research program, in both the current fiscal year and over a longer time frame, is to develop and advance the scientific and technical basis for risk assessment. In addition, some of the research needs identified in this report should prove useful to addressing information needs for regulatory decision making under the Resource Conservation and Recovery Act, the Toxic Substances Control Act and other authorizing statutes which govern the Agency's activities.

It is clear that the existing literature on air criteria pollutants has provided significant information on their health and welfare effects. However, these studies also demonstrate the need to obtain additional data for improved risk assessment. In the past four years CASAC has reviewed air quality criteria documents for four pollutants. These include carbon monoxide (CO), particulate matter (PM), the oxides of nitrogen (NOx) and the oxides of sulfur (SOx).

The Committee has limited its review to these pollutants and will address research needs associated with lead and ozone at a future time. To carry out its review CASAC formed four subcommittees composed of well known experts representing a number of scientific disciplines.

EPA's inhouse and extramural ambient air research program has significant strengths and weaknesses. Some of the inhouse strengths include well developed capabilities in animal toxicology, human clinical studies and environmental assessment. Glaring weakness characterizes the Agency's program in epidemiological research (both inhouse and extramural), the use of its Research Centers Program and the paucity of support provided to the Peer Review/Investigator Initiated Grants Program. For each of these weaker programs EPA has not provided a critical mass of staff and dollar support for them to contribute in a truly meaningful way to generate information and provide technical support to the standards setting process.

Many extramural research programs that can support standards development need a budgetary commitment of more than one or two years, and mechanisms should be established to permit such support. Also, recommendations about which of the peer-review approved grants to fund should be made by a group of senior scientists who are familiar with the needs of the standards development program and who are not influenced by the short-term tactical needs and budgetary exigencies of the Agency. A key recommendation for improving the support of extramural research for standards development is the creation of a Council for Research on Ambient Standards Development. Such a Council would provide direction and oversight of the extramural research program to ensure that appropriate progress was achieved and timely results delivered, and should be supported on a continuing basis by a line item appropriation independent of other EPA research programs. The Council could also be helpful in communicating research needs to EPA, the Office of Management and Budget and the Congress to assist them in budgetary analyses.

To strengthen the scientific basis for its NAAQS regulatory program CASAC recommends that EPA develop and support, on a multi-year basis, a targeted research program that addresses five critical elements which are germane to all NAAQS. These include the development of strong programs in: 1) air pollution epidemiology; 2) extrapolation modeling; 3) research relating concentrations at air monitoring sites to human exposures; 4) research relating air pollution exposures to doses received by target sites within human populations; and 5) biological responses to multiple pollutant exposures.

CASAC further recommends that to improve EPA's risk assessment capability for the four pollutants evaluated in this report EPA should conduct and/or sponsor research to address specific research needs. The following represents the highest priority research needs identified by the Committee; other important needs are discussed in the body of the report. For particulate matter and sulfur oxides the critical research needs include 1) development of direct reading monitors for PM_{10}, and H_2SO_4 (sulfuric acid) or aerosol acidity; 2) development of ambient aerosol and fine particle data bases; 3) deposition efficiencies for SO_2 and particles in humans and experimental animals, the effects of exercise on deposition, and the effect of exercise on the clearance of particles from the tracheobronchial airways; 4) development of an animal model for respiratory airway irritancy bioassay; 5) progression of disease and dysfunction after chronic pollutant exposures; 6) continued studies of the effects of SO_2 on asthmatics and other sensitive population groups; and 7) studies on the effects of SO_2 in combination with and in sequence with other atmospheric factors. For nitrogen oxides the key CASAC research recommendations include 1) the application of state-of-the-art methodology to characterize the progression and reversibility of NO_2 associated chronic lung disease; 2) epidemiological studies that include improved personal exposure measurement of NO_2 to increase understanding of the role of NO_2 in the prevalence of respiratory infection in children living in homes with and without gas stoves; and 3) development of low-cost and widely deployable personal monitors for NO_2. For carbon monoxide, the most important information deficiencies relate to 1) effects on the cardiovascular system, and 2) neurobehavioral effects. A more extensive analysis and discussion of these most significant research needs is presented in the text of the report.

II. INTRODUCTION

A. Background

This report was prepared in response to a September 1, 1983 request of Mr. William D. Ruckelshaus, Administrator of the Environmental Protection Agency. He noted that the data bases available to him through the air quality criteria documents and air office staff papers for carbon monoxide (CO), nitrogen oxides (NO_x), sulfur dioxide (SO_2) and particulate matter (PM) were not much more complete than those on which he had based ambient air quality standards promulations in the early 1970's. He requested that CASAC advise him, by the end of December 1983, on research needs for ambient air standards. He indicated that he would direct the Agency to address those needs so that future EPA Administrators would have a scientifically firmer basis for revising or reaffirming air quality standards.

While the research recommendations contained herein are focused on the National Ambient Air Quality Standards (NAAQS), most of them would be applicable to data gaps affecting standards for Hazardous Air Pollutants (HAPs). They would also provide data which would greatly improve the basis for exposure assessments for airborne chemicals. EPA is currently trying to improve and unify its procedures for exposure assessment as a critical part of its program to apply improved risk assessment procedures to its regulatory programs. Thus, the research proposed here would be of great benefit to many programs other than air, especially those authorized by the Toxic Substances Control Act (TSCA), Resource Conservation and Recovery Act (RCRA) and Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

CASAC was able to respond to Mr. Ruckelshaus' request in the brief time available because of the prompt and effective cooperation it received from members of the EPA staff, especially from representatives of the Office of Air Quality Planning and Standards (OAQPS), and divisions of the Office of Research and Development (ORD) including the Environmental Criteria and Assessment Office (ECAO), Environmental Monitoring Systems Laboratory (EMSL), Environmental Sciences Research Laboratory (ESRL) and Health Effects Research Laboratory (HERL). In addition, CASAC had recently completed reviews of the air qualilty criteria documents for CO, NO_x, PM and SO_x. In the course of these reviews, it became clear that major gaps remain in current knowledge about the nature of the health effects, dose-response relationships, and temporal and spatial variations in the concentrations of criteria air pollutants. Furthermore, for pollutant classes such as NO_x

and SO_x, there are major temporal and spatial variations in the proportions present as vapors and those present as particles. Some of these chemicals are primary pollutants (e.g., nitric oxide [NO], and SO_2) which serve as precursors for atmospheric transformations to more toxic pollutants (e.g., nitrogen dioxide [NO_2], and H_2SO_4), which in turn are transformed to less toxic pollutants, e.g., NH_4NO_3, and $(NH_4)_2SO_4$. For the pollutant class known as particulate matter, which includes secondary aerosols resulting from the oxidation of NO_x and SO_x as well as ash, soil, diesel exhaust particles, etc., there are substantial variations in particle size distribution and trace contaminants which affect public health and welfare.

The gaps in our knowledge make the selection of NAAQS levels very difficult. In the face of the scientific uncertainties, an Administrator may feel impelled to utilize a greater margin of safety in selecting an NAAQS than would be necessary and prudent if there were a more adequate and reliable scientific data base. An excessively stringent NAAQS can impose enormous incremental societal costs in terms of the installation and maintenance of emission controls, additional monitoring of ambient air pollutants, and governmental enforcement activities.

The information gaps can be addressed by research programs which focus on the critical scientific questions confronting policy makers. While some of the information needs identified in the recent round of criteria document and staff paper reviews can be readily filled by short-term, highly targeted research projects, many others cannot. Thus, there is a need for longer term programs which enlist a broad range of investigators willing to make a continuing commitment to research in areas related to setting ambient air standards.

Some of the data gaps are already being addressed by the Office of Research and Development (principally the Office of Health Research, EMSL and HERL in a research program involving both intra- and extramural studies). Additional needed areas of research are being addressed under the auspices of the EPA Peer Review/Investigator Initiated Grants Program, the Health Effets Institute (HEI), and the National Institutes of Health (NIH). However, it is clear that these programs, collectively, fall far short of the needs.

The research proposed by CASAC will not provide all of the information that we can now identify as being useful in setting ambient air quality standards. It is focused primarily, as has been noted, on only four criteria pollutants. Furthermore, it emphasizes research needs in air quality measurements, exposures, and health effects. Due to the time constraints affecting the preparation of this report, it does not include descriptions of much needed research on atmospheric chemistry, physics, transport and transformations, or provide much discussion of research needs associated with welfare effects.

In our next report on research needs, CASAC will focus on atmospheric transport and transformation and on welfare affects, issues which continue to be concerns of CASAC. Our emphasis in this report on health effects and issues directly related to health risk assessment is also based on the greater resources available among current CASAC members and consultants in these areas, as well as the short time period available for preparing this report. As we complete our reviews of the lead and ozone criteria documents and staff papers, CASAC will prepare recommendations for further research on these pollutants.

We believe that a firm commitment to a research program focused on key information needs for standards setting will enlist the enthusiastic support and participation of the scientific community, and will provide a data base adequate for quantitative risk assessment. The commitment, however, must be secure and must ensure long term support for those studies in chronic disease toxicology and epidemiology which require it.

The costs of the identifiable research needs for ambient air quality standards are large in absolute terms, yet relatively small in comparison to the costs imposed by standards which are either too stringent or too lenient. Standards that are too stringent can impose costs for controls that involve extra expenditures of billions of dollars. Standards that are too lenient can cause adverse effects on public health and welfare that are expensive to overcome and degrade the quality of life. Use of an inappropriate pollutant index can also result in huge excessive costs. For example, use of Total Suspended Particulates (TSP) as the index of particulate matter pollution in the primary standard led to many spurious exceedances in the southwestern U.S. because this region was affected by wind blown soil that represented little, if any, health hazard. Spurious exceedances can thus trigger the imposition of unneeded controls.

In summary, a more complete and appropriate data base can be constructed in the next five years. It would permit the Administrator at that time to set ambient air quality standards that protect the public health and welfare without requiring large margins of safety to compensate for an inadequate data base. It could, thereby, help avoid unnecessary societal costs associated with inappropriate levels of controls or controls directed at inappropriate pollutant indices.

B. Organization of this Report

The body of this report is divided into three parts. The first (Section III) addresses CASAC's view of the overall scope of the research program needed to fill critical information gaps identified in the recent air criteria reviews in time to provide a more comprehensive and firmer data base for the next round of standards setting. It also addresses the organizational framework in which the program can most effectively be accomplished, including enlisting the efforts of the larger environmental science community outside of EPA.

The second part (Section IV) is focused on generic research needs for criteria pollutants. This includes the development of techniques and resources for: 1) accumulating quantitative population response data; 2) extrapolation of quantitative experimental animal response data for the prediction of humans responses; 3) relating concentrations at fixed air pollution monitoring sites to exposures of human population; 4) relating human exposures to airborne pollutants to toxic doses at critical sites in the body; and 5) research on responses to exposures to mixtures of pollutants.

The third part (Sections V, VI and VII) provides specific recommendations for priority research needs and a supporting rationale for the criteria pollutants SO_x and PM, CO, and NO_x based upon the CASAC reviews of the criteria documents and staff papers for these pollutants.

CASAC's criteria for the inclusion of the specific research recommendations are relatively simple and straightforward. They include:

1) the data to be generated would provide answers for, or at least go a long way toward defining and/or resolving critical issues relating to the setting of NAAQS;

2) the research can be accomplished using either existing technology or technology that can be developed as needed during the research;

3) most of the research needs identified herein can be addressed and resolved within the time frame mandated by Congress for periodic revisions of the NAAQS.

III. RECOMMENDATIONS ON SCOPE AND ORGANIZATION OF RESEARCH PROGRAMS

The information needs for national ambient air quality standards setting are so diverse and specialized that they require input from virtually all scientific disciplines, both basic and applied. An effective program should take advantage of all of the resources available, including EPA's own specialized laboratory and field investigation capabilities, the Agency's specialized university-based Research Centers Program, and the academic research community in general.

EPA's in-house program has significant strengths and capabilities in clinical studies, animal toxicology and environmental assessment. Strong in-house programs make valuable contributions in themselves by addressing well defined research needs and, at the same time, helping the Agency attract and retain high calibre research personnel. Such staff scientists also make it possible for the Agency to select and monitor research performed by outside scientists under cooperative agreements. Extramural contractual arrangements will always be necessary, since it will never be feasible for the in-house program to have and maintain all the specialized facilities and expertise that may be needed to address high priority critical information needs.

CASAC welcomes the decision by the Agency to begin to re-establish a limited in-house capability in epidemiology so that this critical area of investigation can begin to play its essential role in the overall program. With modest increases in support for epidemiology and for clinical studies, toxicology and environmental studies, the in-house staff should have adequate resources to make their essential contributions to the development of improved NAAQS.

The EPA's Research Centers Program has not yet had any significant impact on the data base for NAAQS. Only two of the Centers are active in areas of potential impact on NAAQS, and neither of them has had a major focus in those areas. The University of California at Los Angeles (UCLA) Center on Intermedia Transport can be expected to make contributions on the environmental fate of airborne emissions, and the University of Pittsburgh Epidemiology Center has investigated exposure-response relationships for fossil fuel combustion effluents. However, there is not now any Center program focused on experimental inhalation studies in humans or animals, or on the characterization of human exposures to air pollutants. An academic center could play a constructive and key role in implementing the research program getting underway in extrapolation modeling. Another center could help EPA to focus on mechanisms of action and exposure-response relationships for the pathogenesis of disease resulting from chronic low-level air pollutant exposures. Centers focused on these research areas could make major contributions toward filling the data base needs for NAAQS.

Academic based centers have great potential for complementary contributions to EPA's overall ambient air research program. They can: 1) take a longer view of research needs than the in-house programs; 2) more readily undertake multidisciplinary research studies; 3) enable EPA to enlist the participation of specialized facilities and personnel otherwise unavailable to the in-house groups, and 4) provide training to a new generation of scientists and engineers.

A third and equally essential component of an effective research program focused on NAAQS needs is the EPA Grants Program. Investigator initiated, peer reviewed grants provide EPA with the kinds of innovative research that the specialized in-house and centers program cannot be expected to provide. They offer the best prospect for "break through" research, and research on important areas which are not within the focus of primary concern of the other program components. While some support for research related to the development of NAAQS is available from the NIH and the National Science Foundation (NSF), these agencies tend not to support research perceived as "practical" or program-oriented, preferring studies perceived as "basic research." Some support for extramural research is also available from the HEI, but this program is confined to pollutants associated with motor vehicles.

EPA is an agency which always has been and probably always will be on the "firing line." Public and Congressional pressures cause it to divert funds and personnel to investigate and control the "crisis-of-the-month." There is, therefore, concern about its ability to effectively manage long-term research programs. On the other hand, EPA is the logical Federal agency to support long-term research that provides the basis for standards development, since standards development will continue to be a major statutory responsibility of the Agency.

EPA already has an effective administrative system for peer review of grants. In this system, which was initiated about four years ago, the Agency has solicited investigator initiated research grant applications directed at specific broad categories of Agency program needs. Each grant application is evaluated for scientific merit by a review panel composed primarily of academic researchers but also including some EPA research personnel. There are currently five panels, and they meet three times each year. The panels review grant applications and have typically approved about 30% of them. Those that are approved are given a scientific rating. These ratings and the relevance of the research to EPA program needs are evaluated by Agency personnel in deciding which of the approved grants to fund. In FY'83, 45 grants were funded. These included five in the environmental health area. However, none were related to the establishment of

NAAQS. Twelve grants were awarded in the areas of Environmental Chemistry and Physics (Air), and eight of these related to NAAQS issues.

The EPA extramural grants program is similar to, and in many respects is patterned after, the highly successful extramural grants programs of the National Institutes of Health. In terms of the scientific peer review procedures, there are no important differences; those differences that do exist are reasonable given the differing responsibilities of the agencies. On the other hand, in terms of the secondary reviews, there are substantial and significant differences. Each NIH Institute (National Cancer Institute [NCI], National Institute of Environmental Health Sciences [NIEHS], etc.) has a scientific council composed of extramural senior scientists. Each council meets three times a year to evaluate the grants assigned to the Institute and previously reviewed by one of the discipline-oriented peer review panels (Study Sections). They weigh the scientific merits of each grant, as outlined to them in the summary statements prepared by the study section, and the relevance of the proposed work to the mission of that particular Institute. As Institute advisors are not employees, they can and do take a long-range view of the needs of the Institute program.

By contrast,the summary statements prepared by the program area peer review panels of EPA (Review Panels) are now reviewed by Agency scientists who are, of necessity, more influenced by perceived short-term needs of the Agency and whose perspectives may be more limited than those who would be chosen to serve on a NIH-type council.

A further critical difference is the length of time that research support can be committed. NIH councils can make five-year commitments of support for approved research grants (subject, of course, to continued funding of the Institute by Congress). On the other hand, EPA has limited funding commitments for research projects to a maximum of two years.

Many extramural research programs that can support standards development need a budgetary commitment of more than one or two years, and mechanisms should be established to permit such support. Also, recommendations about which of the peer review approved grants to fund should be made by a group of senior scientists who have broad perspectives of the needs of the standards development program and who are not influenced by the short-term tactical program needs and budgetary exigencies of the Agency. Therefore, a key recommendation for improving the support of extramural research for standards development is the creation of a Council for Research on Ambient Standards Development to oversee the extramural research program with such a group to be supported on a long-term and continuing basis by a line item appropriation separate and independent of other EPA research programs.

It may be desirable to constitute this Council as a subcommittee or affiliate of CASAC since CASAC has the necessary programmatic perspectives and intimate familiarity with the research needs in support of standards acquired in the course of its reviews of the criteria documents and staff papers. CASAC's major concern, however, is not that it be involved in the activities of the Council, but that such a mechanism be created to assure timely delivery of scientific results. The Council should adopt procedural rules patterned after those of the NIH, designed to eliminate potential conflicts of interest. The Council mechanism could also be helpful in communicating research needs to EPA, the Office of Management and Budget, and the Congress to help in their budgetary analyses.

Our specific recommendations for a new extramural research program to support the development of ambient air quality standards are summarized in Table I.

In summary, a long-term commitment of support by EPA is essential to an effective program. It not only takes time to formulate programs designed to address some of the complex issues in standards development, but it takes time, even for the best investigators, to develop the background, specialized techniques, and perspective needed to perform the experiments and studies that can resolve these issues. In the past, crash programs have been initiated only two years or less before the data were needed for decisions. Such a time frame makes it difficult to enlist the services of the kinds of research talents needed to address the fundamental questions. Some of the research needs that face EPA today were apparent when the initial air quality criteria documents were prepared in 1969. The information gaps might have been resolved had there been a firm commitment of resources guided by a standards development policy and overseen by a suitable group of senior scientific advisors.

IV. GENERAL RESEARCH RECOMMENDATIONS FOR CRITERIA POLLUTANT STANDARDS DEVELOPMENT

A. Development of a Program in Air Pollution Epidemiology

Epidemiological studies are a primary mechanism for identifying human health risks in the environment. A great deal was learned about risks from air pollution from

Table I. CASAC Recommendations for Establishing a Long-term Ongoing Research Program in Support of the Development of Ambient Air Quality Standards

I. Suggested Mechanisms for Support of Research

1. Solicitation of long-term (up to 5 years) applications for research grants and centers (patterned after the systems used by NIH, i.e., Request for Application [RFA], based upon broad description of research needs).

2. Peer review of applications by current EPA supported review panels, or by special review panel with similar qualifications, providing summary statement on approval and priority score or disapproval.

3. Review of summary statements by a Council for Research on Ambient Standards Development for relevance to standards setting (similar to the advisory role of an NIH Council in NIH Grants Program).

4. EPA commitment to continuing support of the approval applications for up to 5 years, contingent upon satisfactory progress.

II. Major Areas of Needed Research for Ambient Standards Development

1. Fundamental Studies of Exposure-Response and Mechanisms of Injury for Criteria Pollutants

   a. Animal toxicology - short-term and chronic exposures.
   b. Extrapolation Modeling - Use of animal studies to determine likely human responses and to link acute responses to chronic diseases.
   c. In Vitro studies - Pollutant interactions with cells and organelles.
   d. Clinical and experimental human studies - short-term exposures of human volunteers
   e. Population studies - epidemiology of exposed humans

2. Fundamental Studies of Atmospheric Composition

   a. Primary pollutants - temporal and spatial distributions downwind of sources and potential for population exposure
   b. Atmospheric transformations - temporal and spatial distributions of secondary pollutants, their chemical and physical properties, and their atmospheric lifetimes under various conditions of temperature, humidity, actinic radiation, transport, etc.
   c. Spatial variations within an airshed
      1. center city vs. suburb
      2. ground levels vs. elevated sites
      3. outdoor vs. indoor

3. Development and Improvement of Air Samplers, Monitors and Devices for Determining Personal Exposures

   a. Samplers for size-selective sampling of aerosols - for both fixed station and personal sampling
   b. Improved samplers and/or monitors for reactive species, such as H_2SO_4, NO_2, HNO_3, volatile and/or reactive organics in or on aerosol particles and in gases, etc.
   c. New and improved personal samplers - additional pollutants and better temporal resolution of exposures.

such studies performed in the 1950's and 1960's. However, some primary confounding factors for contemporary decision makers are the changing mixtures of ambient pollutants and the different effects of the various pollutants in situations involving multiple exposures. New epidemiological studies are needed for today's pollutant mixtures. In addition, it also appears necessary to develop methods for personal exposure monitoring in order to better correlate effects with exposures on an individual basis. The effects of patterns of exposure and of simultaneous exposures to criteria pollutants are best studied by epidemiological means, since it is not possible to simulate all exposure conditions in laboratory studies. Laboratory studies can provide comparisons with, and explanations for, findings in epidemiological studies. In summary, epidemiological studies can provide critical data bases for identifying air pollution risks to public health.

CASAC supports recent EPA decisions to begin restoring an epidemiological component to the health effects research program. For the near term, we favor "program definition" studies. Some near-term funds should also be allocated to supplement ongoing epidemiological programs. In future years (FY'85 and beyond) we strongly recommend that resources for epidemiology be increased to a level more in balance with the two other major components of the health program. We also support cooperative efforts with outside groups such as NIEHS and the Electric Power Research Institute (EPRI).

B. Development of a Program in Extrapolation Modeling

In developing an understanding of the pathogenesis of chronic disease it is seldom possible to use human subjects, and it is usually necessary to resort to animal studies. Such studies permit investigations of the nature of responses to specific air pollutants. They also facilitate the search for long-term effects of low level air pollution, and an elucidation of the mechanisms by which these pollutants exert their effects on a chronic basis. More chronic animal studies are needed to meet EPA's requirements for an expanded data base over the next decade, but their current utility in standard setting is limited by our inability to make quantitative inter-species extrapolations.

It is also vital to appreciate that linkages between acute and chronic effects of specific air pollutants are needed, involving studies that range from *in vivo* human studies all the way down to *in vitro* cellular or molecular investigations of the effects of specific air pollutants. In particular, using cultured preparations of cells or animal or human models, short-term phenomena may indicate the mechanisms by which long-term effects take place. For example, immediate changes in respiratory epithelial permeability properties or inflammatory responses may indicate that longer term sequela will take place if exposures are continued. Furthermore, if chronic effects of a specific pollutant are seen in animal or cellular studies, and if mechanisms for such effects are seen in acute *in vivo* studies in humans, it will lend increased credibility to the suggestion that chronic exposures in humans may be similar to the effects seen in other experimental systems.

In view of these considerations above, we endorse strongly EPA's plans to develop methods for extrapolation of data obtained in cellular or animal studies to human populations. Such extrapolations will involve quantitation of dosimetry of the pollutant to specific target sites in the body. These approaches, when combined with the linkage studies noted above, should allow more intelligent decisions about potential effects on human health of air pollutants based on studies in non-human experimental systems.

C. Research Relating Concentrations at Monitoring Sites to Human Exposures - Assessment of Personal Exposures

The adequacy and margins of safety associated with NAAQS depend greatly on the relations between the concentrations observed at fixed monitoring sites and the actual exposures of people. Outdoor concentrations can vary greatly within a community, and most people spend most of their time indoors. For some pollutants, e.g., SO_2 and ozone (O_3), indoor concentrations are almost always lower than outdoors, while for NO_2, where gas stoves and portable heaters act as indoor sources, indoor concentrations can be much higher.

EPA's program in total exposure assessment should have increased emphasis and should be broadened. The information is critically needed for EPA programs in quantitative risk assessment and in support of expanded activities in epidemiology.

The measurement of personal exposures requires the use of miniature samplers and monitors which can be worn for extended periods by persons engaging in their normal activities. Samplers are available for measuring average daily exposures to CO, NO_2 and PM, but wearable samplers which can measure peak concentrations are either unavailable or prohibitively costly. Research and development is needed on personal samplers and monitors for criteria pollutants, so that such samplers can be used to better define human exposures.

D. Research Relating Exposures to Doses

Exposure alone does not determine dosage of inhaled materials at critical sites in the body. The deposition, translocation and metabolism of inhaled materials vary greatly among individuals in a population according to age, size, breathing patterns, state-of-health, level of physical activity, route of entry (nose or mouth), level of stress, etc. Thus, the fraction of inhaled material reaching a target site or critical organ in the body can be highly variable, and the effective dose depends on both this fraction and the external exposure concentration.

Much of the information needed to translate exposures into doses for target populations should be developed in the EPA Extrapolation Modeling Program. Data on the differences in exposure/dose relationships between humans and animals should also be developed in this program.

Additional research is needed on human volunteers to establish the effect on respiratory tract deposition patterns and efficiencies of route of breathing, level of exercise, ambient temperature and humidity, atmospheric co-contaminants, etc.

E. Responses to Multiple Pollutant Exposures

A number of well-documented cases exist which demonstrate that exposures to two or more air pollutants simultaneously or sequentially produce responses not seen with the individual exposure alone. However, we lack systematic data and understanding of the conditions which lead to these enhanced responses, or, in many cases, the mechanisms by which they occur.

The following does not represent a list of recommendations, but rather serves as examples of some of the combinations of pollutants and the effects of interest which deserve further study:

1) Effects of SO_2, H_2SO_4 and nitric acid (HNO_3) combined with very high humidity (fog) on airway mechanics and lung clearance.

2) Effect of SO_2 and carcinogenic aerosols on lung cancer incidence.

3) Effects of combined exposures to O_3, NO_2 and SO_2 on crops and trees.

V. RESEARCH NEEDS FOR PARTICULATE MATTER AND SULFUR DIOXIDE

A. Introduction

The research needs for particulate matter (PM) are substantially greater than those for any of the other criteria pollutants discussed in this report. SO_2, NO_2 and CO are all vapors of defined chemical composition. PM, on the other hand, includes particles varying widely in size and composition. These variations complicate the measurement of atmospheric concentrations, the relationships between exposures and doses, and the characterization of health and welfare effects.

Because of the large number and diversity of the research recommendations for PM, we have grouped the specific recommendations by category, using the chapter headings of the combined air quality criteria document for PM and SO_2 as an organizational framework. These follow the introductory discussions on PM and SO_2.

1. Particulate matter

The intensive CASAC review of criteria and ranges of interest for proposed standards for particulate matter (PM) resulted in recommendations for substantive changes to the current PM standards. The review also revealed a highly limited data base, particularly where quantitative studies were concerned, and a wide range of views about the effects of specific constitutents of PM and the exposure levels at which adverse health or welfare effects are likely to, or may possibly, occur.

With respect to health effects, the key issues are:

(a) Physicochemical properties of PM as they affect health

The available scientific information supports a size-specific standard based upon penetration of particles into lung airways. Research is needed to determine whether and what further refinements can be made. In the next standard setting round (1989), separate standards may be warranted for fine ($<$ 2.5 um) and coarse ($>$ 2.5 um) particles which differ substantially in chemical properties, or for specific chemical components or classes such as sulfuric acid or carbonaceous material. To significantly address these questions, more knowledge of the physicochemical properties of PM is needed and, in particular, a larger research program on the composition and properties of fine particles is required.

(b) Nature of health effects of PM and its major constituents.

The scientific review of controlled animal and human studies and epidemiological research identified a number of important health effects issues presently of concern for particles as well as identification of effects of potential concern. Further study of these questions is needed using all three scientific approaches. The size and nature of population groups sensitive to such effects should be further delineated, as well as the mechanisms of the toxic response.

(c) Quantitative relationships between PM and health effects in sensitive population groups.

Perhaps the most important need is to improve our ability to assess the risk of acute and chronic PM exposures to the varying particle compositions and conditions found in U.S. atmospheres. Development of improved approaches for using animal and controlled human studies for quantitative risk assessment are of critical concern.

The key welfare effects areas where more work is needed include:

(a) Visibility

Although a relatively good basis exists for relating fine particles to visibility, additional work is needed on relating sources to fine mass and to evaluating effects on visibility in different seasons.

(b) Soiling and nuisance

The most important issues concern which particle compositions and sizes can make substantial contributions to soiling and nuisance and at what concentrations.

2. Sulfur dioxide

For sulfur dioxide the CASAC review revealed a need to consider setting a short-term peak (1-hour) standard to protect asthmatics from difficulties in breathing and symptomatic effects. It would be desirable to ultimately extend investigations of these issues into field settings. The basis for a 24-hour standard is primarily drawn from epidemiological work conducted in England during the 1950's. Additional work is needed to better characterize the kinds of responses and the levels of SO_2 at which such responses can occur over this time period.

The CASAC review of the scientific basis for the long-term (annual) SO_2 standard concluded that considerable uncertainty exists whether long-term SO_2 levels currently experienced in the U.S. can increase morbidity or mortality. Some qualitative support for a long-term standard exists, but this support is weak. Some toxicological studies suggest a possible role of SO_2 in carcinogenic or mutagenic activity, but there was insufficient scientific data to generate serious concern. Due to the apparent interaction of SO_2 and PM observed in epidemiological studies, controlled studies are needed to elucidate the causitive factor(s).

For both acute and chronic exposures personal monitoring studies need to be developed that could provide continuous monitoring of peak concentrations of SO_2. Such information would be useful to test for associations with acute or chronic human health responses.

In regard to welfare effects associated with SO_2, the major areas of concern are effects on vegetation and materials. Studies examining the effects of SO_2 both alone and in combination with other pollutants should examine exposure patterns that might be observed in the ambient air. Because a possible new short-term primary standard could be more stringent than a secondary standard and because there is considerably more information on the effects of SO_2 resulting from acute exposures than longer averaging times, it would seem appropriate to exert greater efforts to examine effects of repeated peak and long-term exposures.

Available information suggests adverse welfare effects may be occurring in several situations at ambient concentrations, demonstrating a need to evaluate effects on agricultural crops, vascular plants, and non-vascular plants. Work is also needed to quantify damage to a variety of materials under differing ambient conditions.

B. Some Specific Recommendations for Research on PM and SO_2

NOTE: (1) Research needs are listed by area, according to Chapter Headings in EPA-600/8-82-029 "Air Quality Criteria for Particulate Matter and Sulfur Oxides"

(2) Research needs are prioritized as follows:

*** Highest priority - very critical need
** High priority - very important need
* Moderate priority - can provide important data for supporting standards development

CHAPTER II. Physics and Chemistry

*1. Ambient air neutralization of H_2SO_4 by NH_3

The source terms for H_2SO_4 in the atmosphere are discussed in 26 pages of the criteria document (CD). The reactions which neutralize H_2SO_4 are discussed in less than one page. Since the ambient air levels depend upon both formation and removal kinetics, we must know more about the sink terms in order to model the ambient concentrations. This is especially important for H_2SO_4, which is the PM component with the greatest known effects on both human physiology and environmental quality.

CHATER III. Collection and Analysis

***1. Development of a direct reading monitor for PM_{10}

If 24-hour or other short-term limits for particles less than 10 um in aerodynamic diameter are to be enforced, control agencies will need monitoring instruments with the capability for continuous measurement and/or concentration readout over a period of about two hours or less. Such instruments do not now exist, and many control agencies resort to such antiquated and crude PM indices as Co-efficient of Haze (CoHs) in making decisions on the presence of alert stage conditions. Such a monitor would also be valuable in health effects studies and in the development and analysis of control strategies.

***2. Development of a direct reading monitor for H_2SO_4 or aerosol acidity

The strong acid component in PM may be the single most important characteristic with respect to health and welfare effects, yet is poorly correlated with PM_{10}, fine particulate (FP) or other mass concentrations. If the strong acid component can be measured directly, it may represent the best index of potential effects and/or be the basis for future standards. Development of such capability should have a very high priority.

**3. Development of a direct reading monitor for FP and/or visibility reduction

Future secondary standards for atmospheric visibility will require compliance and routine monitoring with an instrument or measurement technique for visibility reduction, or for some surrogate such as FP. Such instruments and/or techniques should be developed now for accumulating a suitable data base for standards setting. The only FP data now being collected are from the EPA network of dichotomous samplers.

These are less valuable for FP determinations than are data from continuous monitors, and may not be available in the future as monitoring emphasis shifts to PM_{10}. Such an instrument may also be particularly useful for health effects studies.

**4. Development of a wearable direct reading instrument for SO_2, PM_{10} and FP

Fixed station samplers can provide only indices of actual exposure to SO_2 and PM. Studies of actual human exposures at street level, in vehicles, in public buildings, and in residences, can best be made with lightweight, battery-powered devices which do not inhibit the normal activity of the wearer. Such devices are especially valuable in epidemiological studies. Research is needed on the design of particle samplers, sensors, and inlet pre-cut devices to restrict the particles to be measured to PM_{10} and/or FP. For SO_2, the critical need is for capability of measuring peak concentration levels.

CHAPTER V. Concentrations and Exposures

***1. Ambient acid aerosol data base

While H_2SO_4 is one of the most important constituents of PM, its ambient concentrations have been measured in only a few limited duration campaign studies in various areas of the U.S. A more extensive data base is one of the most critical needs for future PM standards. It should be adequate to establish seasonal and regional variations in exposure, and provide a basis for analysis of trends.

***2. Fine particle (FP) data base

Future primary and/or secondary NAAQS for PM may be based on FP mass concentrations. If the developing data base on effects of FP warrant such standards, then a data base on ambient levels of FP will be needed to determine the relative contributions to PM_{10} mass of coarse and fine mode constituents at various locations and times.

**3. Exposure to wood and coal smoke from domestic fires

The widespread use of coal and wood for domestic heating in several parts of the U.S. has caused odor nuisances and local visibility degradations, and is of serious concern regarding potential health effects. The extent and characteristics of exposures to the smoke and ash particles from such heaters should be determined.

*4. Composition of the ambient particulate organic matter

Much of the mutagenic and carcinogenic activity of ambient particulate matter and the contributions of the polycyclic aromatic hydrocarbons have been investigated in some detail. Further study is needed on other classes of organic particulate matter in order to develop a better understanding of the sources of the mutagenic activity in ambient airborne particles.

CHAPTER VIII. Effects on Vegetation

**1. Dose-response studies for plants

More detailed SO_2 dose-response studies should be conducted with realistic concentrations monitored in the atmosphere. These dose-response data should include both field and laboratory studies on a regional scale.

Studies cited in the criteria document point out that mosses are quite sensitive to low levels of atmospheric SO_2. Thus, effects on mosses could be used to presage effects of SO_2 on other vascular plants in natural forests and economically important crops.

Although more short-term (acute) data that have been verified by different studies are needed, more resources should be allocated for long-term (chronic) low concentration effects of SO_2 on vegetation because less information is available. One then could evaluate the importance of single and multiple acute responses versus continuous chronic SO_2 exposures on different sensitive species of plants.

The limited data base suggests that possible co-occurrence of SO_2, NO_x, and O_3 may produce greater detrimental effects on sensitive vegetation than any one of the pollutants alone. Thus, careful combined exposures should be conducted in the laboratory and the field to determine the effect of ambient SO_2 concentrations and various combinations of NO_x and O_3 on vascular and non-vascular plants. Studies might be focused on the most sensitive life stages (e.g., flowering stages).

*2. Studies to determine the influence of environmental factors on dose-response functions

Studies of the influence of SO_2 as a factor predisposing plants to injury from environmental stresses are needed. The relationship between SO_2 (and sulfate ion) exposure and effects on richness and diversity of non-vascular plants needs clarification. There is also a need to develop a better understanding of the importance of other factors affecting exposure-response relationships. Such factors include soil moisture, stage at time of exposure, and the kinetics of exposures. In addition, some effort to examine the importance of CO and NO_2, which often co-exist with SO_2 point sources, warrants examination.

CHAPTER IX. Visibility

*1. Contributions to visibility reductions by PM constitutents

The major contributors to visibility reductions include sulfuric acid, ammonium bisulfate, ammonium sulfate, ammonium nitrate, diesel soot, other carbonaceous particles within the accumulation mode aerosol, and NO_2. For hygroscopic particles, visibility reduction is strongly dependent on relative humidity. However, the relative effectiveness of the various kinds of particles has been adequately established for only a few limited situations, and primarily in the summer. More data for other seasons is needed. Research in this area could provide a needed basis for any future secondary standards for PM based upon visibility reduction in urban, suburban, rural and recreational areas.

CHAPTER X. Effects on Materials

*1. Material damage by SO_2

Very few quantitative data exist concerning the effects of SO_2 on materials. More information is needed on the seasonal and regional chronic effects on different materials (e.g., paints, fabrics, elastomers, stone, and metals). Some quantitative data exist for nonurban areas, but more data are desirable concerning material effects in urban regions. The studies should deal with long-term low-level SO_2 concentrations that are monitored close to the materials being studied.

*2. Soiling and nuisance by PM

Although the qualitative aspects of the soiling of surfaces by particles is well known, a comprehensive quantitative research approach has been lacking. Studies are needed that will permit an evaluation of the effect of particle size, rainfall, and weathering on exterior soiling effects, with particular emphasis on the role of coarse particles. The results of soiling also must be evaluated from the standpoint of economic aspects, human perception, and of cleaning costs and procedures.

CHAPTER XI. Deposition and Fate

***1. Regional deposition of SO_2 and particles in experimental animals

There are very few data on deposition efficiencies in the heads, lung conductive airways, and alveolated regions of experimental animals, or on how deposition efficiencies vary with particle size or respiratory pattern and volume. There are virtually no data on the patterns of particle deposition within each lung region, or the influence of airway configuration on such patterns. Such data are needed to determine effective doses for given exposures, and to relate such doses and responses to the potential for effects on humans.

***2. Effect of exercise on regional deposition

It is reasonable to expect, although it is not yet been demonstrated, that exercise will change the pattern and efficiency of deposition of both SO_2 and particles along the conductive airways. Exercise-induced oral breathing should increase both SO_2 and aerosol penetration through the extrathoracic airways, and the increased air flow rates should increase particle deposition by impaction on the airway bifurcations. Increased tidal volumes may increase particle deposition in the alveolar zone because convective flow will carry the contaminants into more distal airway generations. Experimental data are needed. Controlled human deposition studies can provide such data, and should be performed.

***3. Effect of exercise on the clearance of particles from the tracheobronchial airways

Exercise could alter the retention times for particles deposited within the lung conductive airways in several ways. The increased flow rate and switch to oral breathing associated with moderate to heavy exercise would increase the amount of particulate matter deposited in large airways and alter its pattern of deposition. It would also reduce the temperature and relative humidity of the air, while increasing pulmonary blood flow. All of these changes can be expected to influence the thickness and viscosity of the mucus on the airways, and thereby the surface transport of the particles deposited on the mucus. Research is needed to define the effects of exercise on particle retention, so that the doses resulting from the particles can be determined.

**4. Influence of oronasal breathing on regional deposition in humans

Little is known about deposition efficiency of SO_2 and particles in oral airways during "normal" oral breathing or oronasal breathing. Current data on oral airway deposition are based on inhalation through a mouthpiece or oral airway which creates a larger cross-section airpath than the natural one. Since thoracic dose depends on fractional removal in the head, it is important to know the extent of the removal, and how it varies with the size and shape of the oral airway, the distribution of flow via nose and mouth, breathing rate, and tidal volume.

**5. Regional deposition in sensitive populations

There are limited data which indicate that tracheobronchial deposition efficiency of inhaled particles is significantly enhanced among individuals with narrowed airways, e.g., people with asthma and chronic obstructive pulmonary disease (COPD), and among children. More data are needed to characterize the extent of the enhancement and the factors which have the greatest influence in causing it. This is important because the standards may be based, in part, on responses among sensitive subgroups of the overall population. Such a subgroup would include individuals with enhanced conductive airway deposition.

**6. Barrier functions of the lung

The respiratory epithelium represents a barrier between the individual and his environment. Changes in the function of the epithelial barrier may be associated with the acute response to pollutant exposures. Consequently, the integrity of the epithelium in response to an insult from an environmental pollutant needs to be evaluated. Epithelial permeability rates and the effective "pore" size can be estimated using (gamma emitting) probe molecules of known molecular size. The rate and clearance off the surface of the airways coated with the radiolabelled particles is measured with the external gamma detectors.

CHAPTER XII. Toxicological Studies

***1. Development of an animal model for respiratory airway irritancy bioassay

Transient changes in mucociliary clearance rates can provide a sensitive bioassay for lung irritants on the basis that similar responses are produced in both humans and animals by such diverse irritant aerosols as cigarette smoke and H_2SO_4. The assay's utility should be extended to other laboratory animals, and it should be evaluated with other irritants which have significant amounts of deposition within conductive airways. These could include NO_2, O_3, and constituents of PM as ambient pollutants of interest. They could also include other acids and bases at various particle sizes to vary dosimetric aspects and determine mechanisms for airway responses to irritants.

***2. Progression of disease and dysfunction after chronic pollutant exposures

An essential element in any chronic study of particulate sulfates is to look for delayed effects. The EPA's "Cincinnati Dog Study" showed that the animals exposed to H_2SO_4 had a progression of effects during the study, as determined by pulmonary function. Morphometric measurements at the end of the study indicated the presence of emphysema, "analogous to human centrilobular emphysema." Limited follow-up studies on shorter-lived animals are recommended to develop a more comprehensive data base, including studies with SO_2 and H_2SO_4 alone.

**3. Effects of the ultrafine fraction of fresh coal combustion fly ash

The ultrafine (< 0.2 um) condensation aerosol from coal combustion contains most of the H_2SO_4, organics, and volatile metals within the overall flyash, and may therefore contribute disproportionately to the overall health hazard of such effluents. No inhalation tests have yet been done with such aerosols, and the tests which have been done with resuspended ash have not been able to show the presence (or absence) of the effects that the ultrafine fraction alone might produce. Tests with fresh ultrafine ash are needed in order to determine the extent of the contribution such particles may make to the overall ambient aerosol inhalation hazard. Endpoints of interest would include airway mechanics, diffusing capacity, clearance functions, and bioavailabilities of trace constitutents.

**4. Identification of host factors which affect responses to inhaled pollutants

Among animals exposed repetitively to irritant aerosols (H_2SO_4 or cigarette smoke), some developed persistently slowed mucociliary clearance, while others developed a persistent clearance acceleration. Such divergent responses among animals with the same exposures provide a model for identifying the host-related factors which govern the responses, and may provide markers for identifying individuals within a population likely to be susceptible to environmental exposures.

CHAPTER XIII. Controlled Human Studies

***1. Continued studies of the effects of SO_2 on asthmatics

SO_2 causes significant bronchoconstriction in asthmatics at relatively low concentrations (0.25 and 0.50 ppm). These same exposures produce no obvious effects on healthy adults. While concentration-response studies have been done, and some information on effects at constant SO_2 concentration with different exercise levels (minute ventilation) is available, knowledge of the relative contributions of SO_2 concentration, minute ventilation and time of exposure to the bronchoconstriction response is desirable. In addition, this response as a function of time of continuous exercise and as a function of repeated exposures needs to be studied. While it is known that substantial response to SO_2 does occur within 5 to 10 minutes, the effects of exercise continued beyond 10 minutes, and the effects of repeated peak exposures on the same day or on subsequent days need to be established.

***2. Studies on the effects of SO_2 in combination with and in sequence with other atmospheric factors

Studies are needed to investigate possible interactions between exposure of SO_2 and other environmental factors known to induce bronchoconstriction in asthmatics. Cold and dry air, for example, are well known as naturally occurring factors producing respiratory distress in asthmatics. The possible synergistic effects of SO_2 combined with cold/dry air need to be investigated.

Interactions with particulate materials also need to be investigated, especially in light of the recent report of effects in asthmatics of exposure to only 100 um/m^3 of H_2SO_4.

Similarly, studies are needed to investigate sequential exposures to SO_2 and other factors such as cold/dry air, pollutants (e.g. O_3, NO_2) and viruses. Such studies would address the question of airway sensitivity, that is, sensitization or desensitization of the airways to one factor (such as SO_2) by prior exposure to another. For example, exposure to ozone followed by exposure to SO_2 may result in an increased response to the SO_2 (sensitization) due to increased bronchial irritability. Conversely, prior exposure to ozone might result in a decreased subsequent response to SO_2 because of ozone-induced mucous secretion which could "protect" the airways. Likewise, persons with pulmonary infections might be more or less sensitive to SO_2 exposure for the same reasons.

**3. Effects of pollutants on pulmonary functions during acute respiratory infections

Exposures to nitrate aerosols during a period when the subjects were suffering from acute lung infections produced pronounced enhancement of the bronchoconstrictive effects of carbachol. Similar studies should be performed with other pollutants, e.g., SO_2, H_2SO_4, $(NH_4)_2SO_4$, carbon, etc., to determine if the response varies with the kind and amount of the pollutant challenge. Studies of similar groups should also be done with other endpoints, e.g., particle clearance, to establish a more complete understanding of the influence of acute lung infection on responses to pollutant challenges.

**4. Identification of other groups of persons hypersensitive to SO_2

Controlled exposure studies are needed to identify subgroups of the population (besides asthmatics) who may be hypersensitive to SO_2. Possible groups are children, the elderly, smokers, and persons with chronic bronchitis or other forms of chronic obstructive pulmonary disease. Ethical considerations will strongly influence the design of such exposure studies, especially those using subjects with compromised pulmonary function.

**5. Studies of mechanisms of SO_2-induced bronchial effects

Understanding of the underlying mechanisms of pollution-induced pulmonary effects is important both for regulation and in the recognition and treatment of pulmonary disease. Accordingly, studies need to continue to delineate the mechanisms of action linking SO_2 exposure with pulmonary tissue response. One area of such study is the stimulation of smooth muscle activity via the autonomic nervous system and via cell-mediated release of inflammatory agents (e.g., histamine, prostaglandins and leukotrienes). Studies using pharmacologic blocking agents (atropine, anti-histamines, cromolyn) have produced very useful insight into the mechanics of bronchoconstriction. Animal research has been used effectively to describe such responses and needs further development and use. Where possible, however, mechanisms studies need also to be conducted in humans.

CHAPTER XIV. Epidemiological Studies

**1. Study exposure-response relationships in foreign cities with elevated pollutant concentrations

Exposures in the U.S. may currently be too low to establish clear cut exposure-response relationships. However, many large urban communities outside the U.S. have much higher pollution levels and provide opportunities for characterizing relevant human exposure-response relationships. The different composition of the pollutant mixture in these urban areas provides an opportunity to determine which constituents make the greatest contributions to any adverse effects which are detected. With appropriate selection of study locations, it may be possible to study the relative impacts of aerosol constituents such as acidity, carbon, coal fly ash, etc., as well as of SO_2, NO_2 and O_3. EPA should seek to establish suitable intergovernmental arrangements for collaborative studies.

*2. Retrospective evaluation of historic health data

It is believed by many that chronic bronchitis was common among United Kingdom nonsmokers when particulate pollution levels were very high, and that it is virtually absent now that pollutant concentrations are much lower. It would be highly desirable to document the extent of the reduction in bronchitis prevalence among nonsmokers, and to relate it to pollutant parameters such as H_2SO_4 concentrations, a likely etiological factor. Possible data sources include general urban health statistics, and/or control populations studied in the course of occupational epidemiological studies.

*3. Develop a system for uniform reporting of hospital admissions

Hospital admissions data for respiratory diseases in Southern Ontario were shown to correlate strongly with O_3 and SO_2 at concentrations within current NAAQS. Such data resources in U.S. communities could provide useful evidence for studies on particulates as well as for pollutant vapors, and such techniques should be developed and refined for future studies.

VI. RESEARCH NEEDS FOR NITROGEN OXIDES

Re-evaluation of the criteria supporting the NAAQS for NO_2 indicates that major uncertainties exist regarding human health risks associated with this pollutant. The purpose here is to describe broad research needs for NO_2 and indicate those being investigated by EPA.

Research needs are prioritized as follows:

*** Highest priority--very critical need
** High priority--very important need
* Moderate priority--can provide important data for supporting standards development

Major research objectives that must be addressed include the need to 1) fill specific gaps in the health data base. Although many publications on NO_2 have provided significant information, they also illustrate the need to obtain additional critical data for improved risk assessment. For more definitive risk assessents, it is necessary to perform human concentration responses studies (including exercising and potentially susceptible subjects) that use state-of-the-art methodology. 2) Increase understanding of the current data base. Mechanism studies are needed to improve the scientific bases for risk assessment. Such knowledge will also be extremely useful in assessing the degree of adversity of observed effects and in developing future hypotheses for more targeted research. 3) Increase utilization of the current health data base. The only controlled chronic studies are conducted with animals and have demonstrated that NO_2 causes emphysema and a variety of other alterations. Until such findings can be quantitatively extrapolated to man (in terms of NO_2 concentrations and times of exposure), they will remain causes of concern only to be used in determining an adequate margin of safety for the NO_2 ambient standard.

An expanded discussion of these issues follows with short descriptions of research needs which pertain to subsets of these issues. The Committee believes it is necessary to obtain information on these topics prior to the next five-year round of re-evaluation of the NAAQS for NO_2 in 1989. A few projects are under way as part of ORD's intra- and extramural research programs, but they do not address the full scope of research needs for this pollutant.

***1. Chronic effects

Previous studies have demonstrated that NO_2 causes emphysema in several animal species. The EPA's "Cincinnati Dog Study," which used 0.64 ppm (parts per million) NO_2 in combination with 0.25 ppm NO, also indicated that the effect was progressive during a two-year clean air post-exposure period. Unfortunately, there are aspects of all of these studies that limit our understanding of the results. There is a need to apply modern techniques to characterize the progression of chronic lung disease morphometrically, physiologically, and biochemically. Additional endpoints of interest include effects on pulmonary host defense mechanisms and the immune system. Limited follow-up studies in shorter-lived animals to develop a more comprehensive data base are recommended, including studies with NO_2 and NO alone.

***2. Epidemiology

Indoor exposures in homes with gas appliances or space heaters can exceed outdoor peak levels. Studies on the prevalence of respiratory infection in children living in homes with and without gas stoves have found equivocal results. Future studies involving improved personal exposure measurements of NO_2 as well as health effects indices are needed to help to better understand these results. Improved indoor measurements of NO_2 would also be useful in designing chronic animal exposure studies using realistic exposure patterns.

3. Exposure assessment

***A. Temporal resolution of NO_2 exposure

A need exists for low-cost portable personal exposure monitors to measure the real time exposures of human subjects to peak NO_2 levels that exist in the kitchen environments of homes with unvented gas stoves and supplementary space heaters. Current badge and tube monitors do not provide continuous readings nor do they have adequate sensitivity.

*B. Measurement methodology for nitric acid and nitrate salts

In ambient outdoor air, a need exists for developing reliable and routine methods for measuring nitric acid vapor and particulate nitrate compounds. These oxides of nitrogen have only been measured in specialized research studies and appear to be a significant portion of total nitrogen oxides in several airsheds.

**4. Non-ventilatory pulmonary effects

A major uncertainty is the interaction of NO_2 with the respiratory epithelium. Although not yet published, several researchers in different laboratories are investigating the development of an inflammatory response in humans following ozone exposure, and such protocols could be used for NO_2 as well. Studies of epithelial integrity should also include measurements of epithelial permeability rates with a variety of techniques both in vivo and in vitro. These measurements may also provide some linkage to mechanisms of change observed with previously discussed measurements of pulmonary function, airway sensitivity, and chronic lung damage. For example, increased epithelial permeability may be associated with an increased access to irritant receptors. Likewise, repetitive or long-term episodes of inflammation may lead to chronic damage. These linkages deserve further attention.

**5. Pulmonary host defenses

Many studies have indicated that NO_2 increases susceptibility to pulmonary bacterial infection. Some studies have shown effects on viral infection, host lung defense mechanisms and the immune systems of animals. Since viral infections are more prevalent than bacterial infections and are likely to be involved in epidemiological observations, emphasis should be placed on viral rather than bacterial infection studies. Very little is known about the effects of NO_2 on particle clearance dynamics. Recent work showing that NO_2 exposure at low levels increased the number of lung metastases from injected tumor cells points to the need to understand the effects of NO_2 on the immune system. Further research to determine effects of NO_2 on host defenses is needed to address these very important data deficiencies.

**6. Dosimetry

Important questions concerning the pattern of NO_2 uptake in the respiratory tract remain unanswered. Understanding the patterns of uptake are important to extrapolation of results from animal to man. These studies are potentially complicated by the complex chemistry of NO_2 dissolution into water. Studies should include nasopharyngeal removal, studies of interactions with lung lining fluids, and comparison of measurements with mathematical models.

*7. Asthmatic pulmonary physiology

There is little information on the acute response of sensitive populations to NO_2. Published clinical studies were performed on non-exercising subjects at exposures to relatively low levels (0.1 to 0.2 ppm) for one hour or less. Pulmonary function studies should be conducted with asthmatics that include moderate exercise and somewhat higher NO_2 concentrations (0.2 to 0.6 ppm), as these higher levels can occur indoors and at a few outdoor locations. Reports of changes in airway reactivity after exposure to relatively low NO_2 levels warrant further investigation of this phenomenon as well.

VII. RESEARCH NEEDS FOR CARBON MONOXIDE

CASAC's re-evaluation of the scientific basis for national ambient air quality standards for carbon monoxide has indicated that uncertainties still exist regarding the human health risks associated with this pollutant. The following areas of research would provide better quantitative dose response data on which to base future NAAQS and improve our understanding of the underlying mechanisms responsible for the health effects of CO.

Research needs are prioritized as follows:

*** Highest priority--very critical need
** High priority--very important need
* Moderate priority--can provide important data for supporting standards development

***1. Effects on the cardiovascular system

Studies of patients with severe coronary artery disease have shown that low concentrations of CO can adversely affect myocardial metabolism. Current regulation of CO is based primarily on studies of patients with angina pectoris from coronary artery disease. It is assumed that the development of angina reflects adverse effects on myocardial metabolism. There is, however, no good evidence to support the validity of this assumption. Nevertheless, time to develop angina is a measurable outcome which needs to be defined as precisely as possible. In view of the questions about the conduct of Aronow's studies, replication is clearly indicated. While some studies will no doubt stick closely to previous protocols, a different type of study should also be carried out. This would focus much more attention on the dose/response relationships in individuals as well as in the group as a whole. By repeated exposures of individual patients with angina over one month or six weeks, it should be possible to obtain good data on variability in time to angina in the absence of CO and from exposures to say 15, 35, and 50 ppm interspersed at random with CO-free air. Each of these concentrations would be replicated. In each run, COHb (carboxyhemoglobin) percentage would be measured and used as the index of exposure against which the time to angina and duration of angina would be evaluated. A study of this kind would provide reliable dose-response curves for each individual. After studying the individual curves, it might be possible to present a curve for the group as a whole.

Objective measures, such as continuous ECG tracing for ST depression and arhythmias, measurement of ejection fraction and left ventricular wall motion, thallium scans, etc. are desirable wherever practicable.

To the extent that in a design of this kind, each individual will be used as his own control, it seems that efforts to obtain a homogeneous group of patients with angina (at least 50% occlusion of at least one coronary artery) is much less necessary than in the previous Aronow type of studies. The possibility of using a far more representative group of patients with angina is important. From a regulatory standpoint, a dose-response curve rather than a simple dichotomy would be more useful.

The use of the Aronow-Anderson technology to determine whether the sorts of individuals who are exposed to automotive pollution in large cities have a decrement in exercise tolerance should be considered. A panel of 100 or more individuals could have stress electrocardiographic studies in the morning and following several hours of exposure to traffic conditions. Aronow did this as his original study, but the observations should be expanded with a wider variety of individuals and carefully determined carboxyhemoglobin concentrations.

The use of ambulatory electrocardiography and ambulatory blood pressure measurement along with breath samples to track individuals through several actual working days in real automotive-polluted environments was also suggested. The Holter monitor ambulatory technique is probably preferable to the treadmill study because it measures electrocardiographic events in actual environments.

Patients with arteriosclerosis of the arteries of the lower limbs who develop intermittent claudication are analogous to patients with angina pectoris. They could be studied in precisely the same way. There is, at present, no evidence to say if time to development of pain in the calves is more or less sensitive and reproducible than time to develop angina. It would be worth finding out.

There are other disease entities that might be studied to evaluate the effects of CO exposure and increased levels of COHb. Patients with anemia may be susceptible to increased levels of COHb, since CO would further reduce the already compromised arterial oxygen content of the blood. Patients with chronic obstructive lung disease might also be studied when exposed to a combination of ozone and CO. Previous work has indicated that, when exposed to ozone, this group has a small but measurable decrease in arterial oxygen saturation. Protocols might be developed to evaluate the response of these patients (e.g., exercise performance) to the combined decrease in arterial oxygen saturation resulting from the ozone exposure with the added decrease in oxygen-carrying capacity of the blood resulting from an increase in COHb. Protocols might also be developed to evaluate the potential interaction between ambient CO and other air pollutants. Studies of such high-risk subgroups, while of interest to the understanding of the effect of exposures to CO, had less obvious immediate relevance to standard setting. A study of sickling in relation to CO concentrations could be done rather simply in vitro in the laboratory and would be worth carrying out.

The CASAC also considered that additional research related to the effects of CO on maximal work capacity was not likely to be of much immediate practical use in the setting of standards. This is not, however, to say that studies of this kind, both at sea level and at altitude, are not of great interest in elucidating the mechanisms of action of CO; only that such studies should have lower priority purely from the regulatory standpoint.

***2. Neurobehavioral effects

Neural and behavioral effects of CO have been reported in healthy young adults with COHb levels as low as 5%. The observed deficits were in (1) hand-eye coordination (compensatory tracking); (2) vigilance (detection of infrequent events); and (3) visual system sensitivity. While the effects of 5% COHb were very small, it is worthwhile to reflect upon the potential consequences of a lapse of coordination, vigilance and visual sensitivity in the operators of machinery such as public transportation vehicles. Even an acute and small reduction in behavioral or sensory ability could be sufficient to cause major accidents. Additional studies are vital to a thorough understanding of the effects of CO on these and other aspects of neurobehavioral function.

Such studies should, when possible, include the determination of dose-effect or dose-response curves. While a number of reports have been published indicating that 5% COHb produces small decrements in human behavior, extended dose-response functions are infrequently published. Since many studies have emphasized COHb levels that appear to be below the critical effects level, it is perhaps not unusual that a large number report no effects. Interpretation of negative studies at low levels would be easier if positive effects were simultaneously demonstrated at high levels. Therefore, in order to reduce this source of controversy it is highly recommended that all studies aim at establishing reliable, well documented dose-effect functions, with dose specified in terms of COHb level.

There are other reasons for improving our knowledge of a continuum of effects, including those occurring at high COHb levels. It is hard to evaluate costs of behavioral or other decrements without knowledge of the slope of the functions, which would give the magnitude of the decrement for each increase in dose. The possibility of nonlinear functions would be important to evaluate for any risk assessment; and, of course, the scientific credibility of any body of knowledge is vastly increased when parametric data rather than point estimates are available.

It is reasonable to predict that certain subgroups in the population are at increased risk from the neural and behavioral effects of elevated COHb. If some individuals are especially likely to show decrements in neurobehavioral functioning due to elevated COHb levels, then knowledge of such sensitivity is extremely important. The consequences of such decrements extend well beyond the sensitive individual's own health to the well-being of those who may be harmed by the consequences of such a person's impaired abilities.

Any condition that would reduce oxygen supply to the brain is a reasonable candidate for exacerbating the effects of elevated COHb. A very large subgroup which is known to have a reduced oxygen supply to the brain is the aged. The extent of such oxygen reduction is unclear for any given age. In order to protect older individuals from the possible consequences of CO exposure, it is important to determine COHb threshold levels and dose-effect functions for neurobehavioral variables with older subjects. Other conditions that might reduce oxygen supply to the brain include certain cardiovascular and pulmonary pathologies.

Another large subgroup that may be at special neurobehavioral risk from CO exposure are those people who take either prescription or over-the-counter medications that reduce alertness or motor abilities. Such individuals would be already compromised behaviorally so that any further impairment due to elevated COHb might have serious consequences. Medications that might have behavioral effects include drugs such as antihistamines, sedatives, antipsychotics, antiseizure drugs, antiemetics and analgesics. The effects of ethanol, caffeine, nicotine, and other nonprescription drugs, including abused drugs, should also not be overlooked. The widespread use of substances such as those listed above makes the subgroup very large indeed.

It would be desirable to include positive controls (substances with known effects) when studying the effects of CO on behavior for several reasons. For one thing, inclusion of a substance such as ethanol would yield information on the sensitivity of the behavioral procedure to another substance. Such information would help greatly in interpreting negative results. It would also allow one to assess the importance of any CO effects by comparing them with those of a known behaviorally-active substance. And, finally, when the second substance is given along with CO, it would yield information on any interaction (e.g., potentiation) between the two substances.

In extending knowledge about the neurobehavioral effects of COHb, coordinated performance, vigilance, and visual functioning are the prime candidates for studies that have immediate relevance for regulation. It is not implied by these recommendations that other neural or behavioral effects should be ignored.

The work on coordinated performance should include studies that both replicate and extend the existing positive studies that point to 5% COHb as the minimum effective level. Parametric variation of the relevant parameters should be encouraged in order to increase test sensitivity and to gain insight into the behavioral mechanisms that are involved in CO effects.

Investigators of vigilance should be concerned with the role of signal rate, task duration and any concurrent activity. All three are variables that themselves interact with many drugs and experimental procedures in determining task sensitivity and so may be crucial in determining the effects of low levels of CO.

Studies of visual function should emphasize both retinal and post-retinal effects of CO. Oxygen metabolism in the retina is quite high. The electroretinogram (ERG), which reflects some aspects of receptor function, would prove useful in studying dark adaptation in both lower animals and man. Cortical evoked potentials and single unit recording can be used to study other aspects of the visual system. And overall visual function can be measured with great sensitivity by using psychophysical methods. Correlated studies of the underlying physiology, pharmacology and biochemistry would be useful.

Some of the behavioral phenomena just described should be investigated in non-human subjects. In such work one can (1) achieve higher dose levels for the dose-effect functions; (2) explore concurrently both behavioral and brain mechanisms responsible for CO effects; (3) perform chronic studies that would be impractical with humans; and (4) perform interaction studies that would be difficult to do in humans (e.g., with drugs or other toxic substances). Animal studies would produce background information and leads for future human research. Extrapolation of conclusions from animals studies to man would be aided if data are collected on a wider range of species.

**3. Epidemiology Studies

Epidemiological studies to date have suggested the possibility that increased mortality from myocardial infarction (heart attacks) and cardiorespiratory complaints may be associated with ambient concentrations of CO. However, due to contradictory results from various studies and various limitations of existing studies (e.g., inadequate characterization of exposure), the question of whether ambient CO exposures are related to serious or irreversible cardiovascular effects and if so at what levels (i.e., dose-response) remains unanswered. Given the availability of small and reliable CO personal monitors, it may be possible to design epidemiological studies to address this question. For example, there is a need to relate COHb levels in sudden and unexpected coronary heart disease deaths, particularly in young individuals, and to follow panels of high-risk individuals (e.g., advanced coronary artery disease, chronic obstructive lung disease and peripheral vascular disease) while monitoring COHb levels, symptomology, morbidity indices, and mortality. There is also a need to examine the combined impact (if any) of high altitude and CO on these same cardiovascular effect endpoints in an epidemiological study.

4. Exposure assessment

**A. CFK equation validation

The Coburn-Forster-Kane (CFK) equation needs to be evaluated for COHb in normal individuals exposed to varying CO concentrations leading to COHb $< 10\%$. Of particular interest is the variation of predicted COHb in a population with a given pattern of CO exposure involving frequent concentration variations.

The distributions of parameters that cannot be readily measured in a clinical study, such as M (Haldane equilibrium parameter), P_AO_2 (alveolar oxygen tension) and V_{CO} (endogenous CO production rate), can lead to a distribution of the equilibrium COHb attained by people exposed to the same CO pattern. The Roughton-Darling equation for total saturation (O_2Hb + COHb $< 100\%$) makes the equation nonlinear, and its effect needs to be documented.

In addition, the CFK equation needs to be evaluated for applications to CO-susceptible subjects with conditions such as chronic anemia (high V_{CO}, low Hb), coronary arterial disease, emphysema (low D_{LO2} and D_{LCO}), abnormal hemoglobins (Hb Zurich), perinates and neonates (low Hb, high V_A), etc. Clinical evaluations of CO uptakes by these CO susceptibles should be considered.

*B. Exposure monitoring and profiles

The state-of-the-art CO personal exposure monitors (PEM) today are satisfactory for use by nontrained subjects, and only minor development needs exist for CO PEMs in contrast to the urgent needs for NO_2 PEMs.

Analyses of the NHANES II COHb data and large urban scale CO exposure and breath CO studies, performed by EPA/ Environmental Monitoring Systems Laboratory, have looked at the distribution of CO exposures and COHb of the general public in terms of a nationwide sample which defined the exposure of "normal" people. Results of both studies show that a small percentage of subjects ($\sim$1%) who are nonsmokers have COHb levels > 3% COHb which cannot be explained by their measured personal exposures to CO or the ambient CO in their communities (NHANES). It is therefore necessary to begin to change our focus from sampling randomly chosen "CO normals" to selectively choosing groups of "CO-susceptible" people for stratified sampling of their CO exposures and COHbs so that a more detailed evaluation of their risks can be quantified. It is possible that clinical studies may show that the effects of tissue PO_2 deficiencies have no threshold for COHb effects and, therefore, a revised CO standard may be required that is determined by an acceptable risk level. Specific needs in this area are as follows:

(1) A careful study of those normal subjects who are self-declared non-smokers and who have inexplicably high COHb or breath CO. (2) A standardization of the 20-second breath-holding end-tidal CO measurement method is required to correct for the ppm CO in the air of the maximal inhalation step prior to the breath-holding step, and the differing values of M, end tidal PO_2, and PCO_2 between people who may have the same %COHb. The effect of altitude on the end-tidal CO in breath equilibrium with COHb also needs documentation. (3) A study of CO exposures of known susceptibles (cardiac and chronic anemia patients) is needed for quantifying their risk from elevated COHb. Such people may unconsciously alter their behavior to avoid microenvironments which have high CO exposures. (4) Infant exposures to CO in the first year of life have been hypothesized as a possible factor in Sudden Infant Death Syndrome etiology. It would be desirable to monitor CO exposures in the infants' bedrooms and in their activities (promenade, in car, etc.) to determine whether or not there is a seasonal difference or a difference with maternal smoking level.

*5. Perinatal effects

The fetus and newborn infant are particularly susceptible to CO exposure for several reasons. The fetus has one-fourth to one-fifth lower oxygen tension in the blood than healthy adults. The newborn infant also has a comparatively high rate of oxygen consumption and lower hemoglobin blood oxygen transport capacity than most adults. Exposure to CO resulting in CO hypoxia can compromise an already marginal condition.

The effects of CO on maternal-fetal relationships are not well understood. In addition to the fetus and newborn infant, pregnant women also represent a susceptible group because pregnancy is associated with increased alveolar ventilation and an increased rate of oxygen consumption, which serve to increase the rate of CO uptake from inspired air. A perhaps more important factor is that pregnant women experience hemodilution with about a 25% decrease in hemoglobin concentration and hematocrit due to the disproportionate increase in plasma volume as compared with erythrocyte volume. Of course, the 5 to 10 percent of pregnant women who are at high risk with various pregnancy complications (such as pregnancy-induced hypertension, diabetes mellitus, and women who smoke, are anemic, or malnourished) are probably even more vulnerable.

In humans, studies of fetal development in relationship to maternal smoking and after birth to passive smoking should be continued. Problems arise because the changes which have been attributed to smoking may not be due to CO but rather to some other constituent of the cigarette, for example nicotine. This problem can be tackled by comparing effects in humans due to smoking with effects in animals produced by CO exposure.

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