Board of Scientific Counselors

Office of Research and Development
United States Environmental Protection Agency

B.O.S.C.

Human Health Research Program Review

Final Report of the Subcommittee on Human Health

May 18, 2005
Revised July 27, 2005

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PROGRAM REVIEW REPORT
OF THE
BOARD OF SCIENTIFIC COUNSELORS

HUMAN HEALTH RESEARCH PROGRAM

Office of Research and Development
U.S. Environmental Protection Agency

MAY 18, 2005
REVISED JULY 27, 2005

SUBCOMMITTEE ON HUMAN HEALTH

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I. EXECUTIVE SUMMARY

Overall Review Goals and Charge

Independent expert reviews are used extensively by industry, federal agencies, Congressional committees, and academia and have been recommended by the National Academy of Sciences as an approach for evaluating federal research programs. Accordingly, the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) enlisted its Board of Scientific Counselors (BOSC) to conduct independent expert reviews of its environmental research programs. ORD plans to use the findings from these evaluations to improve the management and performance of its programs; establish "best practices" in federal research program design, management, and evaluation; and strengthen research accountability as it complies with Office of Management and Budget (OMB) requirements.

At a public meeting in September 2004, the Executive Committee of the BOSC agreed to form a new subcommittee to conduct a program review of ORD's Human Health Research Program. It is expected that the review will provide guidance that will help ORD to: (1) plan, implement, and strengthen the Human Health Research Program; (2) compare the Human Health Research Program with programs designed to achieve similar outcomes in other parts of EPA and in other federal agencies; (3) make research investment decisions over the next 5 years; (4) prepare EPA's performance and accountability reports to Congress under the Government Performance and Results Act of 1993; and (5) respond to evaluations of federal research, such as those conducted by OMB, which highlight the value of recommendations from independent expert panels.

The new eight-member Human Health Subcommittee created by the BOSC is composed of representatives from academia, industry, and government. The Subcommittee was charged with evaluating ORD's Human Health Research Program with respect to four criteria: relevance, quality, performance, and scientific leadership (see Appendix A for the charge questions). A series of questions associated with each of these four criteria was posed to the Subcommittee, and the Subcommittee chose to organize its response according to the long-term goals (LTGs) outlined in the *Human Health Multi-Year Plan* (MYP). Charge questions were answered in the context of each LTG. The salient points within each LTG have been captured and aggregated across the Human Health Research Program as a whole in this Executive Summary.

Subcommittee Members

The members of the Human Health Subcommittee have considerable expertise in the area of human health research, including formal education, training, and research experience in biology, chemistry, biochemistry, environmental carcinogenesis, pharmacology, molecular biology and molecular mechanisms of carcinogenicity and toxicity, toxicology, physiologically based pharmacokinetic (PBPK) modeling, exposure modeling, risk assessment, epidemiology, biomarkers and biological monitoring, and public health, with additional expertise in the areas of children's health, community-based human exposure studies, and clinical experience. The

Subcommittee was chaired by Dr. James Klaunig from Indiana University School of Medicine. Dr. James Clark of Exxon Mobil Research and Engineering Company served as Vice Chair of the Subcommittee. Other members included Drs. Timothy Buckley, Johns Hopkins University; Harvey Clewell, CIIT Centers for Health Research; Michael Jayjock, The LifeLine Group; Joseph Landolph, University of Southern California; Donald Mattison, National Institutes of Health (NIH); and Elaine Symanski, University of Texas Health Science Center at Houston.

Structure of the Program Review

The format of the program review's face-to-face meeting was modeled after the successful reviews conducted at the division level by the National Health and Environmental Effects Research Laboratory (NHEERL). The meeting opened with an explanation of Federal Advisory Committee Act (FACA) rules by the Designated Federal Officer (DFO), after which a synopsis of the Human Health Research Program was presented. A series of presentations organized along the Program's four LTGs followed. For each LTG, an overview of the key issues and the research approaches used to address these issues was presented by the ORD Lead for the LTG. This information was augmented by a poster session in which intramural and extramural researchers presented studies and results in greater scientific detail, also noting the impact and outcomes of their research and the extent to which funding was leveraged with other programs. The poster sessions gave the members of the Subcommittee the opportunity for one-on-one discussions with principal investigators. Following each poster session, the Subcommittee reconvened to summarize and discuss its findings; this discussion session was moderated by the Subcommittee member assigned as Lead for the LTG. The 2 ½-day meeting concluded with testimonials presented by various EPA program and regional office representatives. These individuals discussed their use of the science produced by the Human Health Research Program and offered their perspectives on its relevance and impact. At the close of the meeting, a draft oral report was presented by the BOSC Human Health Subcommittee. Work sessions for the Subcommittee were held at various times throughout the face-to-face meeting, and time was allotted for public comment.

Prior to the face-to-face meeting of the Subcommittee in North Carolina, two public conference calls were held where the charge to the Subcommittee was defined, individual writing assignments were made, and the expectations of the Subcommittee's report was discussed. The members received several electronic and hardcopy documents describing the overall strategy of the Human Health Research Program, as well as a recent review of the strategy by a Science Advisory Board (SAB) Panel. In addition, printed legal-size paper copies of the posters were provided to the panel members upon arriving at the meeting. The Subcommittee members concurred that the structure of the review was well organized, and the presentation of the materials in both platform and poster forms was a very good approach, allowing for interchange between the scientists involved in the four programs and the Subcommittee members conducting the review.

The Subcommittee recognized and appreciates the amount of work that ORD put into developing preparatory materials. Evidence that ORD has responded to previous reviews by the SAB's Human Health Research Strategy Review Panel, the SAB's Drinking Water Committee, the BOSC, and the National Research Council (NRC) is present both in written documentation as

well as verbal presentations. The Subcommittee expressed disappointment, however, that the information provided to the members was not presented in a format that specifically addressed the review criteria (i.e., relevance, quality, performance, and scientific leadership). Future BOSC reviews can be facilitated and enhanced by: (1) providing to the Subcommittee the reports/critiques from previous reviews; and (2) tailoring the EPA presentations to the review criteria and critiques from previous reviews.

The Human Health Research Program: Background

In 1998, EPA sponsored a meeting of scientists and managers from ORD and the regional and program offices. The objective of the meeting was to identify cross-cutting issues of high priority that would form the basis of a core human health research program at EPA. Subsequent to that meeting, ORD developed the *Human Health Research Strategy* (2003), which provided a conceptual framework for human health research and identified and prioritized the research needed to improve the scientific foundation for health risk assessments. Four areas of research were emphasized in the strategy: harmonizing cancer and noncancer risk assessments (which has been subsequently refocused as the use of mechanistic information in risk assessment), assessing aggregate and cumulative risk, evaluating the risk to susceptible human subpopulations, and evaluating public health outcomes. These priority research areas set the strategic direction for the Human Health Research Program in EPA and provided the scientific basis for the development of the LTGs later identified in the Human Health MYP. The Human Health Research Strategy Review Panel of the SAB reviewed EPA's Human Health Strategy document in 2003 and made numerous recommendations. EPA adopted these recommendations, making the program very strong.

The Human Health MYP (2003) is a document that describes in greater detail ORD's plans for a core research program in human health. It provides information to aid and support decisions during budget formulation, focuses on key research questions and scientific results, and demonstrates how the research program will contribute to Agency outcomes and strategic goals. In the MYP, ORD identified four LTGs, each linked to one of the four research areas articulated in the *Human Health Research Strategy* that represent the highest priority research needs. The four LTGs are:

- **LTG 1: Use of Mechanistic Information in Risk Assessment**
  The key research questions for this goal are:
  - What modes/mechanisms of action (MOA) are important for understanding the impact of environmental stressors on human health?
  - What are the attributes (e.g., shape of the dose-response, species specificity) of the MOA that impact risk assessment?
  - How do we measure, model, and/or predict the key attributes of the MOA that could impact risk assessment?
  - How do we incorporate mechanistic tools into risk assessment?

- **LTG 2: Aggregate/Cumulative Risk Assessment**
  The key research questions for this goal are:
  - What are people's real world aggregate exposures?

- What contributes to aggregate exposures?
- How do we predict cumulative risk from aggregate exposures?
- How do we mitigate aggregate/cumulative risk?

✦ **LTG 3: Evaluation of Risk to Susceptible Subpopulations**

The key research questions for this goal are:

- Which subpopulations have differential risk to environmental stressors?
- What is the basis for differential risk?
- What is the risk to each subpopulation?
- How can differential risk be mitigated?

✦ **LTG 4: Evaluation of Public Health Outcomes**

The key research questions for this goal are:

- What public health outcomes need to be examined to evaluate Agency regulatory decisions?
- What approaches/tools are needed to evaluate (and attribute) changes in public health outcomes to Agency actions?
- Did Agency actions have an impact on public health outcomes?

By addressing these questions, it is the goal of the Human Health Research Program to provide fundamental understanding of the physical and biological processes that underlie environmental systems and human populations at risk. It is expected that the products of this program will provide an integrated information base for scientifically defensible risk assessment and risk management decisions.

Conclusions and Recommendations for the Program

Overall Program Strengths

✦ The research of the Human Health Research Program was found to be of high quality and appropriately focused.

- It was multidisciplinary, displayed good stakeholder participation, informed risk assessments, and achieved the goal of reducing uncertainty.

✦ The hallmarks of the program are that the research is multidisciplinary, yet coherent and coordinated.

- The scientists display an overall high level of enthusiasm and commitment.
- Development of new data is encouraged, and extant data are fully explored and utilized to inform the risk assessment decisions of stakeholders.

✦ Interaction is occurring among investigators involved in different LTGs, and this interaction should be acknowledged and encouraged through both formal (e.g., research retreats) and informal means.

- ✦ The research benefits from managerial excellence across all aspects of the program.
  - Managers set a tone and expectation that encourages, spawns, and rewards problem-driven cross-discipline teams at the operational level.
  - Excellent managerial support is reflected in the overall high level of excitement, commitment, and passion displayed by the scientists in describing their work.

- ✦ A remarkably positive and valuable aspect of this program is a decisive propensity within the program to encourage the mining of available data and science to inform the risk assessment decisions of stakeholders.

Overall Program Opportunities

- ✦ To some extent, the direction, choice, and focus of research topics are undoubtedly areas where national politics interact and shape the development of specific scientific programs.
  - Although this is a reality of conducting research in support of the Agency, it is important that ORD priorities continue to integrate the status of scientific knowledge.
  - The overall criteria and framework for decisions regarding why specific elements are vital and have been included in the research program could be enhanced further in the written material presented to the Subcommittee.
  - A more transparent explanation of prioritization and justifications would be most valuable.

- ✦ The Human Health Research Program should monitor, engage in, and advise research efforts of other international organizations such as the European Union (EU).

- ✦ The creation of the new National Center for Computational Toxicology may produce challenges with regard to teamwork.
  - The most quantitatively oriented individuals in the NHEERL and the most biologically oriented individuals of the National Exposure Research Laboratory (NERL) that are moving to the Center should not lose contact with scientists and issues in their former organizations.

- ✦ A greater level of interaction between the externally funded University Centers and in-house research could result in more significant research progress (e.g., the case of the potential role of glutathione S-transferase [GST] polymorphisms in autism).

Conclusions and Recommendations for Each Long-Term Goal

LONG-TERM GOAL 1

Use of Mechanistic Information in Risk Assessment

- ✦ ORD scientists have been and continue to be leaders in developing research to support EPA risk assessments, which has allowed EPA to be a leader for many years in conducting credible, nationally/internationally accepted risk assessments of chemicals of environmental

concern. Veteran scientific administrators are providing exceptional leadership to the Human Health Research Program.

- Mechanistic research by ORD scientists has positively and significantly affected risk assessments and will benefit future assessments of other chemicals. Stakeholders (the Offices of Air, Water, Pesticides, and Toxics and regional offices) are involved in planning/prioritization of ORD's Human Health Research Program.

- The Human Health Research Program has a logical, comprehensive MYP that describes an appropriate flow of work within/across LTG 1 and has made significant progress toward each major area of research within this LTG.

- The Agency has successfully utilized its extramural grants program to advance its research agenda. These programs, however, need to be better advertised and perhaps even better financed and expanded to attract the widest possible competitive applicant pool.

- New, broad strategies should be developed by the Human Health Research Program to manage the risks from the thousands of new chemicals that are being synthesized and put into the environment.

LONG-TERM GOAL 2

Aggregate/Cumulative Risk Assessment

- The research efforts on cumulative risk assessment are highly relevant to the problems faced by the Agency in assessing the risks faced by the public, who are typically exposed to multiple toxic chemicals. The research described in the area of cumulative risk assessment is particularly creative, effective, and well conducted.

- The work shows a propensity to develop new data and to mine available data to inform risk assessment decisions. Assessments should be more comprehensive, however, and include a wider array of chemicals important to human exposure.

- The overall criteria and framework for decisions regarding why specific elements are vital and have been included in the research program could be further enhanced in the written material presented to the Subcommittee. A more transparent explanation of these aspects would be most valuable.

- The Human Health Research Program plays a leadership role in advancing the realm of scientific development in the areas that are currently addressed. The scientific staff is excellent, as are the facilities, and the funding appears to be adequate. Within this realm, the managers and researchers are overseeing and participating in a program that is leading the state-of-the-science.

LONG-TERM GOAL 3

Evaluation of Risk to Susceptible Subpopulations

- The susceptible subpopulations program is well grounded within the ORD strategic plan. There is evidence of good coordination with other programs in the Human Health Research Program, as well as with outside research organizations (nationally and internationally), and there is leveraging of effort across federal agencies. In addition, Agency scientists involved in the research on children's susceptibility are internationally recognized experts in children's environmental health and play a strong role in fostering a continuing emphasis on this research area.

- The current level of involvement of program offices, regional offices, and other stakeholders provides strength to the program; it should be sustained and possibly upgraded. There is a need to expand EPA expertise to include community-based participatory research.

- The single dimensional model presented in this program did not fully represent what is a dynamic multidimensional research program. Although the Agency's focus on children as a susceptible population subgroup appears well justified, the justification can be strengthened by the Agency's own scientific assessment of the public health benefit to be achieved through a research focus on children as a particular subpopulation.

LONG-TERM GOAL 4

Evaluation of Public Health Outcomes

- This area of focus is relatively new to ORD and the Human Health Research Program and is consistent with the overall mission of EPA in the protection of human health. The program on public health outcomes is being built upon the same conceptual framework that supports the three other LTGs, namely the exposure-dose-effect continuum. Overall, the program on public health outcomes is highly relevant to the mission of the Agency and has the potential to serve as the nucleus for integrating and evaluating ORD research.

- The Subcommittee believes that the goals of this program could be further focused to guide future activities and that a process needs to be articulated for making decisions about which actions to evaluate, which endpoints to study, and which environmental indicators to apply. Long-term success of this program will be dependent in part on the ability to develop strong interactions with other programs in EPA and utilize research from other LTGs. Thus, it is recommended that a mechanism be put into place with formal and informal components to promote dialogue among investigators involved in the different LTGs and to provide a process for assessing research outputs.

- The program will require additional monies and personnel to broaden expertise in areas of public health, especially in biostatistics and environmental epidemiology.

II. Overview Comments on Human Health Research Program

Overall Strengths

The research of the Human Health Research Program was found to be of high quality and appropriately focused. It was multidisciplinary, displayed good stakeholder participation, informed risk assessments, and achieved the goal of reducing uncertainty. The hallmarks of the program are that the research is multidisciplinary and yet coherent and coordinated, the scientists display an overall high level of enthusiasm and commitment, and development of new data is encouraged at the same time that extant data are fully explored and utilized to inform the risk assessment decisions of stakeholders.

Interaction is occurring among investigators involved in different LTGs, and this interaction should be acknowledged and encouraged through both formal (e.g., research retreats) and informal means. The Subcommittee was impressed by the high level of cooperation and teamwork among investigators and across organizations that was displayed in the Human Health Research Program. Effective interaction and collaboration across disciplines (e.g., computer modeling, statistics, pharmacokinetics, health endpoint evaluation) and across organizations (NHEERL, NERL), critical to an innovative, effective, and productive human health program, were achieved. ORD management is to be commended for fostering such an effective team research environment.

Managerial excellence appears to be a hallmark of the overall program. Setting a tone and expectation that encourages, spawns, and rewards problem-driven cross-discipline teams at the operational level is a clear and positive result of this managerial effort. Interactions with scientists and programs external to EPA are less formally organized, but where they occur, they appear to be appropriately happening at the lead scientist/principal investigator level. Additional evidence of excellent managerial support is reflected in the overall high level of excitement, commitment, and passion displayed by the scientists in describing their work. It is suggested that this strong positive aspect of this program be explicitly recognized, continually rewarded, and carefully guarded.

Overall Opportunities

To some extent, the direction, choice, and focus of research topics are undoubtedly areas where national politics interact and shape the development of specific scientific programs. Today, there are regulatory mandates playing out in the rest of the world that are driving the overall scientific development of human health exposure assessment for the multitude of common and relatively unstudied substances to which humans are exposed. Significant resources are about to be committed, especially in the EU, to develop the exposure and risk assessment tools needed to reasonably accomplish these mandates.

Even if EPA ORD is not designing this type of research, it should monitor, engage in, and advise these research efforts of others. Scientists within the Human Health Research Program should contribute their considerable skill and knowledge to the EU Research Planning.

The creation of the new National Center for Computational Toxicology may produce challenges with regard to teamwork. It appears that the most quantitatively oriented individuals in NHEERL and the most biologically oriented individuals in NERL will become part of the new Center. Although this reorganization apparently does not involve a change in location, there is a potential for the founding staff of the Center to become focused on the mission of the new organization and to some extent lose contact with the scientists in their former organizations. This transition should be monitored to ensure that collaboration continues to be encouraged and not organizationally impeded.

Program Relevance

Strategic drivers for the Agency's Human Health Research Program are mandates from Congressional actions, mandates from the Administration, needs of the regional and program offices, needs of the scientific community, recommendations of external advisory groups, and goals established by EPA in response to the Governmental Performance and Results Act (GPRA) under Sound Science. Based on these strategic drivers, the Agency has identified two strategic research directions: (1) research to improve the scientific foundation of human health risk assessment, including harmonizing cancer and noncancer risk assessments (which has been subsequently refocused as the use of mechanistic information in risk assessment), assessing aggregate and cumulative risk, and determining risk to susceptible human subpopulations; and (2) research to enable evaluation of public health outcomes from risk management decisions. These two strategic research directions are consistent with EPA's strategic goals, its *Human Health Research Strategy*, and the NRC's recommendations for Core Research Program items.

The presentations and review materials provided by ORD scientists showed that ORD has been diligent in implementing the recommendations in the report of the NRC's Committee on Research Opportunities and Priorities for EPA (referred to as the ROPE report) into its Core Research activities. The formalization of a balance between Core Research and Applied Research is excellent and serves the Agency well.

The core Human Health Research Program is effective and strategic in its coordination of its intramural and extramural research programs. Research programs are defined to achieve separate but complementary objectives. These programs are effectively coordinated, resulting in good synergy with minimal redundancy. Effective participation of program and regional offices in research planning, execution, and evaluation is a major strength of the Human Health Research Program. It is through this participation that EPA's research is grounded in the practical needs of regulatory offices and communities. The interaction with program and regional offices is already occurring, although the strength of the interaction appears to vary across program offices. These strong and valuable interactions take place because of the initiative of ORD scientists, as well the facilitation of ORD management. Of course, constant vigilance is required to assure that practice-oriented research is balanced with basic hypothesis-driven research.

The Subcommittee noted that a greater level of interaction between investigators in the externally funded University Centers and in-house researchers could result in more significant research progress, as seen, for instance, in the case of the potential role of GST polymorphisms in autism. EPA has established an Extramural Research Grants Program and an Extramural Environmental Health Centers Program that both utilize the efforts of scientists at research institutes and universities to aid the Agency in developing research projects in areas of toxicology and carcinogenesis that need to be explored beyond the Agency's immediate capabilities.

The EPA also has established a program by which outside scientists can be hired on a temporary basis (Interagency Personnel Agreement [IPA], 4-year terms) to work inside the Agency and bring it new expertise. Cooperative Research and Development Agreements (CRADAs) also are available to extend the expertise of the Agency by incorporating the expertise of external scientists as extramural contractors. The posters and publications of ORD scientists showed clear evidence that collaboration is occurring between Agency scientists and scientists from other governmental agencies (e.g., the National Institute of Environmental Health Sciences [NIEHS]). A listing of intergovernmental agency collaborations between the Human Health Research Program of ORD and its sister governmental agencies, however, was missing from the review documents, so the full extent of this partnering could not be judged accurately and given appropriate credit.

The public benefits from doing good science could be further enhanced in the written materials presented to the review Subcommittee. Certainly, understanding and substantially reducing cancer and noncancer risks are vitally important and clearly recognized in this plan. The Subcommittee advises that it also is important and valuable that the technical work products be able to render the scientific determination of *de minimus* or acceptably low levels of human health risk from chemical exposure. The value of confident knowledge regarding the relative safety offered by improved exposure and risk assessment tools of previously feared exposures and putative risks represents an arguably significant improvement to the public health.

Program Quality

The Human Health Research Program is of high quality and appropriately focused. There appear to be good multidisciplinary approaches to the research, effectively mixing multidisciplinary research from the level of the cell to human populations and back again. In addition, there is an overall high level of excitement and commitment displayed by the scientists in describing their work. The research described was creative, effective, and well conducted. The Agency scientists have shown considerable skill in applying quantitative techniques ranging from statistical analysis to PBPK modeling, as required for the various aspects of the research. In conducting research on cumulative risk, EPA scientists have been able to simultaneously provide rapid response to the needs of the Agency's regulatory program while still maintaining a strong, long-term research effort. In addition, peer review is recognized as a critical component of EPA's Human Health Research Program.

To better evaluate the quality and performance of the Human Health Research Program, reviewers would have benefited from a bibliometric analysis of publications; such an analysis

would be a useful parameter for showing the impact of EPA research on the field. This analysis should differentiate the intramural from the extramural programs to facilitate assessments of Agency capabilities and the efforts of funded scientists, as well as assess collaborative efforts. It was brought to the attention of the reviewers that a bibliometric analysis was underway at the time of the review, but it was not available in time for the reviewers to take the results into consideration.

Program Performance

A remarkably positive and valuable aspect of this program is a decisive propensity within the program to encourage the mining of available data and science to inform the risk assessment decisions of stakeholders. The Subcommittee encourages the use of consensual scientific deliberation by teams of experts to provide the best advice possible relative to the critical questions facing risk assessors and risk managers.

EPA's overarching conceptual framework description for the core Human Health Research Program that represents the LTGs and their interaction could be expanded and more fully developed. The overall criteria and framework for decisions regarding why specific elements are vital and have been included in the research program were not always clear to the Subcommittee members. Although the research program appears appropriately directed and focused, its scientific basis, justification, and conceptualization could be further developed. The presentation of the justification of research priorities appeared to some members of the Subcommittee to be largely defined by external advisory bodies, such as the NRC. Although advice from such advisory groups provides an important element of justification, further clarification of the role of the scientists of the Human Health Research Program in defining and setting these priorities is suggested. The presented materials lacked sufficient detail relating the specific program elements to be able to reasonably conclude that the focus is consistent with the stated goals. Details such as exactly how the work is going to be planned and processed are critical, and although not presented in the premeeting materials, were in most cases clearly articulated during the meeting.

Program Leadership

The majority of the Subcommittee members thought that the scientific leadership of the Human Health Research Program was excellent. The team of veteran scientific administrators provides professional leadership to the Human Health Research Program and ORD scientists in EPA. The NRC's ROPE report stressed strengthening the core research of ORD within EPA and using this core research program to aid that Agency and its programs. ORD has worked hard to implement recommendations of the NRC report and demonstrated success in supporting key advances in human exposure and health effects research. The scientific leadership of the program is strong. A minority of the Subcommittee members expressed concern, however, that the direction and leadership of the program was strongly influenced by external advisory groups.

Program scientists contribute and frequently have taken on leadership roles in environmental science, toxicology, carcinogenesis, risk assessment, exposure assessment, and public health. Most of the researchers participating in the Human Health Research Program have made

significant contributions to the peer-reviewed scientific literature. The Subcommittee reviewed an extensive bibliography of publications derived from the Human Health Research Program. ORD scientists also serve in key positions in advisory committees and technical panels for governmental and industrial research programs, in key positions for scientific societies, and in undergraduate and graduate teaching programs at universities. Also, within EPA, ORD scientists have been leaders in developing research to support EPA risk assessments for many years, and they continue to lead in this area. This research strength of ORD has allowed EPA to be a leader in conducting credible, nationally and internationally accepted risk assessments on chemicals of environmental concern for many years. The Subcommittee noted an area of opportunity for further participation (i.e., examining involvement and potential collaboration with similar programs in the EU and Health Canada). These interactions should be coordinated at a much higher level within the Agency than is currently occurring.

Another area of opportunity relates to leadership transition. There is evidence of a gap in the Human Health Research Program between the number of senior, established scientists currently holding leadership positions and younger, less experienced researchers. Some thought should be given by EPA to culturing and developing individuals for leadership positions (perhaps through mentorship) and making the emerging roles and responsibilities clear to all stakeholders. The Subcommittee recommends that EPA plan for leadership succession in both the technical and management arenas.

III. LONG-TERM GOAL 1: USE OF MECHANISTIC INFORMATION IN RISK ASSESSMENT

Relevance

Strategic drivers for EPA's Human Health Research Program are mandates from Congressional actions, mandates from the Administration, needs of the regional and program offices, needs of the scientific community, recommendations of external advisory groups, and goals established by EPA in response to GPRA under Sound Science. Based on these strategic drivers, the Agency has identified two strategic research directions: (1) research to improve the scientific foundation of human health risk assessment, including harmonizing cancer and noncancer risk assessments (which has been subsequently refocused as the use of mechanistic information in risk assessment), assessing aggregate and cumulative risk, and determining risk to susceptible human subpopulations; and (2) research to enable evaluation of public health outcomes from risk management decisions. These two strategic research directions are consistent with EPA's strategic goals, its *Human Health Research Strategy*, and the NRC's recommendations for Core Research Program items.

The presentations and review materials provided by ORD scientists showed that ORD has worked hard to implement the recommendations of the NRC's ROPE report into its Core Research activities. ORD has worked to balance its research efforts between Core Research and Applied Research to the extent of 50 percent in each of these activities, as recommended by the ROPE report. Presently, the balance stands at approximately 60 percent Core Research and 40 percent Applied Research, which is appropriate. This formalization of a balance between Core Research and Applied Research is excellent and serves the Agency well.

Consistency With Agency Strategic Goals, the Human Health Research Strategy, and Recommendations of the NRC

Development of mechanistic data to guide risk assessments is crucial to ensure risk assessments produced by the Agency are accurate. Within EPA, ORD scientists have been leaders in developing research to support EPA risk assessments for many years, and they continue to lead in this area. This research strength of ORD has allowed EPA to be a leader in conducting credible, nationally and internationally accepted risk assessments on chemicals of environmental concern for many years. The work of ORD scientists on molecular mechanisms of the carcinogenicity of arsenic and dioxin has contributed significantly to cancer risk assessment in these areas.

The EPA research program on dioxins has proved to be of high value in supporting EPA's risk characterization for these chemicals. Important products of this research effort that have been incorporated into the dioxin risk assessment include: (1) the demonstration that steady-state body burden should be used as the measure of exposure for cross-species equivalence, instead of the traditional default of dose rates (mg/kg/day); (2) scientific support for the toxicity

equivalency factor (TEF) approach for assessing exposure to mixtures of dioxins; and (3) establishment of the human relevance of the mode of action for dioxin effects. This work has been used by other agencies internationally. Moreover, the importance of using body burden instead of dose rate in risk assessments for persistent chemicals is a major step forward that will impact many future risk assessments.

Mechanistic research on atrazine by ORD scientists has had a similarly valuable impact on the risk assessment for this chemical and will benefit future assessments of other chemicals that disrupt the luteinizing hormone (LH) surge. This work demonstrates the importance of using mode of action studies to elucidate the interactions between toxic chemicals and biological systems instead of assuming simple equivalence of effects across species. The research efforts on atrazine demonstrated that effects in animals that were the initial concern (mammary cancer) were not likely to be relevant to humans. The mode of action for atrazine suggests that humans would be at risk for different toxic effects. The results have been highly influential in the Agency's consideration of the risk from this chemical. The efforts to identify shortcomings in the standard developmental test protocols that failed to detect the developmental effects of atrazine provide important insight into the limitations of current animal testing protocols. These research efforts of ORD are very useful to the Office of Pesticides at EPA. Both the dioxin and atrazine research efforts clearly demonstrate the valuable interactions taking place in the Agency between the research program and the regulatory program.

A further example of research relevant to EPA's strategic mission was the demonstration that, for drinking water disinfection byproducts (DBPs) that share a common mechanism of action, effects of these chemicals can be added to generate a common additive risk. Starting with adjustments to internal animal dose, these investigators adjusted that dose to an internal human dose equivalent, allowing these investigators to develop dose-response curves for human response. This approach has significant utility in the calculation of the risk of humans to a mixture of DBPs.

ORD researchers contributed an excellent piece of research on component-based methods for investigating chemical mixtures in toxicology. These investigators showed that at lower concentrations (i.e., close to relevant environmental exposure to pesticides) there is an additivity or antagonism in the hepatotoxicity of four trihalomethanes when these chemicals are administered to animals as mixtures, based on mixing and concentrations administered to animals. For organochlorine pesticides, there were greater than additive (synergistic) activities of these chemicals for inhibition of blood and brain cholinesterase, inhibition of motor activity, and gait score. They also studied chemicals that disrupt homeostasis of the thyroid gland (thyroid disrupting [TD] chemicals) and found that addition of mixtures of TD chemicals caused a dose-dependent decrease in thyroid hormone (T4) levels. The researchers found that at low doses, they obtained additivity for mixtures of TD chemicals. Intriguingly, at high doses, they found synergistic effects on thyroid hormone disruption. This interesting work is relevant to environmental exposure to these chemicals in mixing ratios to which humans are exposed, and the work should continue.

Public Benefits

The public benefits of LTG 1 in the Human Health Research Program are clearly articulated. The utility of collecting mechanistic data as part of ORD's basic science programs in toxicology and carcinogenesis is obvious and clearly dedicated to generating the basic science necessary to allow the development of mechanistically based risk assessments. This is clearly shown by the support and enthusiasm of the Office of Pesticides for the mechanistic research ongoing at ORD in the area of conazoles and atrazine. The public has clearly benefited by the strict regulation of these pesticides based on mechanistic data generated by ORD researchers. Further effort needs to be invested in articulating the benefits of the program to the public, so they appreciate the many past, present, and future successes of the EPA in protecting human health and the environment.

Stakeholder Involvement

Stakeholders (e.g., program and regional offices) are involved in the planning and prioritization of research. As best represented by the flow diagrams presented during the meeting by the Executive Director of the Human Health Research Program and by the Region 5 Regional Science Liaison (RSL) to ORD, the program offices (Air, Water, Pesticides, and Toxics) and the regions communicate their needs to ORD, which communicates them to the Agency. The program offices and regions also communicate their needs directly to the Agency itself. Hence, the two major groups of stakeholders— the program offices and the EPA regional offices—are involved in the planning and prioritization of the research by communicating their needs for information to the Agency and to ORD. An excellent specific example of this is the very strong program on mechanisms of arsenic carcinogenesis research, which originated as a result of the needs of the Office of Water and the Office of Pesticides for scientifically sound, credible mechanism-based cancer risk assessments for arsenic in drinking water and for arsenic-containing pesticides in air. An area that needs to be better addressed by ORD is the Office of Water's need for information on the carcinogenicity of compounds containing hexavalent chromium when administered by the oral (drinking water) route. NIEHS' National Toxicology Program (NTP), however, already is conducting animal carcinogenesis studies by the ingestion route. ORD scientists are encouraged to track and leverage with these studies.

Industry stakeholders also have been working with scientists in the Human Health Research Program and in ORD to be involved in the planning and prioritization of research conducted by ORD. A good example of this is the collaboration between the industrial consortium called the Triazole Group and the Conazole Research Group of the ORD. The Triazole Group provides animal feed dosed with various conazole fungicides to ORD investigators for their use and has an active dialogue with these investigators on the research results that they acquire.

Several presentations were provided on interactions of ORD scientists with EPA offices and programs, including the Extramural Research Program, the Office of Pesticides, regional offices, and the Program on Children's Environmental Health. From these presentations, it is clear that ORD scientists collaborate closely with the program and regional offices. Many examples were provided of the nature of this partnering. An excellent example includes the continuing support ORD scientists have provided to the Office of Pesticides to support cumulative exposure of

pesticides and pesticide cancer risk assessment. ORD scientist support in the Regional Applied Research Effort (RARE) Program and the crucial role of ORD scientists in collaborating with the Program on Children's Environmental Health are two more examples.

These strong and valuable interactions take place largely because of the willingness of ORD scientists and the strong support of the management of ORD. The Agency is to be commended for maintaining a highly collaborative scientific environment. Of course, constant vigilance is required to assure that practice-oriented research is balanced with basic hypothesis-driven research.

There was less evidence of interaction between the intramural scientists and the extramural Children's Environmental Health Research Centers. A greater level of interaction between investigators in the externally funded University Centers and in-house researchers could result in more significant research progress (e.g., in the case of the potential role of GST polymorphisms in autism).

Coordination With Outside Research Organizations

The Agency already has Congressional and Administrative mandates placed upon it, which it must accomplish. There has been good collaboration between investigators in ORD and in the NIEHS in areas relevant to LTG 1. A good example of this is the collaborative work showing that methylated arsenic metabolites generate oxygen radicals and damage DNA. This could be an important mechanism by which arsenic compounds contribute to the molecular mechanism of arsenic carcinogenesis. More such collaborations should be encouraged, where appropriate. EPA's extramural grants program is well coordinated to extend capabilities of ORD scientists into needed research areas that are lacking within ORD. This promotes synergistic collaborations and avoids duplication of effort. The Human Health Research Program focuses on environmental health, rather than pure basic science, hence minimizing overlap with the NIH and other federal agencies.

Utilization of Other Agencies To Advance EPA's Research Agenda

EPA has established an Extramural Research Grants Program and an Extramural Environmental Health Centers Program, both of which utilize the efforts of scientists at research institutes and universities to aid the Agency in developing areas of toxicology and carcinogenesis that need to be explored beyond the Agency's immediate capabilities. A specific example of this is studies by the extramural Children's Environmental Health Centers in the mechanisms of autism in children and causes of autism in children. This is a very effective collaboration.

EPA also has established a program by which outside scientists can be hired on a temporary basis (IPA, 4-year terms) to work inside the Agency and bring it new expertise. CRADAs also are available to extend the capabilities of the Agency by incorporating the expertise of external scientists as extramural contractors. The posters and publications of ORD scientists showed clear evidence that collaboration is occurring between Agency scientists and scientists from other governmental agencies (i.e., NIEHS). A listing of intergovernmental agency collaborations between ORD's Human Health Research Program and its sister governmental agencies,

however, was not provided during the review, so the full extent of this partnering could not be judged accurately and given appropriate credit.

The Subcommittee was impressed by the high level of cooperation and teamwork among investigators and across organizations that was displayed in the Human Health Research Program. This collaborative atmosphere is particularly remarkable given the number of natural and organizational impediments that must typically be overcome to develop a team approach. Natural impediments include the natural tendency for scientists to pursue their personal research interests and extend their chosen areas of expertise. There also are likely to be difficulties in communication and collaboration between scientists in different disciplines (e.g., engineering, computer programming, statistics, and toxicology). In the case of ORD, it would be expected that these natural impediments might be exacerbated by the fact that the investigators come from several different organizations (e.g., NHEERL, NERL, etc.), which could result in conflicts over organizational responsibility (e.g., "turf battles") and manpower/budget issues (e.g., time utilization, travel funds, etc.). It was clear from the presentations and discussions with Agency scientists that these impediments have to a large extent been overcome. ORD management is to be commended for the efforts that it is taking to maintain such an effective team research environment.

The creation of the new National Center for Computational Toxicology may produce additional challenges in this regard. It appears that the most quantitatively oriented individuals in NHEERL and the most biologically oriented individuals in NERL will become part of the new Center. Although this reorganization apparently does not involve a change in location, there is a potential for the founding staff of the Center to become focused on the mission of the new organization and to some extent lose contact with the scientists in their former organizations. A high level of management attention will be required during the transition period to assure that current and future collaborations are not impeded by this change of organizational structure.

Quality

The Human Health Research Program of ORD uses the efforts of external advisory committees extensively to review its research products at regular intervals. Examples of this are the reviews of the drinking water research of ORD by the Drinking Water Committee of the SAB, reviews of the human health effects research by the Human Health Research Strategy Review Panel of the SAB, and reviews of the peer-reviewed manuscripts of scientists in the Human Health Research Program, as well as all programs in ORD by the Science and Technology Achievement Awards Committee. These reviews utilize external scientists to conduct peer review of the scientific accomplishments of scientists from ORD's Human Health Research Program.

The Agency ensures high quality research initially through the Extramural Research Funding Programs, which are highly competitive, merit-based funding. These programs do, however, need to be better advertised and perhaps even better financed and expanded to attract the widest possible competitive applicant pool.

Funds are competitively awarded in the extramural grants program (Science To Achieve Results [STAR] Program). Each intramural investigator is reviewed internally every year. Established

programs are peer reviewed every 4-5 years at the level of the laboratory and at the level of ORD. Criteria for the review process are established by the Laboratory Director with approval of the Assistant Administrator of the Agency. For new initiatives, such as Computational Toxicology and the Children's Health Initiative, there is an internal Request for Proposal (RFP) process.

Overall, the work of the EPA scientists is of very high quality, particularly that on arsenic, dioxins, conazoles, and atrazines. The research on atrazine, in particular, demonstrates the high scientific quality of the research being conducted at the Agency. EPA scientists have conducted a high quality, hypothesis-derived research strategy that uses a systems biology approach. Here, investigations of the mode of action of atrazine are informed by an understanding of the underlying biological system. This work has provided important insights into the nature of the interaction of atrazine with crucial processes in the hypothalamus-pituitary-thyroid axis.

Performance

Research Themes

The research theme, use of mechanistic data to guide cancer and noncancer risk assessments, is clearly defined in the overview section. It is necessary and appropriate in LTG 1 for risk assessors and risk managers to use ORD's methods and models to increase accuracy and decrease uncertainty in risk assessments. This will reduce the adverse health risks of humans exposed to environmental stressors. It is appropriate to ask the four questions in the overview regarding: (1) mode/mechanisms of action that are important to understand the impact of environmental stressors on human health; (2) attributes of the MOA that impact risk assessment; (3) how to measure, model, and/or predict key attributes of the MOA that impact risk assessment; and (4) how to incorporate mechanistic data and computational tools into risk assessment. The Human Health Research Program and all of ORD's research programs clearly define use of mechanistic data in risk assessment.

The research theme for LTG 1 is clearly addressed in several areas:

1. EPA has taken a leadership role in developing a mode of action for chlortriazine pesticides, which they showed acted on the hypothalamic-pituitary-gonadal axis and blocked the LH surge, which blocked fertilization. Development of this MOA for chlortriazines allowed EPA scientists to predict the risk of adverse health outcomes to humans as a result of chlortriazine exposure by extrapolating from data in mice.

2. NHEERL scientists, in collaboration with NIEHS scientists, made a pioneering contribution to the toxicology and carcinogenicity of arsenic showing that metabolism of arsenic to its methylated, reduced species [MMA(V), DMA(V), MMA(III), DMA(III)]—which generate oxygen radicals, damage DNA, and are genotoxic—is critical for its toxicity and carcinogenicity to be exerted. These important insights into molecular mechanisms of arsenic carcinogenesis advance cancer risk assessment for arsenic delivered by inhalation or ingestion routes of exposure.

3. ORD scientists began a new initiative to study the role of oxidative stress in asthma, atherosclerosis, cancer, infertility, and neurodegenerative disorders. ORD developed methods to quantitate oxygen radicals in exposed tissues and showed dietary antioxidants lower levels of oxidative stress in rodents and humans. They are studying if and how chronic diseases, such as asthma, involve lowering antioxidant defenses and if biomarkers of oxidative stress, such as four single nucleotide polymorphisms (SNPs) in oxidative damage-related genes, can predict adverse outcomes. They showed that in women in China exposed to polycyclic aromatic hydrocarbons, these SNPs correlate with an increased lung cancer risk.

4. ORD scientists demonstrated that specific members of the conazole family of fungicides induce liver cancer, thyroid cancer, and/or reproductive effects, and investigated why these conazole members are carcinogenic. They found that metabolism of specific conazoles explains part of their tissue specificity but not patterns of thyroid tumor development. The scientists are working to determine molecular mechanisms of conazole-induced thyroid carcinogenesis.

5. EPA also has been a leader in developing new cancer risk assessment guidelines incorporating all biologically relevant information, including data on MOA by which a chemical causes cancer in laboratory animals and/or humans. They finalized cancer risk assessment documents for chloroform, ethyl tertiary butyl ether, vinyl acetate, and formaldehyde. EPA scientists also initiated computational approaches to dose-response modeling through development of specific software that utilizes MOA data for cancer and noncancer outcomes, such as the benchmark dose software (BMDS). The BMDS is now utilized by 2,000 scientists from industry, academia, and governments in 80 countries.

6. ORD scientists developed approaches to collect data from newer genomics technologies and convert them into mechanistic data to support the risk assessment process. This includes creation of the National Center for Computational Toxicology, as recommended by EPA's own internal groups, the SAB's Drinking Water Committee, and the Human Health Research Strategy Review Panel.

In the research on dioxins and atrazines, EPA scientists supported the short-term needs of the regulatory offices while maintaining focus and programs on longer term, hypothesis-driven research geared toward elucidating mechanisms of adverse health effects. For dioxins, the risk assessment model was based on binding of dioxins to the Ah receptor and use of PBPK modeling to show that this MOA was concordant across a range of species, including rodents and humans. This research led to the interesting and logical conclusion that steady-state body burdens of dioxins should be used as the dose metric for cross-species extrapolation. This approach has been widely accepted. It is interesting and surprising that even after this exercise was completed on a carcinogen that binds to the Ah receptor to exert its effects, the models resulted in a linear extrapolation for cancer endpoints. It is even more interesting that linear extrapolation was found to be optimal for noncancer endpoints, based on biochemical and toxicological endpoints. EPA should be commended for its scientific leadership in resolving uncertainties for dioxin risk assessment.

ORD's Program has clearly articulated its focus and the rationale behind its approach to study the use of mechanistic data in risk assessment (Research Theme #1). ORD has many demands placed upon it. ORD must satisfy the Agency's strategic priorities, and must also support EPA's program offices, regions, other governmental and nongovernmental organizations, and the public through scientific and technical advice and assistance. ORD also provides scientific leadership in identifying, studying, and resolving critical environmental health and ecological effects issues and in shaping the environmental health and ecological effects research agenda. ORD scientists do this primarily by developing data on the molecular and cellular mechanisms of carcinogenicity, neurotoxicity, and reproductive toxicity of chemicals of environmental interest. ORD scientists then provide these data to risk assessors and risk managers of EPA program and regional offices that need such data.

The Human Health Research Program has clearly stated that its key research questions for mechanistic research are the following: (1) What MOAs are important for understanding the impact of environmental stressors on humans? (2) What are the attributes (e.g., shape of the dose-response curve, specificity of the MOA) that impact risk assessment? (3) How do we measure, model, or predict the key attributes of the MOA that could impact risk assessment? (4) How do we incorporate mechanistic data into risk assessment? These four questions clearly articulate the focus and rationale behind the approach of ORD's Human Health Research Program to study this theme and to use the results for accurate risk assessments.

There is evidence of integration across themes. A good generic example of this is the contribution of ORD scientists to multilaboratory, multiagency risk assessments based on data developed outside EPA. A specific example of this is the integrated characterization of human health and eco-toxicological risk for perchlorate based on the proposed MOA. This involved each center and laboratory within ORD, the program and regional offices, NIEHS, and the National Institute for Occupational Safety and Health (NIOSH). This effort is necessary because perchlorate causes toxicity, carcinogenesis, and developmental abnormalities as a result of the hypothyroidism that it can induce.

The theme of development and use of mechanistic data in risk assessments is a logical and important theme that needs to be pursued by ORD to place the risk assessments on sound scientific footings. It is crucial to determine whether the risk assessments follow a linear or threshold model to make these risk assessments scientifically robust and accurate to enhance the confidence of scientists, stakeholders, regulatory agencies (e.g., the Office of Water and the Office of Pesticides), and the public in the credibility of these risk assessments.

Use of a Multi-Year Plan

The Human Health Research Program has a logical design. The SAB's Human Health Research Strategy Review Panel thoroughly reviewed the program 2 years ago. As a result of this review, EPA's Human Health Research Program was revised appropriately and is now very strong. The design of the program is logical and comprehensive, tempered with a necessary and appropriate focus on the important areas relevant to human health, the needs of EPA regions and program offices, and the Agency's strategic needs as mandated by the Administration and Congress. The goals and the priorities of the Human Health Research Program are clear. There also are well-

delineated schedules for the program to be implemented. There are some apparent discrepancies, however, between the specific projects and performance measures listed in the 2003 LTG 1 and the current suite of projects relevant to today's Human Health Research Program and their deliverables and performance measures. This should be addressed by updating these items in the next iteration of the MYP.

The MYP describes an appropriate flow of work within and across Research Theme #1, Development and Use of Mechanistic Data in Risk Assessment. This research theme of development of mechanistic data for the actions of environmentally relevant toxins and carcinogens has been well developed. There is collaboration between basic scientists and risk assessors and between these two collaborating groups and regulatory offices and policy makers. The resultant data generated then are passed in collaborative fashion to clients and stakeholders within and outside the Agency.

The Human Health Research Program uses the MYP to address a logical sequence of questions. It also uses this plan as the basis for prioritizing its work. The MYP, however, is in need of updating to reflect current research activities.

Progress to Meet the Long-Term Goals

ORD has made significant progress toward each of its LTGs for the Human Health Research Program. Particularly impressive has been the progress made toward elucidating molecular mechanisms of arsenic carcinogenesis and arsenic toxicity, conazole carcinogenesis, and atrazine toxicity. Further significant progress has been made toward elucidating molecular mechanisms of dioxin toxicity and carcinogenesis. Risk assessments based on these mechanistic advances for arsenic, dioxin, and conazole carcinogenesis should shortly result in finalized cancer risk assessment documents for arsenic and dioxin.

Certainly, within the areas of arsenic, dioxins, atrazines, conazoles, and LHs, the program is clearly addressing key research questions for each area. Little is known about mechanisms of conazole carcinogenesis. The research is showing that there may be novel, unique mechanisms of conazole-induced thyroid carcinogenesis. Rapid progress is being made in the area of LHs and carcinogenesis. It is impressive that this group of investigators utilizes a broad, interdisciplinary array of scientific approaches, including chemistry, biochemistry, cell biology, animal carcinogenicity studies, epidemiology and human studies, and population-based studies. It is noteworthy that in this program, toxicologists, molecular biologists, epidemiologists, and risk assessors collaborate effectively.

Rationales to address all questions for the current suite of projects in the Human Health Research Program have been clearly articulated. Many of these rationales, based on elucidation of the mechanisms of action of toxic and carcinogenic chemicals, are straightforward and have been articulated properly. The rationale for many of the research questions derives directly from the needs of the program offices (Offices of Air, Water, and Pesticides) and the regional offices. As such, the rationales to address the questions have been clearly articulated and address meeting the objectives of these EPA offices for regulatory purposes. The end goal that is clearly articulated

throughout is to gather relevant data on mechanisms of toxicity and carcinogenesis for environmentally important chemicals to support risk assessments conducted on them.

Research questions are being addressed in a reasonably timely manner. This is particularly true in the context that development of new scientific information occurs along a timeline that often embodies unexpected delays and changes in strategy based on unexpected research findings. A good example of this is the newly acquired data on the molecular mechanisms of the carcinogenicity of arsenic. This project took many years to come to fruition, because it has been a very difficult problem. EPA, however, has made rapid progress on this problem within the last 5 years.

Another good example of EPA progress in this area is the steady advancement that the Agency scientists have continued to make on understanding the molecular mechanisms of the toxicities and carcinogenicities of dioxin and dioxins.

A third example of ORD scientists addressing questions in a timely manner is their work on elucidating the molecular mechanisms of the carcinogenicity of conazoles. EPA's Office of Pesticides asked ORD for assistance to establish risk assessment procedures for conazole fungicides, a high priority for the Office of Pesticides. ORD responded rapidly to elucidate the molecular mechanisms of the toxicity and carcinogenicity of conazoles and has provided these data to the Office of Pesticides. In addition, an industrial working group, the Triazole Task Force, has collaborated with ORD in this effort. ORD researchers responded in a timely fashion to the necessity for regulation of conazoles by providing basic science data on mechanisms of action of conazoles for use in risk assessments for these chemicals.

Use of Outputs by Stakeholders

The program has generally met stakeholder needs in a timely and useful way. Stakeholder needs often arise in a precipitous way, when no database exists on the chemicals in question and an environmental crisis arises. An example is the carcinogenicity of arsenic in drinking water. Progress was hindered because of lack of understanding of the molecular mechanisms of arsenic carcinogenesis. The work of ORD scientists gave significant insight into this problem by showing that arsenic needs to be methylated and reduced to MMA(III) and DMA(III), which then could generate oxygen radicals and cause DNA damage. These breakthroughs by ORD scientists are being utilized in the new risk assessment calculations for the carcinogenicity of arsenic in drinking water. These data eventually will be used by the Office of Water and also will aid the Office of Pesticides in regulating arsenical-containing pesticides.

There was extensive confirmation that ORD scientists are helpful to the various EPA regions in terms of hosting regional scientists in ORD laboratories, collaborating on regional environmental problems, providing scientific consultation to help ameliorate regional environmental problems, and providing scientific consultation when they are asked by the public for information on specific problems in environmental toxicology that arise in the regions. According to testimony by the Region 5 RSL, by representatives from the Office of Water and the Office of Pesticide Programs, and by the Science Director of the Office of Children's Health Protection, the research of ORD scientists in the Human Health Research Program has and continues to meet

stakeholders' needs in useful ways and in a timely manner. Studies on perturbations in breast development by exposure to dioxins and pesticides and the resultant increased cancer risk in children are examples of the utility and timeliness of the research efforts of ORD scientists. ORD has contributed to and collaborated with the Office of Children's Health Protection in developing RFPs for targeted studies.

The extramural Environmental Health Center Grants Program was discussed by the Director of one of these Centers (Rutgers, New Jersey). His testimonial made it clear that these Centers are making progress in identifying the causes of and understanding the molecular mechanisms of asthma, neurodevelopmental defects, autism, cancer, and other chemically induced adverse health effects in children. This research output is very useful to EPA's Office of Children's Health Protection, to the community of environmental health scientists, and to the public in general.

The Human Health Research Program has been effective in developing outputs that support the risk assessment/risk management process. An important example is data generated by ORD showing that methylated arsenic metabolites [MMA(V), MMA(III), DMA(V), DMA(III), etc.] generate oxygen radicals and cause DNA damage in mammalian cells. These data will support the risk assessment calculations for arsenic cancer risk assessment and arsenic risk management processes to control arsenic in air and water. These data eventually will resolve if there is a threshold in the cancer risk assessment for arsenic in drinking water as a result of metabolism of arsenic, which follows a reductive methylation set of processes. Data generated by the TEF approach has supported risk assessment for dioxins. Additional research efforts by ORD scientists to understand MOA of and toxicity and carcinogenicity of mixtures of conazoles, carbamates, atrazine, and pyrethroids have aided and will continue to aid risk assessments for these chemicals.

The panel heard extensive testimony from EPA offices and programs regarding the utility of research products developed by ORD scientists in the Human Health Research Program. Research on arsenic carcinogenesis by ORD researchers is used by the Office of Water and the Office of Pesticides and will play an important role in cancer risk assessments for arsenic in drinking water and in pesticide formulations. The finding by ORD scientists of the genotoxicity of methylated arsenic metabolites should answer the question of whether arsenic cancer risk assessment curves are linear or have a threshold. These important data will be used by the Office of Water and the Office of Pesticides. The Office of Pesticides is very enthusiastic about the research products from ORD on the toxicity and carcinogenicity of pesticides (e.g., conazoles, atrazines, carbamates, and pyrethroids). The Office of Water also is highly enthusiastic about the research products being developed by ORD scientists to aid it in regulating toxic and carcinogenic water contaminants, including arsenic, conazoles, and DBPs.

The Region 5 RSL testified regarding the strong enthusiasm of all 10 regions for the value of the mechanistic data developed by ORD scientists and its use in mechanism-based risk assessments developed by ORD scientists. He described regional workshops (Emerging Pollutants Workshop, Chicago, 2003; Cumulative Risk Workshop, Dallas, 2002), seminars, regional methods initiatives, and regional research partnership programs in which ORD scientists collaborate with EPA regions, and regional personnel spend time in ORD laboratories working

with ORD scientists. These programs make strong connections between EPA regions and ORD scientists. ORD scientists clearly help the regions with scientific consultation and collaboration.

Scientific Leadership

The team of veteran scientific administrators provides professional leadership to the Human Health Research Program and ORD scientists in EPA. The NRC's ROPE report stressed strengthening the core research of ORD within EPA and using this Core Research Program to aid EPA and its programs. ORD has worked hard to implement recommendations of the NRC report and demonstrated success in supporting key advances in human exposure and health effects research. ORD's scientific leadership is strong. Research scientists in the Human Health Research Program are internationally recognized experts on dioxin toxicology and are applying their unique expertise to understand toxicities of other persistent chemicals, such as polychlorinated biphenyls and polychlorinated dibenzofurans.

Researchers conducted studies to support LTG 1 of the Human Health Research Program have made significant contributions to the peer-reviewed scientific literature on MOA of the toxicity and carcinogenicity of environmental toxicants. The Subcommittee reviewed an extensive bibliography of publications derived from this program. ORD scientists also serve in key positions in advisory committees and technical panels for governmental and industrial research programs, in key positions for scientific societies, and in undergraduate and graduate teaching programs at universities. Several ORD scientists have won numerous scientific awards within and outside EPA and are well known nationally and internationally. Younger scientists at ORD should continue to develop and establish strong scientific reputations in human health research. ORD needs to do some transition planning to ensure a smooth transition to new leaders when senior leaders retire.

IV. LONG-TERM GOAL 2: AGGREGATE/CUMULATIVE RISK ASSESSMENT

Managerial excellence appears to be a hallmark of the overall Human Health Research Program. Setting a tone and expectation that encourages, spawns, and awards problem-driven cross-discipline teams at the operational level is a clear and positive result of this managerial effort. Indeed, the Subcommittee observed established networks in place to keep ORD researchers connected within the Agency, with particular reliance on interactions among lead scientists/principal investigators. Interactions with scientists and programs external to EPA are less formally organized but they appear to be appropriately happening at the lead scientist/principal investigator level.

Additional evidence of outstanding managerial support is reflected in the overall high level of excitement, commitment, and passion displayed by the scientists in describing their work. It is suggested that this strong positive aspect of this program be explicitly recognized, continually rewarded, and carefully guarded.

Another remarkably positive and valuable aspect of this program is a decisive propensity within the program to encourage the mining of available data and science to inform the risk assessment decisions of stakeholders. The Subcommittee encourages the use of consensual scientific deliberation by teams of experts to provide the best advice possible relative to the critical questions facing risk assessors and risk managers.

The overall criteria and framework for decisions regarding why specific elements are vital and have been included in the research program were not clear to the panel. A more transparent explanation of these aspects would be most valuable.

The public benefits from doing good science are not clearly or completely presented within the proposed work. Certainly, understanding and substantially reducing cancer and noncancer risks are vitally important and clearly recognized in this plan. The Subcommittee advises that it also is important and valuable that the technical work products be able to render the scientific determination of *de minimus* or acceptably low levels of human health risk from chemical exposure. The value of confident-knowledge regarding the relative safety offered by improved exposure and risk assessment tools of previously feared exposures and putative risks represents an arguably significant improvement to the public health. In addition to calming fear and its potential adverse consequences, these scientifically supported determinations allow for the continuing focus of finite resources on other potentially significant health risks. Some of the "delisting" examples in the plan point up these successful scientific determinations, but this factor is not articulated as a decided and very important benefit of the program.

It appears as if EPA's program and regional offices are involved in the planning and prioritization of the program's research; however, the Subcommittee suggests a broadening of

this list to include other members listed as stakeholders. This would include qualified scientists with professional standing in the other stakeholder groups mentioned in the background material.

To some extent, the direction, choice, and focus of research topics are undoubtedly areas where national politics interact and shape the development of specific scientific programs. The current focus of EPA ORD research on pesticides and only a relatively few substances has remained unchanged for some time and was the subject of some previous comments during Agency reviews in past years. The difference today is that there are regulatory mandates playing out in the rest of the world that are driving the overall scientific development of human health exposure assessment for the multitude of common and relatively unstudied substances to which humans are exposed. Significant resources are about to be committed, especially in the EU, to develop the exposure and risk assessment tools needed to reasonably accomplish these mandates.

Because these mandates are quite different, the tools being developed will have a dissimilar perspective and approach than that displayed in the ORD Research Plan. Even if ORD is not designing this type of research it should monitor, engage in, and advise these research efforts of others. This commitment should happen with greater intensity and at a significantly higher level within the EPA research organization than has occurred to date. This will allow the Agency to advise and participate in the development of this particular piece of science. At the very least, scientists within ORD should contribute their considerable skill and knowledge to the EU research planning effort. Given this interaction and interchange, the outstanding scientific management extant within ORD might also benefit these international programs simply by virtue of its powerful example. This contact and participation would assure that the Agency's scientific staff remains in touch with and knowledgeable about what is transpiring in this critical realm. It also would put them in an excellent position to enlist and act as full collaborating and operational partners in developing these tools if the decision is made to do so.

Relevance

The list of themes, topics, and poster titles, along with the other background materials, certainly contains all of the elements of the Agency's strategic goals and the *Human Health Research Strategy*. Inspection indicates reasonable consistency and relevance. That is, the outlined work as presented in the background materials looks fine; however, these materials did not present enough substance or details relating the specific program elements to be able to reasonably conclude that the focus is consistent with the stated goals. Details, such as exactly how the work is going to be planned and processed, are critical and, although not presented in the premeeting materials, were in most cases clearly articulated during the meeting.

The research efforts on cumulative risk assessment are highly relevant to the problems addressed by the Agency in assessing the risks faced by the public; people are typically exposed to multiple toxic chemicals. The high level of public concern, together with the large extent of uncertainty regarding the effects of mixtures, provides ample support for the Agency's research emphasis in this area.

The overall ORD research program for Aggregate/Cumulative Risk appears to remain focused on pesticides and a few other specific toxicants, such as dioxin, chlorinated solvents, metals, and

glycol ethers. Focusing a program on pesticides and specific toxicants makes sense for the early efforts in the nascent field of exposure and risk assessment. These areas certainly are the most data rich and are well supported by a strong U.S.-based regulatory mandate, as well as the recommendations of various advising groups. There was no evidence, however, provided in the reference material or presented during the meeting of a general research effort to understand and evaluate the exposure and risk to the literally thousands of existing chemicals to which people are exposed today.

It is reasonably well established that the risks of most types of personal chemical exposures are not being assessed at this point. These are the exposures that are happening predominately from residential exposure sources. Many, perhaps the vast majority, of these exposures and risks may be *de minimus* or insignificant; however, any scientific research plan designed to render answers about the aggregate and cumulative risk to humans from chemical exposure should reasonably address this significant portion of the total amount of chemical exposure experienced by humans. Any technical program that aspires to lead in the realm of human health risk assessment from chemicals should not ignore this reality. Similarly, any rational plan should have a specific and a systematic research strategy to address the multitude of substances to which individuals are exposed everyday.

Given the well-defined source-exposure-dose-effect continuum that currently exists in the plan, the actual research should logically start with defining a critical taxonomy and characterization of the universe of sources extant or entering into typical human microenvironments. Given this universe, a reasonable number of hypothesis-driven models should be formulated and tested within it. All of this should be followed up with the development of fate and transport models to characterize the contact and delivery of these substances to people via various routes.

Methods, Measures, and Models to Advance the Science of Aggregate and Cumulative Risk Assessment

This is an important effort focused on methods, measures, and models to advance the science of aggregate and cumulative risk assessment. It involves new analytical methods, measurements, and mathematical and computational models. The development of the Human Exposure Database System (HEDS) is very important and will capture data for human exposure to chemicals in a Web-based format, making it available to all investigators and stimulating further epidemiological studies of exposure to toxic chemicals and adverse health outcomes. The Consolidated Human Activity Database (CHAD) also is very important in compiling demographic information for each subject in questionnaire format and is very useful in exposure/intake dose modeling and/or statistical analysis. The National Human Exposure Assessment Survey, designed to evaluate comprehensive human exposure to multiple chemicals on a community and regional scale, also is a very important database, containing data on exposure factors from the pilot studies. This tool provides available data to exposure assessors so that they may summarize data on exposure factors for conducting human health exposure assessments. This database has provided consistency among exposure assessments, which is excellent.

Component-based methods for investigating chemical interactions in toxicology are promising. Studies discussed with the Subcommittee showed new and interesting results. At lower

concentrations, close to those relevant to environmental exposure to pesticides, the studies find indicate that there is an additivity or antagonism in the hepatotoxicity of four trihalomethanes and for organochlorine pesticides that inhibit brain cholinesterase activity, when they are administered to animals as mixtures, depending on the mixing ratios and upon the concentrations administered to animals. For organochlorine pesticides, there were greater-than-additive (synergistic) activities of these chemicals for inhibition of blood and brain cholinesterase, inhibition of motor activity, and gait score. ORD scientists also studied TD chemicals and found that addition of mixtures of TD chemicals caused a dose-dependent decrease in thyroid hormone (T4) levels. They found that in the lower portion of the curve, at low doses, they obtained additivity for mixtures of TD chemicals. Interestingly, at higher doses, they found synergistic effects on thyroid hormone disruption. This is interesting and important work relevant to environmental exposures to these chemicals in mixing ratios to which humans are exposed.

Case Studies and Risk Assessment Application of Aggregate and Cumulative Risk: An Overview

An interesting presentation of cumulative risk assessment of DBPs showed that for DBPs acting through a common mechanism, the effects of these chemicals can be added to generate a cumulative dose, and a common, additive risk can be calculated. Starting with adjustment to internal animal dose, these investigators adjusted that dose to internal human equivalent dose (HED). PBPK modeling or allometric scaling generated an internal HED. This allowed these investigators to develop a dose-response curve for human responses. This approach has significant utility to estimate the risk to humans of DBPs as a mixture, which is very important.

Source to-exposure pathways for dioxin-like compounds under the dioxin exposure initiative are a critical area of study. It is very important to delineate and quantify the pathways of dioxin exposure from all sources of dioxin release through the environment and into the food to assist development of a regulatory strategy for this important class of compounds. It is likely that these compounds cause cancer even at environmental levels, and this needs to be thoroughly studied. There is equivalent work ongoing that focuses on the use of the TEF methodology for cumulative risk for dioxins, with justified conclusions that TEF methodology provides a reasonable approximation of the toxic effects of a mixture of dioxin-like chemicals. These predictions are best for effects strictly mediated by the Ah receptor (enzyme induction). Thyroid hormone decrements are under predicted by the TEF methodology.

Research on the relative potency factor assessment of organophosphate pesticides showed that the organophosphate group operated through a common mechanism of inhibition of acetylcholinesterase; therefore, the dose of congeners should be additive to predict toxicity of mixtures of these compounds. This research helps to answer important questions in this area and to make risk assessment for these compounds for neurotoxicity more reliable.

The development of an ORD probabilistic exposure model—Stochastic Human Exposure and Dose Simulation (SHEDS) Model—allowed ORD to conduct a health risk assessment for children who contact chromated copper arsenic (CCA) on treated playsets and wooden decks. This useful work on applying SHEDS generated an exposure assessment model that was used by regulators in collaboration with ORD to generate accurate risk assessments for CCA-treated

wood. Other important work from this group of scientists linked exposure measurements with human activity data to assess dose in human tissues by applying the exposure models. They used a PBPK model to determine interactions among and individual contributions of multiple chemicals from aggregate exposure on an absorption, distribution, metabolism, and excretion basis. This model accurately predicted clearance of trichloroethylene from the body and formation of 1,1,1-trichloroethane in the body. They used very important uncertainty analysis employing Monte Carlo Techniques and made good predictions. Another set of very important experiments showed that all carbamates produced dose- and time-dependent inhibition of cholinesterase and decreased motor activity. ORD scientists are working with PBPK models to address these questions. They found that for pyrethroids there was a common endpoint for use in cumulative risk calculations. They showed that adding *in vitro* clearance data improves the PBPK rat model. They eventually will generate models for use in determining the cumulative risk of carbamates and pyrethroids and allow EPA to conduct state-of-the-art cumulative assessment for carbamate and pyrethroids and reduced uncertainties in risk assessments for these two important classes of pesticides.

Quality

The research described in the area of cumulative risk assessment is particularly creative, effective, and well conducted. The Agency scientists have shown considerable innovation and skill in developing and applying quantitative techniques ranging from statistical analysis to PBPK modeling, as required for the various aspects of the research. The leadership of the ORD in defining research directions in the field of exposure assessment and risk assessment is evidenced by several large-scale efforts that include the National Human Exposure Assessment Survey and work focused on evaluating risks associated with exposure to multiple contaminants, as well as the development of HEDS, SHEDS, and CHAD.

To the extent that Agency scientists typically seek to have their work published in peer-reviewed journals, the program appears to be functioning very well. In general, the program scientists have an excellent publication record and reputation for the quality of their publication submissions.

Performance

In conducting research on cumulative risk, ORD scientists have been able to simultaneously provide rapid response to the needs of the Agency's regulatory program while still maintaining a strong, long-term research effort. The ability of the Agency to promote effective collaboration across disciplines (e.g., computer modeling, statistics, pharmacokinetics, health endpoint evaluation) and across organizations (e.g., NHEERL, NERL) is remarkable. The high effectiveness of the research program owes a great deal to the atmosphere of cooperation and teamwork that has been created and maintained by EPA management. It is crucial that efforts to maintain this highly effective environment be continued and perhaps increased when the new National Center for Computational Toxicology is created.

In general, there appears to be a concerted effort to provide excellent coordination and integration across the program's research themes; however, there seems to be little integration of exposure assessment across themes that deal primarily with health effects.

As mentioned above, the general outline and definition of the program and these themes appears to be reasonably well defined. The rational level of detail regarding how the program is specifically set up to identify and address critical issues is not obvious, however.

The research theme aggregate/cumulative risk assessment is an overall term designed to include another critical theme of better exposure assessment models. It appears that this critical aspect may have gotten somewhat lost in the combination, and any reasonable focus or attention relative to exposure assessment model development under aggregate/cumulative risk is not plainly stated.

Scientific Leadership

The program definitely plays a leadership role in advancing the realm of scientific development in the areas that currently are addressed. The scientific staff and facilities are excellent, and the current funding appears to be adequate. Within this realm, the managers and researchers are overseeing and participating in a program that is leading the state-of-the-science.

As noted above, there are specific scientific activities occurring in the EU that should receive intense Agency interest, interaction, and potential coordination. It is highly probable that specific elements of the ORD research effort will not overlap with these EU programs, but both entities could certainly benefit from such interaction.

The EU has significant resources and a strong regulatory mandate for the assessment of existing chemicals. Health Canada also has a strong regulatory mandate to conduct exposure and risk assessments on literally thousands of existing chemicals in commerce. EPA interaction and potential collaboration with these programs should be coordinated at a much higher level within the Agency than is currently occurring.

The human health research initiatives conducted by these nations could subsequently be viewed as being very relevant. A lack of significant EPA participation in these research efforts could possibly threaten the Agency's current leadership position.

V. LONG-TERM GOAL 3: EVALUATION OF RISK TO SUSCEPTIBLE SUBPOPULATIONS

EPA's overarching conceptual framework for the core human health research program that represents the long-term training goals and their interaction needs to be more clearly and fully developed. The conceptual models provided in EPA's *Human Health Research Strategy* (i.e., Figures 1-3, 1-4, and 1-5) do not clearly represent its risk assessment context, the long-term research goals, or the importance of their interaction. The conceptual model should reflect the fundamental features of the core human health research program including: (1) it resides within a risk assessment framework; (2) the Long Term Research Goals; and (3) the strength of the program comes through interaction across LTGs.

Related to the need for a more fully developed conceptual framework for EPA's core human health research strategy is the need to provide a more clear health rationale. The actual research strategy appears well defined and appropriately directed, but its rationale (i.e., how and why this research has been selected) is less clear. To a large extent, ORD assumes its public health rationale based on the advice and consultation of external advisory groups including the National Academy of Sciences. Although the perspective of such science-based bodies is an important element to the rationale, ORD needs to clearly articulate its own rationale. At the level of the research program and the individual research project, the core Human Health Research Program can be strengthened by presenting a clear public health rationale.

The Subcommittee noted that this program has emphasized/embraced the strength/benefits of multidisciplinary interaction within and between the researchers in the different LTGs. This is likely to be fertile ground for environmental health discovery. This interaction appears to be occurring and is a strength to the current program. EPA should acknowledge the importance of this interaction, take credit for it, and encourage its continued development.

Peer review is recognized as a critical component of EPA's Human Health Research Program. The program review process can be facilitated and enhanced by: (1) providing the reports/critiques from previous reviews; and (2) tailoring the EPA presentations to the review criteria and critiques from previous reviews.

The core Human Health Research Program is effective and strategic in its coordination of its intramural and extramural research programs. These research programs are defined to achieve separate but complementary objectives. Both programs are effectively coordinated, resulting in good synergy with minimal redundancy.

Effective participation of program and regional offices in research planning, execution, and evaluation is a major strength to the ORD Human Health Research Program. It is through this participation that EPA's research is grounded in the practical needs of regulatory offices and communities. Furthermore, considerable talent and complementary expertise resides within program and regional offices that can only enhance and leverage ORD's Human Health Research Program capability. Similar to the interaction between LTGs, this interaction already is

occurring but the strength of the interaction seems to vary across program offices. The Subcommittee noted that interaction with the Pesticides Program is especially effective.

Relevance

Consistency With the Agency's Strategic Goals, the Human Health Research Strategy, and Recommendations of the National Research Council

Organization of EPA's core Human Health Research Program around susceptible subpopulations is both relevant and strategic to environmental health and the establishment of a risk assessment scientific foundation. There is strong historical evidence that much of the environmental health impact is related to susceptible populations where exposures are excessive, individuals are biologically susceptible, or both (e.g., lead and chlorpyrifos). Because environmental exposures in general are quite low, population adverse health effects are likely only manifested on the tails of the exposure or biologically susceptible distribution. The need for research related to susceptible subpopulations has been identified as an important area where human health risk assessments could be improved by: (1) NRC's 1994 *Science and Judgment in Risk Assessment*; (2) NRC's 1993 *Pesticide in the Diets of Infants and Children*; (3) the Food Quality Protection Act (FQPA) of 1996; and (4) the Safe Drinking Water Act of 1996. Whereas ORD was effective in describing the relevance of this LTG to ORD's Strategic Plans, as well as the Human Health Research Plan, it failed to discuss this particular LTG relative to the NRC core research priorities.

EPA has identified children as the susceptible subpopulation of interest. Emphasis on children (which includes all early life stages beginning at gestation) as a susceptible population is appropriate in view of the high level of societal and Congressional interest, as well as the fact that toxicity testing has traditionally been performed primarily on adult animals and may not be optimal for detecting effects in early life. Furthermore, this research focus is broadly supported by EPA program offices, the NRC, and legislative concerns. The products of the research will not only improve the Agency's ability to perform risk assessments that appropriately consider children's health, but they will also provide data that will be useful to many other agencies and health research organizations.

Although the Agency's focus on children as a susceptible population subgroup appears well justified, the justification presented was largely based on a consensus of recommendations across external advisory bodies (e.g., Office of Pollution Prevention and Toxics, NRC). This justification can be strengthened by the Agency's own scientific assessment of the public health benefit to be achieved through a research focus on children as a particular subpopulation. Such justification is likely to become more important in considering future potential subpopulation research foci that may be less obvious than children.

ORD has identified susceptible and highly exposed groups defined by: life stage, genetic factors, and/or health status. Intramural and extramural research within this LTG spans a wide range of research categories of significant environmental health relevance including: (1) pesticides and children; (2) modeling source-to-effects in children; (3) exposure assessment support to the National Children's Study; (4) risk assessment/risk management; (5) aging; (6) asthma; and

(7) uniquely vulnerable populations. Within each of these categories, research activities appear strategic and systematic, addressing short-term methodological needs while developing longer term community-based measurement and modeling approaches. This research is appropriately focused and directed to satisfy critical research needs particularly related to children as a susceptible subpopulation. Furthermore, there appears to be effective coordination and interaction within and between both intramural and extramural research programs.

The National Children's Study is a very interesting study, with study locations selected with the help of expert statisticians to provide an appropriate sample. The potential benefits of this research are numerous and can lead to mitigation of exposures that contribute to adverse health effects in children. It is expected that in approximately 7 years, information from these projects will begin to be published in the peer-reviewed literature as part of this long-term (20 years or more) study. A series of exposure projects to support the National Children's Study have been proposed. These efforts marry the unique capabilities of EPA in analytical chemistry with its capabilities in epidemiology. Newer techniques, such as satellite sensing to detect toxic air pollutants and toxic pollutants in rivers on a geographic basis, and novel sensing methodologies also will be incorporated into this study. It is a broad-based study dedicated to answering the question, "Can we identify exposures that correlate with adverse health effects on children?" Initially, EPA will look broadly to determine correlations. Although this study will take a long time to complete, it is an appropriate use of ORD resources.

The Agency's asthma research involves establishment of a new Cell Biology Group, which should be a dynamic group with very strong leadership. The finding of this group that exposure of transgenic IL-5 mice to diesel combustion products caused airflow obstruction in the presence of a methacholine challenge is very interesting. There is a very good set of collaborations here between immunologists, cell biologists, and engineers. It would be very useful to have regular group meetings within ORD and for the group to participate in interagency meetings at which regulatory representatives from EPA are present, to strengthen the focus of this group.

Research related to susceptibility from aging is focused on a limited number of pollutants. Chief among these are trichloroethylene (TCE), benzene, pesticides, and particulate matter (PM_{10}). It appears that this group meets frequently and is very active in attending meetings of the Society of Gerontology and other aging societies and presenting its research at these meetings. It is important that this group meets with the Children's Health Group at least once each year in a Super-Group of Susceptible Populations to share data and approaches and determine whether common approaches can be adopted by both groups in studying these two types of susceptible populations.

The studies described in the area of source-to-effects modeling of early life exposure have primarily focused on the kinetic half of the modeling spectrum, from source to target-tissue dose. Future efforts should begin to extend quantitative evaluation into the area of dynamics, from target-tissue dose to response. The creation of the new National Center for Computational Toxicology will provide the opportunity to apply the latest genomic and systems biology techniques to investigate child-adult differences in tissue response.

Stakeholder Involvement

There are clear indications that EPA human health research stakeholders, including program and regional offices, are substantively involved in the research planning and prioritization for the program, although it also appears that the extent of involvement varies by region and program office. Stakeholder participation in research planning and prioritization provides a clear and compelling advantage to ORD's Human Health Research Program in assuring research relevance and providing research opportunity. Involvement of regional and program office stakeholders varies. The Office of Pollution Prevention and Toxics is very effectively involved in acquiring research findings and in planning and defining the research agenda, but involvement of other program offices, such as the Office of Air and Radiation and the Office of Drinking Water, and regional offices does not appear to be as consistently strong. This variability, however, may stem from the relevance of the program office to the core Human Health Research Program.

Community-based research permeates LTG 3 and is one of its strengths. There is growing recognition of the value of community-based participatory research as a means for conducting such research. Although STAR grantees have embraced principles of community-based participatory research, there appears to be little or no ORD intramural capacity or expertise. If community research continues to be a part of this LTG (as it should), ORD should acquire this intramural capability.

Coordination With Outside Research Organizations

The LTG 3 research activities appear to be well coordinated with outside research organizations (nationally and internationally), providing two significant benefits: minimizing duplication and leveraging research opportunities. A good example of this coordination is the National Children's Study where EPA is substantively involved and contributing to the projects. Effective and substantive collaboration also are occurring with the U.S. Food and Drug Administration (FDA), the U.S. Department of Housing and Urban Development (HUD), and the Centers for Disease Control and Prevention (CDC). In general, research coordination appears to occur at two levels and varies across the program. The most effective level of coordination occurs informally at the level of the bench scientist. Laboratory managers play an important role in enabling and encouraging this interaction. The second level of coordination occurs at the level of the laboratory manager where research programs are coordinated more generally and at a broader scale. Information about research coordination was largely available through conversations with scientists and managers. This feature of ORD's Human Health Research Program is a strength that should be more prominently described and presented.

Quality and Performance

In general, the quality and performance of research under LTG 3 is very high. The research is characterized by hallmarks of quality and success, including its multidisciplinary focus and the extensive publication of the research in high-quality peer-reviewed technical journals. Over the 5-year period 1999-2005, there were more than 500 peer-reviewed articles published, providing an indication of the productivity of this research program. The studies described in the area of source-to-effects modeling of early life exposure have been very effectively planned and

conducted. The scientific quality of the research in this area provides a standard of excellence for investigations of other susceptible populations.

Research within LTG 3 is effective in systematically addressing a wide range of research issues associated with improving risk assessment for susceptible populations. Research is being conducted to assess children's exposure, susceptibility, and differential risks from pesticides. This work relies on a variety of approaches, including laboratory, exposure, and epidemiologic studies to inform children's pesticide susceptibility and risk. These measurement-based studies form the basis for the development and/or validation of sophisticated exposure to dose models. These modeling efforts are state-of-the-art and are effective in providing a quantitative conceptual framework for estimating exposure and risk and elucidating data and research gaps. Plans are underway to link the source-to-exposure-to-dose models with PBPK modeling efforts to derive comprehensive models for source-to-effect modeling. EPA has played a productive and strategic role in the multi-agency National Children's Study initiative. Under LTG 3, EPA has contributed substantively in conducting pilot studies to inform planning related to exposure measurement methods. Although children are a current focus of research within LTG 3, ORD also appropriately recognizes the elderly as an important susceptible group. ORD is conducting appropriate initial work to effectively build this program, applying many of the relevant concepts and approaches from its children's work. Susceptibility as a result of asthma is well justified because of this disease's high prevalence rate and evidence that indoor and outdoor air pollutants play an important but uncertain role in its occurrence. Given emerging evidence of the significance of particulate matter, the complexities of exposure to air pollution mixtures, and exposure assessment issues associated with indoor allergens, ORD is poised to provide a significant research contribution.

Scientific Leadership

ORD scientists involved in the research on children's susceptibility are internationally recognized experts in children's environmental health and play a strong role in fostering a continuing emphasis on this research area. EPA's leadership in children's exposure assessment is especially valuable because this research focus appears to be unique to EPA. Very significant contributions are being provided related to methods, measurements, and models for susceptible population exposure.

Scientific leadership is demonstrated at multiple levels within this LTG. First and foremost, much of the research being conducted is cutting edge. This is particularly true within research realms of relevance to the Agency regulatory purview (e.g., methods, measurements, and models for assessing children's exposure to pesticides). ORD's scientists and their research agendas are clearly out front and defining the science in a number of areas under this LTG. Through effective use of its intramural and extramural research programs, ORD is defining the state-of-the-art in the development of measurements and models for children's exposure assessment, including biological monitoring, quantifying activity patterns, and residential measurement methods. This developmental work feeds into observational studies providing rare objective measures of children's pesticide exposure through multiple pathways. At the same time, ORD is providing leadership with research to better understand the biological basis for children's differential sensitivity to pesticides. Significant public health discoveries are emerging from ORD's

extramural research program from epidemiologic studies identifying significant associations between mothers' pesticide exposure and birth outcomes. ORD scientists are taking on a valuable and significant leadership role with the National Children's Study in defining methods for exposure assessment and the development and implementation of pilot projects to address key data gaps necessary to optimally design and implement the study.

VI. LONG-TERM GOAL 4: EVALUATION OF PUBLIC HEALTH OUTCOMES

Relevance

ORD carries out the research activities of the Agency and provides the scientific basis upon which its programs, policies, and regulations are developed. In articulating the LTGs for research over a 10-year period, ORD's *Human Health Research Strategy* (EPA, 2003a) and Human Health MYP (EPA, 2003b) have identified an area of focus on public health outcomes. Research on the evaluation of public health outcomes builds upon an earlier initiative to develop indicators for measuring improvements in human and ecological health and thereby demonstrates quantifiable benefits of the Agency's policies and regulatory actions (EPA, 2003c). Evaluating public health outcomes associated with environmental policies and regulations is consistent with the overall mission of the Agency to demonstrate that EPA is protecting human health, as well as with the accountability directive issued by former EPA Administrator Christine Whitman. The program also is consistent with the outcomes-based approach that is being applied in many areas of public health. Given the shift in the Agency to develop environmental health indicators to support decision making within the Agency, a new area of research is being developed within ORD to address this issue.

The program on public health outcomes is being built upon the same conceptual framework that supports the three other major areas of research, namely the exposure-dose-effects continuum. Unlike the programs that support LTGs 1, 2, and 3, however, this program will not only benefit from integration with other programs, but such integration is viewed as critical for its success. To facilitate coordination, it is recommended that a mechanism be put into place that has both formal and informal components, not only to promote dialogue but also to elaborate a process for evaluating research outputs as suitable inputs for the activities carried out by the program. Within this rubric, the Human Health Research Program has the potential—in the future—of providing the nucleus for evaluating the research of the ORD, in terms of its relevance to environmental health. As an emerging area of research with a clear public health focus, it will be incumbent upon the leadership to highlight the relevance and importance of this program as it relates to the research carried out in the areas of: (1) harmonization of cancer and noncancer risk assessments; (2) aggregate and cumulative exposure and risk; and (3) susceptible subpopulations.

In addition to the need for substantive interaction between the Public Health Outcomes Program with the three other core areas of the Human Health Research Program, collaborations with other public health entities that monitor trends in environmental quality and human health (e.g., the CDC or the Agency for Toxic Substances and Disease Registry) are critical. With respect to interagency interactions, a memorandum of understanding (MOU) has already been established between EPA (via ORD and the Office of Environmental Information) and the CDC (signed September 30, 2003) to create a partnership to develop an environmental health tracking network at the national level. As part of the MOU, a pilot project has been launched (the Public Health Air Surveillance Evaluation [PHASE] project) to evaluate existing air quality and public health

surveillance data and determine if useful linkages between the two data sources can be established. In addition to EPA (NERL and the Office of Air Quality, Planning, and Standards) and the CDC, collaborators in the PHASE project include state health departments from New York, Maine, and Wisconsin. Other collaborative activities should be identified to allow for the sharing of expertise and for leveraging effort across agencies.

Quality

The primary goal of the research program on evaluation of public health outcomes is to develop and apply reliable measures to assess the effectiveness of Agency policies and regulations in reducing human health risks. Clearly, this LTG is overarching and relates to every action and program that supports the EPA mission to improve public health. Given the magnitude of the scope of this evaluation, it is recommended that the program specify focused goals that will guide its activities over the near term, as well as articulate a process for making decisions regarding which action to evaluate, which health endpoint to study, and, most importantly, which environmental health indicator to apply. Without question, the greatest challenge will lie in developing, selecting, and applying environmental health indicators that might provide the linkages between risk management decisions and specific health endpoints.

There is evidence that a deliberative process has guided the initial activities of the program. For example, the pilot project initiated under the MOU established between EPA and the CDC was selected on the basis of its applicability and relevance. The involvement of state health departments enhances the project, as they (together with their partners at the regional, county, and city level) will play an important role in evaluating existing data, identifying data gaps, and facilitating changes in data collection methods to better meet the needs of efforts to assess public health outcomes. With respect to the intramural "Demonstration" project that was initiated recently, the Subcommittee was informed that criteria will be developed for evaluating and selecting projects on the basis of quality, relevance, and feasibility over the short term. It is recommended that these criteria be made explicit and communicated to the program and regional offices so that projects are developed and selected with the greatest potential for success. The importance of these early efforts is underscored, as they will provide the lessons that may serve to catapult the program into the future.

Performance

The evaluation of public health outcomes as a result of policies of the Agency is a relatively new research program within ORD and, therefore, cannot be assessed using the same evaluation criteria as those used for assessing the other components of the Human Health Research Program. Several surveys of existing databases already have been carried out, including an inventory of exposure databases conducted by the National Risk Management Research Laboratory (NRMRL) as part of the annual performance measures supporting the LTG of the public health outcomes research agenda. The intramural program has been launched with a call for preproposals from the program and regional offices to develop the tools to evaluate public health outcomes associated with policies or actions. In addition, a Request for Applications (RFA) is being drafted with NCER to focus on studies to develop and establish linkages among

monitoring, exposure, and health effects databases that might be used to develop indicators of the effectiveness of risk management decisions made by the Agency.

The program is new and, thus, has shared a relatively small proportion of the available budget of ORD. In the MYP (EPA, 2003b), less than 7 percent of the FY2004 budget earmarked for human health research was allocated for public health outcomes research. Likewise, a relatively small percentage (< 4%) of the total full-time equivalents committed to the Human Health Research Program was directly involved in public health outcomes research. The program has experienced increases in the budget for FY2005, with monies allocated to support the intramural "Demonstration projects", as well as an RFA (approximately $1 million) to focus on studies that evaluate the utility of existing monitoring, exposure, and public health data for developing indicators of the effectiveness of risk management decisions.

It is anticipated that as the program matures, additional monies will need to be made available to provide adequate support for the activities that are conducted. In addition, the program will likely require additional expertise that currently is not represented within ORD. Specifically, it is anticipated that the program would benefit from biostatistical support and additional expertise in environmental epidemiology. Additional areas of needed expertise may emerge as the program develops.

Scientific Leadership

Current leadership for the program has the appropriate background and professional leadership to take the Human Health Research Program to the next steps. It is recommended that as the program expands, recruiting scientists with expertise in the area of evaluating public health outcomes would strengthen the leadership of the program. As the program gains definition, it is also recommended that ORD solicit external review of its activities on a periodic basis to aid the leadership in evaluating the program's activities as they relate to short-term goals and in articulating the scope of activities that are likely to allow the program to achieve its LTGs.

References

U.S. Environmental Protection Agency. Human Health Research Strategy. Washington, DC: Office of Research and Development, 2003a, EPA/600/R-02/050.

U.S. Environmental Protection Agency. Human Health Multi-Year Plan. Washington, DC: Office of Research and Development, 2003b.

U.S. Environmental Protection Agency. Draft Report on the Environment. Washington, DC: Office of Research and Development, 2003c, EPA 260-R-02-006.

VII. TESTIMONIALS

Testimony on the interactions of the Human Health Research Program with EPA's regional offices, other programs, and extramurally supported investigators was provided during the face-to-face site visit of the Subcommittee. According to testimony by the Region 5 RSL, by representatives from the Office of Water and the Office of Pesticide Programs, and by the Science Director of the Office of Children's Health Protection, the research of ORD scientists in the Human Health Research Program has met and continues to meet stakeholders' needs in useful ways and in a timely manner. Effective participation of program and regional offices in research planning, execution, and evaluation is clearly a major factor in maintaining the relevance of the ORD research program. It is through this participation that EPA's research is grounded in the practical needs of regulatory offices and communities. Furthermore, considerable talent and complementary expertise resides within program and regional offices that can only enhance and leverage ORD's capability. Like the interaction between LTGs, this interaction is routinely occurring, although the strength of the interaction seems to vary across program offices. The Subcommittee noted that interaction is particularly effective with the Pesticides Program.

The panel heard extensive testimony from EPA offices and programs regarding the utility of research products developed by ORD scientists in the Human Health Research Program. Research on arsenic carcinogenesis by ORD researchers is used by the Office of Water and the Office of Pesticides, and it will play an important role in cancer risk assessments for arsenic in drinking water and in pesticide formulations. The Office of Pesticides is very enthusiastic about the research products from ORD on the toxicity and carcinogenicity of pesticides (conazoles, atrazines, carbamates, and pyrethroids). The Office of Water also is highly enthusiastic about the research products being developed by ORD scientists to aid it in regulating toxic and carcinogenic water contaminants, including arsenic, conazoles, and DBPs. ORD also has contributed to the goals of the Office of Children's Health Protection and has collaborated with them in developing RFPs for targeted studies.

There was extensive confirmation that ORD scientists are helpful to the various EPA regions in terms of hosting region scientists in ORD laboratories, collaborating with the regions on regional environmental problems, providing scientific consultation to the regions to help ameliorate their environmental problems, and providing scientific consultation to the regions when they are asked by the public for information on specific problems in environmental toxicology that arise in the regions. The Region 5 RSL testified regarding the strong enthusiasm of all 10 regions for the value of the mechanistic data developed by ORD scientists and its use in mechanism-based risk assessments developed by ORD scientists. He described regional workshops (Emerging Pollutants Workshop, Chicago, 2003; Cumulative Risk Workshop, Dallas, 2002), seminars, regional methods initiatives, and regional research partnership programs in which ORD scientists collaborate with EPA regions, and regional personnel spend time in laboratories of ORD scientists. These programs make strong connections between EPA regions and ORD scientists. The Subcommittee concluded that ORD scientists clearly help the regions with scientific consultation and collaboration.

There was less evidence of an interaction of the in-house program with the extramural Children's Centers. A greater level of interaction might result in useful in-house research initiatives, for example in the area of the potential role of GST polymorphisms in autism. EPA has established an Extramural Research Grants Program and an Extramural Environmental Health Centers Program, both of which utilize the efforts of scientists at research institutes and universities to aid the Agency in developing areas of toxicology and carcinogenesis that need to be explored beyond EPA's immediate capabilities. The extramural Environmental Health Center Grants Program was discussed by the Director of one of these Centers (Rutgers, New Jersey). His testimony made it clear that these Centers are making progress in identifying the causes of and understanding the molecular mechanisms of asthma, neurodevelopmental defects, autism, cancer, and other chemically induced adverse health effects in children. This research output is very useful to the Office of Children's Health Protection, to the community of environmental health scientists, and to the public in general. Specific examples of this are studies by the extramural Environmental Health Centers in the mechanisms of autism in children and causes of autism in children. A greater level of interaction between the externally funded University Centers and in-house research could result in more significant research progress, for instance, in the case of the potential role of GST polymorphisms in autism.

Summary

Several presentations were provided on the interactions of ORD with other EPA offices and programs, including the Extramural Research Program, the Office of Pesticide Programs, the regional offices, and the Program on Children's Environmental Health. It is clear from these presentations that the program is very closely coupled with the program and regional offices. Many examples were provided of the benefits of this partnering. Particularly laudable examples include the continuing support ORD has been providing to the Office of Pesticides to support cumulative exposure and risk assessment, the interactions with regional scientists through the RARE Program, and the crucial role of ORD in the Program on Children's Environmental Health.

These strong and valuable interactions could not take place without the willingness of the ORD scientists and the support of ORD management. The Agency is to be commended for maintaining such a highly collaborative environment. It must be recognized, of course, that constant vigilance is required to assure that the amount of time spent on these collaborative efforts does not interfere with the productivity of the hypothesis-driven research program.

VIII. APPENDIX A: CHARGE QUESTIONS

DRAFT Charge for the Human Health Research Program

1.0 Objective. The objective of this review is to evaluate the relevance, quality, performance, and scientific leadership of the Office of Research and Development's (ORD's) Human Health Research Program. The independent external peer-review panel's evaluation and recommendations will provide guidance to ORD to help:

- Plan, implement, and strengthen the program;
- Compare the Human Health Research Program with other programs designed to achieve similar outcomes in other parts of the Environmental Protection Agency (the Agency) and in other federal agencies;
- Make research investment decisions over the next 5 years;
- Prepare the Agency's performance and accountability reports to Congress under the Government Performance and Results Act; and
- Respond to evaluations of federal research, such as those conducted by the Office of Management and Budget (which highlights the value of recommendations from independent expert panels in guidance to federal agencies[1,2]).

2.0 Background Information. Independent expert review is used extensively in industry, federal agencies, Congressional committees, and academia. The National Academy of Sciences has recommended this approach for evaluating federal research programs.[3]

Because of the nature of research, it is not easy to measure the creation of new knowledge as it develops or the pace at which research progresses or scientific breakthroughs occur. Demonstrating research contributions to outcomes is very challenging[4] when federal agencies conduct research to support regulatory decisions and then rely on third parties[5] (such as state environmental agencies) to enforce the regulations and demonstrate environmental improvements. Typically, many years may be required for practical research applications to be developed, and decades may be required for some research public benefit outcomes to be achieved.

Most of the Agency's environmental research programs investigate complex environmental problems and processes, combining use-inspired basic research[6,7] with applied research and integrating several scientific disciplines across a conceptual framework[8] that links research to environmental decisions or outcomes. In multidisciplinary research programs such as these, progress toward outcomes cannot be measured by outputs created in a single year. Rather,

research progress occurs over several years, as research teams explore hypotheses with individual studies, interpret research findings, and then develop hypotheses for future investigations.

In designing and managing its research programs, ORD emphasizes the importance of identifying priority research questions or topics to guide the research directions. Similarly, ORD recommends that its programs develop a small number of performance goals that serve as indicators of progress to answer the priority questions and to accomplish outcomes. Short-term outcomes are accomplished when research is applied by specific clients to strengthen environmental decisions or regulations. These decisions and resulting actions (e.g., reducing or preventing exposure of humans to environmental stressors posing a high risk) ultimately contribute to the improved health of the American public.

In a comprehensive evaluation of science and research at the Agency, the National Research Council recommended[9] that EPA substantially increase its efforts to explain the significance of its research products and to assist clients inside and outside the Agency in applying them. In response to this recommendation, ORD has engaged science advisors from client organizations to serve as members of its research program teams. These teams help identify research contributions with significant decision-making value and help plan for their transfer and application.

For the Agency's environmental research programs, periodic retrospective analysis at intervals of 4 or 5 years is needed to characterize research progress, to identify when clients are applying research to strengthen environmental decisions, and to evaluate client feedback about the research. Conducting program evaluation at this interval enables assessment of research progress, the scientific quality and decision-making value of the research, and if research progress has resulted in short-term outcomes for specific clients.

A description of the Office of Science and Technology Policy/Office of Management and Budget *Research and Development Investment Criteria* is included in Appendix I. These investment criteria of relevance, quality, performance, and leadership of the scientific program on human health risk assessment are pertinent to the draft charge questions.

3.0 Draft Charge Questions for ORD's Human Health Research Program

The following charge questions will help evaluate the relevance, quality, performance, and scientific leadership of ORD's human health research:

Relevance

1. Is the focus of ORD's Human Health Research Program relevant to and consistent with the Agency's strategic goals, the Agency's Human Health Research Strategy, and recommendations for core research priorities developed by the National Research Council?
2. Are potential public benefits of the program clearly articulated?
3. Are stakeholders (e.g., program and regional offices) involved in the planning and prioritization of the research?

4. Is the program well coordinated with outside research organizations, nationally and internationally, to avoid duplication of effort and promote synergistic collaboration?
5. To what extent has EPA established and utilized other agencies (inside and outside the government) in advancing EPA's research agenda? What are the impediments, if any, to collaboration with other organizations?

Quality

1. Does the program use peer review to ensure the quality of its products?
2. Does the program ensure high-quality research through competitive, merit-based funding?
3. If funds are not competitively awarded, what process does the program use to allocate funds? Does this process ensure that quality is maintained?

Performance

Research Themes

1. Are the four research themes (i.e., use of mechanistic data in risk assessment, aggregate/cumulative risk, susceptible subpopulations, and evaluation of public health outcomes) clearly defined?
2. Has ORD's program clearly articulated its focus and the rationale behind its approach to study the four research themes?
3. Is there evidence of integration across themes?
4. Do these four themes represent a logical framework for organizing the research and for identifying long-term goals that meet the needs of the Agency, science, and program customers?

Use of a Multi-Year Plan

1. Does the program have a logical, comprehensive design and Multi-Year Plan (MYP) with clear goals, schedules, and priorities?
2. Does the MYP describe an appropriate flow of work within and across the research themes?
3. Does the program use this MYP to address a logical sequence of questions and does it use the plan as a basis for prioritizing its work?

Progress to Meet the Long-Term Goals

1. Has the program made significant progress toward each of the long-term goals?
2. Does the research address the key research questions?
3. Is the rationale to address the questions clearly articulated?
4. Are the questions being addressed in a timely manner?

Use of Outputs by Stakeholders

1. Has the program met stakeholder needs in a timely and useful way?
2. Has the program been effective in developing outputs that support the risk assessment/risk management process?
3. Are outputs from the program used by stakeholders?

Scientific Leadership

1. Has the program played a leadership role in advancing the state-of-the-science of human health research and solving important research problems?
2. Have ORD's human health researchers demonstrated leadership in their respective human health disciplines?

4.0 Potential Peer-Review Panel Approach for Program Review

- ✦ Hold up to two conference calls in the month preceding a face-to-face meeting.
  - Allows ORD to present background materials to the peer-review panel.
  - Allows the peer-review panel to review and comment on the charge.
  - Allows the peer-review panel to ask clarifying questions about the program under review.

- ✦ The Contractor shall distribute background materials and documents requested by the peer-review panel in advance of the progress review.

- ✦ The peer-review panel Chair makes review and writing assignments to panel members in advance of a face-to-face meeting.

- ✦ Hold a 2-3 day face-to-face meeting for the program review at a location where a critical mass of ORD scientists is located.
  - The first 2 days of the meeting will involve ORD presentations and poster sessions.
  - On the morning of the 3rd day of the meeting, the peer-review panel prepares a draft report that addresses all of the charge questions.
  - It is a goal to have a draft report available for circulation among the panel members and comment at the end of the face-to-face meeting.

- ✦ If needed, hold one to two conference calls to finalize the report within 1 month after the face-to-face meeting.
  - It is a goal to have a final report approved by the peer-review panel available to ORD within 1 month following the face-to-face meeting.

References

[1] Budget Data Request 04-31. Executive Office of the President, Office of Management and Budget. March 22, 2004. "Completing the Program Assessment Rating Tool (PART) for the FY06 Review Process," pp. 50-56.

[2] Memorandum for the Heads of Executive Departments and Agencies. Executive Office of the President, Office of Management and Budget. June 5, 2003. "FY 2005 Interagency Research and Development Priorities," pp. 5-10.

[3] Evaluating Federal Research Under the Government Performance and Results Act, National Research Council, 1999.

[4] The House Science Subcommittee. Letter to Dr. Bruce Alberts, President of the National Academy of Sciences, from F. James Sensenbrenner, Jr. and George E. Brown, October 23, 1997.

[5] The Government Performance and Results Act: 1997 Governmentwide Implementation Will Be Uneven. U.S. General Accounting Office, GAO/GGD, 1997.

[6] Building a Foundation for Sound Environmental Decisions. (National Research Council, 1997).

[7] "Renewing the Compact between Science and Government," Stokes DE, in *1995 Forum Proceedings, Vannevar Bush II—Science for the 21st Century*, pp. 15-32, Sigma Xi, 1995.

[8] Risk Assessment in the Federal Government: Managing the Process, National Research Council, 1983.

[9] Strengthening Science at the U.S. Environmental Protection Agency, National Research Council, 2000, p. 141.

Appendix I:

OSTP/OMB Research and Development Investment Criteria

(Provided in hardcopy only)

IX. APPENDIX B: MEETING AGENDA

B • O • S • C

U.S. EPA BOARD OF SCIENTIFIC COUNSELORS
Human Health Subcommittee Meeting

AGENDA
February 28 - March 2, 2005

Environmental Protection Agency
Room C-111A/B/C
109 T.W. Alexander Drive
Research Triangle Park, NC 27711

Monday, February 28, 2005

8:00-8:30 a.m.	Registration	
8:30-8:40 a.m.	Welcome and Opening Remarks	Dr. James Klaunig Chair, Human Health (HH) Subcommittee Dr. James Clark, Vice-Chair, HH Subcommittee
8:40-8:45 a.m.	DFO Welcome and Charge - Administrative Procedures and FACA Rules - Objective of This Subcommittee and Charge	Virginia Houk (EPA) DFO, HH Subcommittee
8:45-8:50 a.m.	ORD's Welcome	Dr. William Farland (EPA) Acting DAA–Science, ORD
8:50-9:10 a.m.	Introduction to the Review of ORD's HH Research Program	Dr. Lawrence Reiter (EPA) Director, NHEERL
9:10-9:45 a.m.	Overview of the HH Research Program	Dr. Larry Cupitt (EPA) ORD/NERL

HH Research Program LTG 1: Use of Mechanistic Data in Risk Assessment

9:45-10:15 a.m.	LTG 1: Overview - Use of Mechanistic Data in Risk Assessment	Dr. Julian Preston (EPA) ORD/NHEERL
10:15-10:30 a.m.	Break	
10:30 a.m.-12:00 noon	LTG 1: Poster Session (Atrium)	HH Subcommittee
12:00-12:30 p.m.	LTG 1: Discussion	HH Subcommittee
12:30-1:30 p.m.	Working Lunch	HH Subcommittee

HH Research Program LTG 2: Aggregate/Cumulative Risk

1:30-2:00 p.m.	LTG 2: Overview - Aggregate/ Cumulative Risk	Dr. Jerry Blancato (EPA) ORD/NERL
2:00-3:30 p.m.	LTG 2: Poster Session (Atrium)	HH Subcommittee
3:30-4:00 p.m.	LTG 2: Discussion	HH Subcommittee
4:00-4:15 p.m.	Break	
4:15-5:30 p.m.	Discussion and Work Session - Work on Draft Report	HH Subcommittee
5:30 p.m.	Adjourn	

Tuesday, March 1, 2005

8:30-8:40 a.m.	Review of Yesterday's Activities Overview of Today's Agenda	Dr. James Klaunig Chair, HH Subcommittee

HH Research Program LTG 3: Susceptible Subpopulations

8:40-9:10 a.m.	LTG 3: Overview - Susceptible Subpopulations	Dr. John Vandenberg (EPA) ORD/NCEA
9:10-11:15 a.m.	LTG 3: Poster Session (Atrium)	HH Subcommittee
11:15-11:30 a.m.	Break	
11:30 a.m.-12:15 p.m.	LTG 3: Discussion	HH Subcommittee
12:15-1:30 p.m.	Working Lunch	HH Subcommittee

HH Research Program LTG 4: Evaluating Public Health Outcomes

1:30-1:50 p.m.	LTG 4: Overview - Evaluating Public Health Outcomes	Dr. Hal Zenick (EPA) ORD/NHEERL
1:50-2:10 p.m.	LTG 4: Discussion	HH Subcommittee
2:10-2:25 p.m.	Public Comments	
2:25-2:40 p.m.	Break	
2:40-3:10 p.m.	Relevance of HH Research Program EPA Extramural Perspective	Dr. George Lambert Robert Wood Johnson Medical School
3:10-5:30 p.m.	Discussion and Work Session - Work on Draft Report	HH Subcommittee
5:30 p.m.	Adjourn	

Wednesday, March 2, 2005

8:30-8:40 a.m.	Review of Prior Day's Activities Overview of Today's Agenda	Dr. James Klaunig Chair, HH Subcommittee
8:40-9:00 a.m.	Relevance of HH Research Program EPA Program Office Perspective	Dr. Randy Perfetti (EPA) Office of Science Coordination and Policy
9:00-9:20 a.m.	Relevance of HH Research Program EPA Regional Perspective	Dr. David Macarus (EPA) Region 5
9:20-9:40 a.m.	Relevance of HH Research Program EPA Office of Children's Health Protection (OCHP) Perspective	Dr. Michael Firestone (EPA) OCHP
9:40-9:55 a.m.	Break	
9:55-11:00 a.m.	Discussion and Work Session - Develop Oral Report	HH Subcommittee
11:00 a.m.-12:00 noon	Oral Report on Charge Questions	HH Subcommittee
12:00 noon	Adjourn	

X. APPENDIX C: LIST OF ACRONYMS

BMDS	Benchmark Dose Software
BOSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
CHAD	Consolidated Human Activity Database
CRADA	Cooperative Research and Development Agreement
DFO	Designated Federal Officer
EPA	U.S. Environmental Protection Agency
EU	European Union
FACA	Federal Advisory Committee Act
FDA	U.S. Food and Drug Administration
GPRA	Government Performance and Results Act
GST	Glutathione S-Transferase
HED	Human Equivalent Dose
HEDS	Human Exposure Database System'
HUD	U.S. Department of Housing and Urban Development
LH	Luteinizing Hormone
LTG	Long-Term Goal
MOA	Modes/Mechanisms of Action
MOU	Memorandum of Understanding
MYP	Multi-Year Plan
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Research Laboratory
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NRMRL	National Risk Management Research Laboratory
NTP	National Toxicology Program
OMB	Office of Management and Budget
ORD	Office of Research and Development
PHASE	Public Health Air Surveillance Evaluation
PBPK	Physiologically Based Pharmacokinetic
PM	Particulate Matter
RARE	Regional Applied Research Effort
RFA	Request for Applications
RFP	Request for Proposals
ROPE	Research Opportunities and Priorities for EPA
RSL	Regional Science Liaison
SAB	Science Advisory Board
SHEDS	Stochastic Human Exposure and Dose Simulation
SNPs	Single Nucleotide Polymorphisms
STAR	Science To Achieve Results
TCE	trichloroethylene
TEF	Toxicity Equivalency Factor