UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-CASAC-89-021

June 15, 1989

OFFICE OF
THE ADMINISTRATOR

Honorable William Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Mr. Reilly:

We are pleased to transmit via this letter the advice of the Clean Air Scientific Advisory Committee (CASAC) concerning its review of the Agency's Clinical Research Plan. The Clinical Lab Review Subcommittee of CASAC conducted this review on February 9, 1989 in Chapel Hill, North Carolina. The process included a review of the Agency briefing document, "Clinical Research Branch - A Research Strategy for the Future", detailed presentations from Laboratory personnel, and public dialogue. The full CASAC has reviewed this effort and is pleased to endorse the views of its Subcommittee and adopt them as a CASAC report. A detailed presentation of our views is contained in the attached report.

We appreciate the opportunity to present our advice concerning this research effort and would appreciate receiving a written response which addresses our recommendations.

Sincerely,

Mark J. Utell, M.D.
Chairman, Clinical Lab
Review Subcommittee

Roger O. McClellan, D.V.M.
Chairman, Clean Air Scientific
Advisory Committee

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

June 21, 1989

OFFICE OF
THE ADMINISTRATOR

The Honorable William Reilly
Administrator
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, D.C. 20460

Dear Mr. Reilly:

The Environmental Effects, Transport and Fate Committee of the Science Advisory Board has completed its review of the Risk Assessment Forum's proposed Guidelines for Exposure-Related Measurements. The review was conducted at the request of EPA's Risk Assessment Forum, and was conducted on December 2, 1988, in Washington, D.C.

The Subcommittee recognizes these proposed guidelines as a logical complement to the previously issued Guidelines for Estimating Exposures. The prior guidelines, published and reviewed by the SAB in 1986, provide a framework for exposure assessment that may be integrated with the current guidelines resulting in a useful tool for exposure assessors. The Committee recommends that such integration take place with careful attention to the necessary linkages between measurements and modeling.

In addition to integration of the two sets of guidelines, the Committee recommends some modifications. Since the guidelines address exposure assessment for human health effects, this bias should be acknowledged. Alternatively, the guidelines, which have generic elements that can be brought to bear on effects to ecosystems, should be expanded to encompass exposure assessments in an ecological context. The focus and intended audience of the guidelines also need to be defined, and revisions made accordingly. The Committee discussed quality assurance and control stringency, the importance of exposure duration considerations, and needs concerning development and analysis of data. In addition, a recommendations was made to incorporate demographics, population dynamics, and population activity patterns into the process for assessing exposures. Finally, the Committee requests that the guidelines be amended to include references to other bodies of work that contain useful information on exposure assessment.

Independent comments were received from two members of the Indoor Air Quality and Total Human Exposure Committee. These members reviewed the Exposure Measurement Guidelines and provided a response. These independent comments are attached to the report to provide further feedback and critiques of the Guidelines.

The Subcommittee appreciates the opportunity to conduct this scientific review. We request that the Agency formally respond to the scientific advice transmitted in the attached report.

Sincerely

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Executive Committee
Science Advisory Board

Rolf Hartung

Dr. Rolf Hartung, Chairman*
Environmental Effects,
Transport and Fate
Committee

ENC

cc: Dorothy Patton
Michael Callahan
Bill Wood
Peter Preuss
Donald Barnes

* Dr. Hartung served as Chairman until December 31, 1988. Dr. Ken Dickson currently serves as Chairman of the Environmental Effects, Transport and Fate Committee. Since this review was initiated during Dr. Hartung's tenure, his efforts have seen it to completion.

United States
Environmental Protection
Agency

Office of the Administrator
Science Advisory Board
Washington, DC 20460

EPA-SAB-CASAC-89-021
June 1989

Report of the Clean Air Scientific Advisory Committee (CASAC)

Review of the Clinical Research Branch (CRB) of the Health Effects Research Laboratory (HERL)

ABSTRACT

The Clinical Lab Review Subcommittee of the Clean Air Scientific Advisory Committee (CASAC) reviewed the EPA's Clinical Research Branch (CRB) in order to provide the Agency with advice concerning current and future directions in health research at the EPA clinical facility. The Subcommittee concluded that the Research Plan was being conducted in a professional and technically adequate manner. The Subcommittee recommended that additional professional support be provided to two of the three sections of the Clinical Research Branch, and that the third section be supported in its goal of increased involvement in field and epidemiologic studies. The Subcommittee commented on the proportion of effort devoted to specific pollutants, and advised that a reduction in research on sulfur dioxide and carbon monoxide was warranted along with a substantial increase in research on acidic aerosols and a modest increase in research on nitrogen dioxide. The Subcommittee strongly encouraged that research on ozone clinical studies continue at the same level of effort for the next 3-5 years, and was clearly concerned about the lack of proper justification for the specific projects on indoor air and toxic pollutants. Finally, the Subcommittee recommended that a standing, external scientific review/advisory committee be established for the research program.

KEY WORDS: clinical research; national ambient air quality standards (NAAQS)

NOTICE

This report has been written as part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency; and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency or other agencies in the Federal Government. Mention of trade names or commercial products does not constitute a recommendation for use.

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1.0 EXECUTIVE SUMMARY

In February 1988, the Office of Research and Development (ORD) requested that the Clean Air Scientific Advisory Committee (CASAC) establish a peer-review Subcommittee to review the strategy and philosophy guiding the research program at the Clinical Research Branch (CRB) of the Health Effects Research Laboratory (HERL). The CRB conducts studies into the effects of environmental pollutants on human health. As a result of restructuring within the HERL, the CRB is now a component of a new division, the Human Studies Division. The CRB includes three sections, i.e., Physiology, Human Dosimetry, and Cell and Molecular Biology.

At a public meeting held on February 9, 1989 in Chapel Hill, North Carolina, the Subcommittee concluded that the restructuring of the HERL represents a significant and appropriate regrouping, providing good opportunities for programmatic growth. It recommended that additional professional support be provided to both the Human Dosimetry Section and Cell and Molecular Biology Section in order to support these new and highly productive programs. In addition, it recommended that full support be given to the Physiology Section's goal of increasing its involvement in field and epidemiologic studies. The Subcommittee called attention to the past productive exchange between the Clinical Research Branch and the personnel involved in other aspects of inhalation toxicology and pulmonary biology within HERL. The Subcommittee cautioned the Agency to nurture this collaboration and avoid having it inadvertently diminished in any way by the recent reorganization.

At the meeting, the Agency projected that the overall CRB program level of effort would remain relatively constant over the next five years and that the proportions of the effort devoted to specific pollutants and programs would shift. Reduced activities with ozone, sulfur dioxide and carbon monoxide are anticipated while increased activities in nitrogen dioxide, acid aerosols, indoor air, toxic pollutants, and biomarkers are likely. There was a clear Subcommittee consensus that reduction in research on sulfur dioxide and carbon monoxide was warranted as well as a substantial increase in research on acidic aerosols and a modest increase in research on nitrogen dioxide. However, the Subcommittee strongly encouraged that the present level of commitment to clinical studies of the effects of ozone, alone and/or in combination with other pollutants, be maintained during the next 3-5 years. There was a clear concern about proper justification for the specific projects on indoor air and toxic pollutants. It was recommended that any projected clinical studies in these areas be better justified and both scientific and programmatic issues be subjected to external review before any strong commitments are made.

Finally, the Subcommittee recommended that a standing external, scientific review/advisory committee be established for the research program of the CRB. This review process could not only help strengthen the research program but also provide support to a long-term research strategy.

2.0 INTRODUCTION AND BACKGROUND

In February 1988, the Director of the Office of Health Research (OHR), with concurrence from the Assistant Administrator for the Office of Research and Development (ORD), requested that the Science Advisory Board (SAB) review EPA's Clinical Research Branch (CRB). The purpose of the review was to obtain commentary and advice from the SAB on current and future directions in health research at the EPA clinical research facility. The review panel, constituted as a Subcommittee of the Clean Air Scientific Advisory Committee (CASAC), was advised that this was not a "scientific program review" in the traditional peer review sense, but rather an examination of the overall strategy and philosophy guiding all aspects of the clinical research program

The Clinical Research Branch conducts studies into the effects of environmental pollutants on human health. The CRB, situated in the Health Affairs area on the campus of the University of North Carolina (UNC) at Chapel Hill, is a research laboratory of the EPA within the Human Studies Division (HSD) of the Health Effects Research Laboratory (HERL). The research environment and activities of the CRB are unique. Five human exposure chambers are operated by the CRB. Volunteer subjects are exposed to environmental pollutants, and the acute responses during and following the exposures are measured using techniques drawn from a variety of disciplines, including cardiopulmonary physiology, immunology, biochemistry, cell biology, molecular biology, and the physical sciences. The UNC Center for Environmental Medicine and Lung Biology (CEMLB) developed under a cooperative agreement with EPA, has been closely involved with CRB in this research to the mutual benefit of the Agency and the University. In addition to the research collaboration, the University provides access to the Committee for the Protection of the Rights of Human Subjects as well as to large numbers of volunteers, both healthy and those considered to be potentially at increased risk. These include children recruited from the UNC Frank Porter Graham Center for Child Development. The scientific investigative team, including EPA investigators from both the CRB and other HERL units, together with collaborating investigators, have had a profound impact on the regulatory and risk assessment process in EPA related to criteria air pollutants.

The Subcommittee was provided with a briefing document entitled "Clinical Research Branch -- A Research Strategy for the Future". The Subcommittee was requested to examine the conceptual

framework for this strategy and to consider the mix of ongoing and planned research. Specifically, it was to focus on the six questions presented below:

1. Is the present balance of scientific expertise in the Clinical Research Branch appropriate and sufficient?

2. Does the current program take adequate advantage of the wide range of skills and expertise within the Health Effects Research Laboratory?

3. Is the clinical research program addressing the most appropriate health issues facing the Agency?

4. Is it appropriate and plausible to begin placing less emphasis on National Ambient Air Quality Standard (NAAQS) pollutants and more on other pollutants, such as volatile organic compounds?

5. Is there a potential role for clinical research in answering the health questions associated with biotechnology?

6. Are there additional environmental health questions which the clinical research program should address over the next 5-10 years?

3.0 CLINICAL RESEARCH BRANCH

The briefing document (with four appendices) provided to the Subcommittee prior to the meeting included a description of the CRB and how it fits into the newly reorganized Health Effects Research Laboratory. The CRB is comprised of three sections, Human Dosimetry, Cell and Molecular Biology, and Physiology. It was apparent that many research projects are multidisciplinary, using expertise from all three sections. A broad spectrum of expertise is available in the CRB, and this is supplemented by faculty from the UNC campus via the cooperative agreement. The appendices consisted of laboratory organization charts, a summary of the major research accomplishments, a list of publications, and the curriculum vitae of the Principal Investigators.

Decisions as to specific pollutants of interest, protocol design, endpoints, and other features of the studies are made primarily by the Laboratory Director, Division Director, Branch Chief, and Section Chiefs. These individuals must be knowledgeable in the relevant sciences as well as in the Agency's mission and programmatic needs. Investigators within the CRB present their scientific results at national and international meetings and often at CASAC meetings; in addition, they maintain close ties with the Agency's program offices.

The Clinical Research Branch provides data that can be used directly for regulatory and risk assessment activities. The testing capabilities of the CRB assess the biologic response to inhaled pollutants and evaluate the health significance of the observed response. The investigators develop exposure-response relationships in a variety of population segments. In addition, they work closely with animal toxicologists to facilitate better extrapolation across time and species. Mechanistic studies have been an essential part of this extrapolation process.

The briefing document also examined the approaches to human research, including both in vitro and in vivo exposure techniques, combinations of pollutants, and a variety of testing methods. The identification of sensitive individuals and populations such as asthmatics and perhaps even immunocompromised individuals is essential in developing accurate risk characterization. Epidemiology should continue to play a key role in identifying environmental hazards.

Because exposure to many pollutants of concern may span years or decades, it is often necessary to predict the consequences of long term, low-level exposures in humans. Since it is not feasible (or ethical) to expose humans over long periods of time, extrapolation of testing results from acute exposure may, in conjunction with results from animal and epidemiological studies, be relied upon to make these predictions. Considerable emphasis has been given to extrapolation development in the CRB.

The briefing document concluded with a preview of emerging issues and research priorities. New issues included indoor air pollutants, air toxics, development of new techniques, biomarkers, and biotechnology. All of these issues may experience growth in the CRB in the next 5-10 years.

Members of the Subcommittee agreed that missing both from the briefing document and subsequent presentations was a discussion of the expected legislative and regulatory pressures on the Agency over the next few years. The Subcommittee found itself in the uncomfortable position of having to provide opinion on the worthiness of a research plan without being provided the driving forces behind the plan. For example, if the Agency believes that regulatory needs will require substantially more information on the health effects of indoor air, then it makes sense to consider an expanded research program in that area. The development of a research plan guided in part by administrative needs and scientific issues is a laudable goal. The Subcommittee strongly recommended continuing efforts to further define and develop a research strategy which logically evolves from Agency needs and key research questions. Other SAB efforts, such as the recent report on Future Risk, discuss this further.

4.0 RESTRUCTURING OF THE CLINICAL RESEARCH BRANCH

The Clinical Research Branch is now a component of a new division within HERL, the Human Studies Division (HSD). The HSD's other branch, Epidemiology, represents a regrouping and programmatic expansion of field and population data base studies within HERL. While a review of current and future directions in health research within the Epidemiology Branch is beyond the scope of the charge to this Subcommittee, the plans and opportunities for closer research ties between the two branches warrant our comment, especially as they may influence the research activities within the CRB.

The new organizational structure has considerable merit insofar as it encourages and facilitates closer ties between the two groups studying the human health effects of exposures to environmental chemicals. Some of the new and sensitive assays developed in the laboratory can be used in field studies. Field demonstrations of the efficacy and power of these new assays and biomarkers of exposure could provide powerful resources to the emerging subspecialty of environmental epidemiology. The CRB's research program will also benefit from the participation of its scientists in field studies in terms of their broadened appreciation of "real-world" exposures and responses, and of desirable modifications of laboratory protocols and apparatus for their effective utilization in the field.

The new organization has the potential significant risk of diminishing the currently productive interchange and collaboration between CRB staff and pulmonary toxicology staff at Research Triangle Park also working on dosimetry and extrapolation modeling. The separation of these two branches of the former Inhalation Toxicology Division of HERL should not, and may not, diminish such collaboration, but the possibility exists and warrants a continued concern by the Directors of the two Divisions and of HERL managers.

The restructuring within the CRB into three sections, i.e., physiology, cell and molecular biology, and human dosimetry also represents a significant and highly appropriate regrouping, providing good opportunities for programmatic growth and significant enhancement of CRB contributions to HERL, to the field, to public health protection, and to peer recognition. The Subcommittee's specific comments on current and future directions within each of the three sections follow.

4.1 Human Dosimetry Section

This Section, headed by Dr. Timothy Gerrity, is the newest independent entity in the CRB. It provides a means for significant advances in the CRB's developing programs in human dosimetry and extrapolation modeling. Dr. Gerrity has the background,

perspectives, and skills needed to direct and lead an expanded research Program in this very important area, and the leadership of the OHR, HERL, and HSD should make every possible effort to provide the staff and resources he will need to accomplish the rather ambitious plans outlined at the CRB program review.

Dr. Gerrity described plans to introduce or expand laboratory capabilities for radioisotope clearance studies of lung permeability and particle clearance; dosimetry and metabolic studies of the nonradioactive ^{18}O isotope as a tracer of gases such as ozone, nitrogen oxides, and sulfur oxides; aerosol bolus dispersion as a test of small airways size and function; 3-D NMR imaging of airways; dual-laser aerosol photometry for volatile aerosols; and magnetopneumography for studying retention of ferrimagnetic tracer particles. Each of these techniques is complex and far from routine, and each has considerable utility and merit for CRB research. Dr. Gerrity himself is familiar with their essential features and could certainly see to their effective implementation if he were supervising the use of only one or two of them. However, he clearly needs additional professional staffing to integrate all or most of these into the Section and Branch research projects in a timely and efficient manner. Furthermore, it is not clear that all of these new technologies should be pursued simultaneously. It would be desirable to seek external peer review to establish priorities for the methods development and applications.

In addition to the introduction and incorporation of these complex and powerful measurement methodologies into CRB research, the Human Dosimetry Section clearly needs to pursue its research on dosimetry and extrapolation modeling. Here again, Dr. Gerrity has an excellent background as a researcher himself and can readily provide input and leadership in this research. However, as in the case of the application of the state-of-the art measurement methodologies, the rate of progress will be limited by his time commitment and access to additional resources. He will need and should have at least one more professional staff member with appropriate background and/or training in such modeling.

4.2 Cell and Molecular Biology Section

The Section on Cell and Molecular Biology, headed by Dr. Hillel Koren, involves a relatively young program with responsibility to investigate the effects of pollutants on human pulmonary inflammatory, immunological and systemic responses. Human cells and fluids are obtained from the lungs and airways by bronchoalveolar lavage (BAL) and/or nasal lavage, or from peripheral blood, and can be analyzed by state-of-the-art immunological, biochemical, and molecular biological techniques. Studies are conducted with human materials collected following *in vivo* exposure or materials collected from unexposed subjects can be exposed to pollutant materials *in vitro*. In addition, *in vivo*

and in vitro exposures can be combined. Dr. Koren is highly qualified to head up this basic science program in the CRB and is ably assisted by Dr. Robert Devlin, a molecular biologist. Despite its short existence, the productivity of this Section has been substantial. The Subcommittee was impressed particularly by the leadership role this laboratory has played in its research on biomarkers in BAL of humans exposed to ozone.

Dr. Koren described plans to continue in vivo studies with ozone, nitrogen dioxide and pollutant mixtures; to introduce in vitro studies with air toxics and hazardous waste products; to develop new molecular techniques including assays for messenger RNA, 2-D protein gel electrophoresis, and human lung cell cultures to increase sensitivity for detecting pollutant effects; and to enhance extrapolation between species using ^{18}O isotope studies. The Subcommittee is highly supportive of continuing in vivo studies in humans with criteria air pollutants, including ozone and nitrogen dioxide. Likewise, the efforts to introduce new molecular biology methodologies is a logical progression of current activities. The efforts to pursue extrapolation from animal to man is one that extends across all three sections of the CRB. The Subcommittee was far less certain as to the merits of the in vitro studies with air toxics and indoor air pollutants. Furthermore, it is not clear which studies should be undertaken and how they will increase our understanding of adverse health effects. It would be desirable to seek external peer review to establish priority regarding the relative merits of in vitro studies with oxidants, air toxics, fibers, hazardous waste incineration effluents or pesticides. As with the Human Dosimetry Section, the Subcommittee advocated increased staffing of this Section.

4.3 Physiology Section

Physiology is the largest and, operationally, the oldest section within CRB. Dr. Donald Horstman presently heads a group of six professionals and two technicians. As with the other Sections in the CRB, the research program has focused principally on acute responses to criteria pollutants. Ozone has received the greatest attention followed by carbon monoxide and sulfur dioxide. The variety of assays utilized in these studies, and the range of information gathered, has expanded notably in recent years. In great measure, this reflects collaboration with other Sections in the CRB as well as collaboration across branches of HERL and with the staff of CEMLB. For example, ongoing studies on ozone are examining possible inter-relationships among changes in pulmonary function, airway reactivity, membrane permeability and, in association with Dr. Koren's Section, both cells and mediators lavaged from peripheral lung. In a joint effort with Dr. Gerrity, the aerosol bolus technique is being established to assess changes in small airway function associated with these exposures.

The Physiology Section merits praise for high levels of productivity and scientific caliber, and for the relevance of its work to regulatory needs. The recent series of studies clearly demonstrating the cumulative effects of ozone on the lung during a single 6 3/4-hour exposure is likely to have profound influence on the experimental design of future studies and to carry important implications for regulatory policy.

In future chamber studies, one goal is to place increased emphasis on what Dr. Horstman termed "real world conditions". This will include studies of interactions between pollutants, between pollutants and environmental variables (temperature, relative humidity), and of the consequence of varying the pattern of exposure for a specified inhaled dose.

A second complementary goal of the Physiology Section is to increase its involvement in field and epidemiologic studies. In part, this goal is reflected in Dr. William McDonnell's candidacy for a Ph.D. in epidemiology (to complement his M.D. and M.P.H.) at UNC and Dr. Horstman's personal inclination to move toward direct participation in such studies. While the Subcommittee was not charged with reviewing the Epidemiological Branch and its programs, we support enthusiastically the Physiology Section's goal -- and by extension, the CRB goal -- of greater involvement in field and epidemiological studies.

5.0 RISK ASSESSMENT AND THE CLINICAL RESEARCH BRANCH

The Agency is relying increasingly on risk assessment methods for decision making. This increased role for risk assessment will have significant consequences for the Clinical Research Branch which has already provided the Agency with valuable risk assessment input. Nonetheless, these increased demands on the CRB, in the presence of limited resources, can create tensions.

The first step of risk assessment is hazard identification, the objective of which is to indicate the existence of a health concern for the pollutant studied. This step often uses high exposure conditions and sensitive subgroups to detect evidence of toxicity. The second step of risk assessment collects data needed to estimate the dose-response relationship for the groups studied. For several pollutants, little work has been done to characterize the general shape of the dose-response curve, and the optimal dosing regimen that would be dependent upon the shape of this curve. In general, when quantal dose-response models are to be estimated, dose levels should be considered which give rise to a range of responses; this consideration is unnecessary for the hazard identification step of risk assessment.

The ultimate objective of the risk assessment process is to estimate the health risk of a given population and is carried out

in the risk characterization step. This step requires a thorough characterization of the object population and the development of methods to extrapolate results from the study population to the object population. This could require the development of dose-response curves for several elements (subpopulations) of the object population. If risk assessment is to provide a framework for future research, these multifarious data needs must be recognized.

Risk assessment requires several extrapolation efforts, animal results to humans; high to low-dose response; acute response to chronic response; in vitro to in vivo response; and the relationship between observed biological responses and human disease. These extrapolation issues are not unique to the CRB. It is important that strong links be built between this Branch and other parts of the Agency which address the same issues. These efforts should be linked to an Agency-wide effort to address these extrapolation problems (see letter of SAB Extrapolation Models Subcommittee to the EPA Administrator, May 26, 1987). There are, however, specific elements of the clinical research program which are key for extrapolation issues with ozone. Human dosimetry work which complements similar animal dosimetry work is necessary to allow eventual extrapolation from animal data.

Similarly, efforts that allow interpretation of observed biological responses so that they can be factored into risk assessment are to be applauded. Many of the biological responses observed in clinical study research require difficult judgments about medical significance. It is important to develop as much information as possible to aid this judgment. Complementary chronic animal and epidemiology studies can be designed to help interpret the clinical response data. Another approach is to compare the responses observed in experiments to underlying variability. The Clinical Research Branch is encouraged to develop a data base to allow estimates of this variability. An understanding of the magnitude of changes that occur independent of environmental insults can help place the biological response in perspective.

6.0 PROGRAMMATIC EMPHASIS FOR THE CLINICAL RESEARCH BRANCH

Dr. John O'Neil, Chief of the CRB, projected that the overall CRB program level of effort would remain relatively constant over the next five years and that the proportions of that effort devoted to specific pollutants and programs would shift. He projected reduced activities for ozone, sulfur dioxide, and carbon monoxide research and increased activities in nitrogen dioxide, acid aerosols, indoor air, toxic pollutants, biomarkers, and possibly pollutants associated with alternative fuel systems. There was a Subcommittee consensus that program efforts should shift in relation to program needs and the completion of

high priority ongoing projects. There was, however, some serious concern about the decision process used, and the rationale for, some of the projected shifts, especially in light of the current skill mix of the staff and of the prospects for productive research in some of the areas projected to receive additional efforts. Furthermore, the selection of research areas in the bar chart presented by Dr. O'Neil leaves out important areas of CRB research, such as studies of mixtures, methods development, dosimetry and extrapolation modeling. The EPA Staff agreed that a graphic depicting these issues would be helpful.

With respect to the projections as stated, the Subcommittee views the proposed reduction in commitment to ozone research with concern. Ozone is highly reactive and injurious to the lungs in experimental studies at realistic concentrations. Huge numbers of people are exposed to multiple exceedances of the current national ambient air quality standards (NAAQS) for ozone each year and troubling questions about the possible relationship between the acute effects of ozone and chronic, irreversible lung damage remain unresolved. The Subcommittee also calls attention to the remarkable progress made by CRB scientists on ozone research in recent years. We believe that they are now crossing the threshold from ozone exposure-response characterizations to more fundamental and mechanistic understandings. They should clearly proceed on the highly productive research lines now underway. Furthermore, these studies are highly likely to lead to effective research focused on the chronic health effects of ozone, an issue which should be, and is likely to be a high priority research area for EPA in the next five years.

While a reduction in clinical studies involving ozone in purified air may well be warranted, we recommend that serious consideration be given to including ozone in any projected study of the effects of pollutant mixtures. One reason is that ozone is almost always present in ambient pollutant mixtures. A second is that synergism in mixtures generally requires that at least one component of the mixture be highly biologically active by itself. Ozone is clearly a good model toxicant in this regard. Finally, there is evidence from animal toxicology that ozone potentiates responses to both nitrogen dioxide and acidic aerosols, two of the pollutant classes slated for additional research.

There was a clear Subcommittee consensus that reductions in research on sulfur dioxide and carbon monoxide were warranted as well as a substantial increase in research on acidic aerosols and a modest increase in research on nitrogen dioxide. On the other hand, there was a clear concern about whether the projected increases in research on indoor air and toxic pollutants were adequately justified. The Subcommittee views with reservation the apparent commitment to research on issues such as the Sick Building Syndrome (SBS) and Environmental Tobacco Smoke (ETS). Our concern was in regard to the opportunities for productive clinical research

in these areas, and not with regard to HERL's overall need to support health research on these classes of pollutants. We strongly recommend that any projected clinical studies in these areas be better justified and that the study design and protocols be carefully peer-reviewed before any resource commitments are made. We are also concerned that the staff's background and skill mix, while highly suitable for clinical studies on irritant air pollutants, may not be suitable for research activities on organic solvents and other constituents of indoor air mixtures at low concentrations. SBS and ETS are complex challenging issues, but it is not clear whether the CRB has sufficient experience and judgment born of experience to move ahead in this field in the near future.

7.0 PEER-REVIEW IN THE CLINICAL RESEARCH BRANCH

The Clinical Research Branch has achieved national leadership in the past few years in health-related scientific research on criteria pollutants. The accumulated experience, knowledge and judgment appear to have earned for the staff a considerable degree of independence in the establishment of priorities in design of experimental research. Nonetheless, a number of the individual projects, and in particular the overall direction of the research program would likely benefit from periodic scientific peer review. This is particularly true with regard to emerging issues about which the staff may be less confident. Several models of effective scientific advisory councils exist, including that of the National Institutes of Health, to assist HERL in designing one to meet the needs of CRB. A standing advisory/review group of scientists convening on a regular basis would provide continuity and familiarity with the issues. This review process could not only help strengthen the research program, but also reduce the frequency and time required for other ad hoc reviews to which CRB is subject from time to time. Such a formal process might also provide support for the continuation of ongoing programs in the face of external pressure to shift directions depending on the popular issue of the period.

8.0 RECOMMENDATIONS

a. Additional professional support should be provided to both the Human Dosimetry Section and Cell and Molecular Biology Section in order to support the ambitious, novel, and highly productive programs in these Sections.

b. Full support should be given to the Physiology Section's goal of increasing its involvement in field and epidemiologic studies.

c. The present level of commitment to clinical studies of the effects of ozone, alone or in combination with other pollutants, should be maintained during the next 3-5 years.

d. Current plans to initiate research on indoor air pollution and hazardous air pollutants should be subject to both external scientific and programmatic review, to determine their appropriateness and priority levels.

e. A standing external, scientific review/advisory committee should be established for the research program of the CRB.