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December 1, 2009

Mr. Lek Kadeli
Acting Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC 20460

Dear Mr. Kadeli:

On behalf of the Board of Scientific Counselors (BOSC), I am pleased to provide you a review report of the Office of Research and Development's (ORD) Human Health Research Program (HHRP) at the U.S. Environmental Protection Agency. A nine-member BOSC Subcommittee, which included a member of the Executive Committee who served as the Subcommittee Vice Chair, conducted the program review that culminated in a face-to-face meeting held January 13-15, 2009 in Research Triangle Park, North Carolina. This was the third BOSC review of the HHRP. The BOSC conducted the first program review of the HHRP in 2005, and a mid-cycle review of the Program in 2007.

The BOSC was charged to conduct a retrospective and prospective review of the relevance, structure, performance, quality, scientific leadership, coordination and communication, and outcomes of the HHRP and to provide qualitative ratings relative to the Program's performance with respect to its Long-Term Goals (LTGs). In that regard, the BOSC is pleased to find that the HHRP's research relative to the LTGs meets or exceeds expectations. Overall, the HHRP has matured and is a well integrated, high-quality research program that demonstrates outstanding scientific leadership.

The review report is organized according to the LTGs outlined in the 2006 version of the *Human Health Research Multi-Year Plan* (MYP). The review report has been fully vetted, revised, and approved by the BOSC Executive Committee.

The review report is responsive to the ORD charge and we anticipate that it will assist ORD in evaluating the strength and relevance of the HHRP

and aid in guiding future course adjustments to the Program. We will be happy to provide any additional information concerning the format of the review process or answers to any questions you may have.

Sincerely,

Gary S. Sayler
Chair, Board of Scientific Counselors

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REVIEW OF THE OFFICE OF RESEARCH AND DEVELOPMENT'S HUMAN HEALTH RESEARCH PROGRAM AT THE U.S. ENVIRONMENTAL PROTECTION AGENCY

Final Report

BOSC SUBCOMMITTEE ON HUMAN HEALTH RESEARCH

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December 1, 2009

A Federal Advisory Committee for the U.S. Environmental Protection Agency's Office of Research and Development

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This report was written by the Human Health Research Subcommittee of the Board of Scientific Counselors, a public advisory committee chartered under the Federal Advisory Committee Act (FACA) that provides external advice, information, and recommendations to the Office of Research and Development (ORD). This report has not been reviewed for approval by the U.S. Environmental Protection Agency (EPA), and therefore, the report's contents and recommendations do not necessarily represent the views and policies of EPA, or other agencies of the federal government. Further, the content of this report does not represent information approved or disseminated by EPA, and, consequently, it is not subject to EPA's Data Quality Guidelines. Mention of trade names or commercial products does not constitute a recommendation for use. Reports of the Board of Scientific Counselors are posted on the Internet at http://www.epa.gov/osp/bosc.

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I. EXECUTIVE SUMMARY

Program Assessment

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 Executive Committee of the Board of Scientific Counselors (BOSC) of the Office of Research and Development (ORD) within the U.S. Environmental Protection Agency (EPA or Agency) has agreed to undertake a series of reviews of major EPA research programs. It accomplishes this by forming subcommittees having appropriate expertise for the specific program. This report is a BOSC review of ORD's Human Health Research Program (HHRP or Program). The members of the Human Health Subcommittee (the Subcommittee) are James E. Klaunig, Ph.D (Chair); Henry Falk, MD, MPH (Vice Chair); Paul D. Blanc, MD, MSPH; George P. Daston, Ph.D.; David G. Hoel, Ph.D.; Donald Mattison, M.D.; Edo Pellizzari, Ph.D.; Christopher J. Portier, Ph.D.; and Joel Schwartz, Ph.D. The affiliations of the members are provided in Appendix A.

The program review was structured to address charge questions provided by the BOSC that relate to program relevance, structure, performance, quality, scientific leadership, coordination and communication, and outcomes (the charge to the Subcommittee is included in Appendix B). To facilitate this review, the Subcommittee was provided with written materials and heard presentations on the goals, management, and research of the Program. The Subcommittee members also reviewed posters and reports prepared and assembled by Program staff related to research activities, accomplishments, and user applications. Presentations (testimonials) were provided by major clients of the Program. The Subcommittee has chosen to organize its response according to the Long-Term Goals (LTGs) outlined in the *Human Health Research Multi-Year Plan* (MYP). Charge questions were addressed in the context of each LTG, and salient points within each LTG have been captured and aggregated across the Human Health Research Program as a whole in this Executive Summary.

Overall, there was consensus among the Subcommittee members that there has been a maturing of the HHRP. The Program is much more integrated, and the level and quality of science has improved. There is considerably more emphasis on human health and human health-related issues, and there is movement toward more of a public health-themed program. The HHRP, as a whole, appears to be robust and responsive to emerging issues. The scientific content is excellent and, compared to previous reviews, is more integrated within each LTG and among the LTGs as well. The presentations of the poster session overviews by the LTG leaders and the poster session presenters were outstanding and were well received by the Subcommittee, as were the presentations by senior EPA leadership during the meeting and the conference calls that preceded it. The Subcommittee also appreciated the general EPA staff attendance at the poster sessions. There was notable enthusiasm in the presentations and the question-and-answer discussions that followed. The Subcommittee recognizes and appreciates the extensive work required to organize and present this review, and applauds the efforts by all those involved.

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There appears to be good evidence for strong scientific productivity and a formidable impact of the work produced by the Program overall. In general, the members found the Program leadership to be excellent to outstanding from the senior level to the laboratory/field study levels.

Program Relevance

The Subcommittee found that the current HHRP objectives for achieving EPA's Strategic Plan were appropriate and that each of the LTGs used suitable science to address the objectives of the HHRP and of its stakeholders. The research plans of the LTGs were appropriately responsiveness to outside advisory groups and stakeholders. The HHRP scientists are participating in and contributing to Agency workgroups engaged in identifying and addressing research needs. The Subcommittee concluded that the current HHRP objectives are appropriate to achieving the Agency Strategic Plan and providing a clear public benefit. These objectives are essential for EPA to improve its risk assessment methodologies and to further incorporate chemical mixtures and other exposures that influence risk into such assessments. The goal to reduce the uncertainty in exposure quantification used for estimating risk is an appropriate one. A challenge for the HHRP is to successfully integrate mode of action (MOA) results into the quantitative risk assessments. In addition, in future reviews, the Subcommittee recommends that more evidence be provided on the use of completed research products in cumulative risk assessments.

The focus on specific scientific methods and techniques selected by the HHRP to address research questions within the LTGs was deemed appropriate. The computational toxicology and reproductive toxicology efforts were particularly well received by the Subcommittee. The studies of MOA and biologically based dose response (BBDR), while needing more integration to provide biological plausibility to the epidemiology studies, are nonetheless important and timely. The Subcommittee noted that the HHRP was fully aware of the changing nature of risk assessment and the need to incorporate new tools to evaluate chemical mixtures and complex exposure patterns. There is clear evidence that the HHRP recognizes the need to include susceptibility and the role of other types of stressors (e.g., socioeconomic status, age, sex, and disease co-morbidity) into its research base. As such, the Subcommittee suggests that the HHRP consider broadening the assessment of susceptibility to include epigenetics and genetic polymorphisms into the Program. The HHRP, in general, appears very responsive to the issues raised by the stakeholders. The Subcommittee notes that with increasing use of dose-response estimates in epidemiology, there comes a greater need for interface with MOA. It was not clear to the Subcommittee, however, that the Program has shown to its stakeholders specific examples of how the incorporation of MOA considerations can benefit quantitative risk estimates. The incorporation of the pharmacological literature pertaining to human data also should be explored to support human risk evaluations. Finally, the Subcommittee suggests that the Program validate its models, when possible, through the use of human data (e.g., National Health and Nutrition Examination Survey [NHANES] and pharmacological data).

Program Structure

In general, the structure of the HHRP is well organized and clearly defines its priorities and outcomes. The MYP showed appropriate work flow and, as outlined, reflected a reasonable pace

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of scientific progress. The Program, overall, demonstrated the potential to respond to changing priorities and areas of need in order to help fulfill the needs of its clients (e.g., EPA regions and program offices). Research planning has been guided by the MYP and thus has tended to be very vertical-centric.

The framework of the proposed research and the planning of the specific research activities from basic research to modeling to human health effects to risk assessment appear to be properly structured. The planning and organization of the overall Program is logical and linked to the MYP. Since the last review, the leadership of the HHRP has made substantial strides in bringing the scientific programs together. Nonetheless, the Subcommittee felt that the overall program could improve in terms of its comprehensiveness. There is evidence of cross-LTG planning; however, this is an area in need of substantive further improvement. Although scattered successes were noted, the further interaction and linkage with other federal agencies could be enhanced. It was also a concern that a small number of investigators with experience in epidemiology and biostatistics reside within the HHRP. These skills are critical to integration of data and modeling issues. The Subcommittee identified this as an area of need in terms of scientific personnel recruitment.

Program Quality

The overall quality of the programs within the HHRP was evaluated by the Subcommittee to be excellent to outstanding. The Subcommittee, however, did recognize a need for improvement in selected projects within the Program. For example, concerns surfaced that, in several of the projects, outdated statistical methods were being used. Similarly, modeling and other statistical "tools" that already had been developed elsewhere were being re-invented. There also is extensive expertise on the uses of ecological studies (i.e., studies that analyze exposures and outcomes at a population level, as opposed to an individual level) that does not appear to have been tapped fully in the research of the HHRP. Finally, the narrow focus of susceptibility/ vulnerability studies in humans to the childhood life-stage was highlighted as an important limitation. The BOSC strongly recommends the further consideration by the HHRP of additional life stages as well as other aspects of susceptibility, such as pre-existing morbidities.

The Subcommittee noted some excellent success stories within the Program. For example, the cumulative risk assessments that have been completed for the Office of Pesticide Programs (with the organophosphates, carbamates, and pyrethrin insecticides) appear to be well-conducted and at an appropriate level of complexity. The use of the Stochastic Human Exposure and Dose Simulation (SHEDS) model to drive the exposure scenarios is a good example of cooperation across multiple laboratories and of the use of validated models as part of the assessment. The Report on the Environment (ROE) also reflects a commendable effort in tracking trends in exposure and health, thus providing an initial framework through which to "close the loop" in assessing the effectiveness of Agency actions.

To further such efforts, the Subcommittee suggests that the HHRP consider incorporating additional sets of data sources for looking at health trends (e.g., Centers for Medicare and Medicaid Services [CMS] data on Medicare and Medicaid, Homeland Security monitoring networks for emergency room visits, state hospital admission databases, etc.). The

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Subcommittee also was impressed with the early results of HHRP community-based studies. These studies combined science with appropriate interactions with community leaders, resulting in the transfer of policy-relevant information.

Coordination and Communication

Overall, the research within the LTGs appears to be very well coordinated. The scientific leaders of the Program are to be commended for their attempts to enhance the coordination and communication efforts with program offices and through interagency collaborations. There is good evidence of interactions between ORD and HHRP staff. In contrast to these positives, the Subcommittee had concerns as to the extent of the interactions *across* the LTGs, specifically with regard to LTG 2. For example, the science developed in LTG 1 and LTG 3 could further impact the research conducted in LTG 2 if there were greater planning efforts and knowledge sharing between these LTGs. The need for further integration and collaborations between the four LTGs was evident across HHRP. Specific recommendations on the integration are noted in the *Recommendations for the Long-Term Goals* section below.

The Subcommittee believes that better "translation" of the potential impact of MOA in terms of quantitative risk estimation and management needs to be made in transmitting such products to EPA program offices. In the case of LTG 3, the utilization of the combined strengths on both the intramural and extramural fronts was noted as commendable. This coordination serves as a model within the Program for intramural–extramural coordination and interaction. It is evident that HHRP scientists across all the LTGs are very much engaged in communicating knowledge developed from their research endeavors to the national and international scientific community. This occurs through publications, presentations at national and international conferences, briefings and seminars, and preparation of reference compendiums (e.g., pesticide exposure factors for children).

Program Performance

There was evidence of significant progress within each of the LTGs in addressing their programmatic milestones. Outcome measurement for the LTGs is, for the most part, well defined and appropriate. Excellent progress has been made to demonstrate the performance of the formulated concepts and approaches. The Program has managed resources efficiently for achieving its LTGs.

The BOSC strongly encourages the HHRP to continue "thinking outside of the box" in regard to evaluation methods for the impact of policy and regulations on human health. Such evaluation is a key step in bringing more accountability to the decisions made about environmental health.

The indicators selected in the LTGs for monitoring exposures or adverse effects have been selected on solid scientific principles. As an example, the Subcommittee noted the success of using decreasing levels of cotinine, a nicotine metabolite, in urine as a monitor of the impact of public education on smoking and environmental tobacco smoke (ETS) exposure. The Subcommittee found it difficult to fully evaluate the productivity of the HHRP as a whole, however, based on the bibliometric data provided. Although there appears to be good evidence

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for strong scientific productivity and a formidable impact of the work produced by the Program overall, there also were elements of the bibliometric analysis presented in the review material that were difficult to interpret and understand. Moreover, the co-mingling of intramural and extramural publications made it difficult to evaluate the overall contribution of the LTGs to the scientific program, and the relative contributions of intramural and extramural research to each of the goals.

Scientific Leadership

In general, the Subcommittee members thought the Program leadership is excellent to outstanding from the senior level to the laboratory/field study level. Substantial evidence exists that researchers within the HHRP are providing intellectual leadership by participating in a variety of boards, panels, and workshops, by making presentations at conferences, and by publishing in quality journals. The HHRP is providing scientific leadership to the entire field of toxicology in areas such as reproductive and developmental toxicology, computational toxicology, and respiratory health effects. The Subcommittee also noted the important role of the HHRP specifically, and EPA in general, as a scientific leader in regard to the National Children's Study. As is evident within the HHRP, the coordination of extramural and intramural efforts has produced significant results in childhood vulnerability to environmental stressors, in particular in terms of childhood asthma. In addition, the community-based tools and Websites being developed within the Program are an example of leadership—providing tools to local communities that can be used to make local decisions on environmental health matters. Similarly, the role of the HHRP in epidemiological research represents a substantive maturation of the Program. There always is a need to cultivate new leaders within the Program; this was acknowledged by the senior leaders of the HHPR. Continued efforts should be made to ensure that new leaders are developed or recruited to the Program and that the institutional memory of the retiring leaders is captured. The BOSC also strongly recommends that additional resources be invested in developing the science in cumulative risk assessments, as well as in epidemiology and biostatistics as noted earlier.

Summary Assessment for Each Long-Term Goal

Summary Assessment of LTG 1: Meets Expectations

The scientific quality of the program and its outstanding leadership makes it an essential component of the Agency's HHRP. The program is at the forefront in computational biology as well as the traditional areas of developmental and inhalation toxicology. Although the experimental studies supporting the development of MOA information were judged to be excellent and highly pertinent to the mission of the Program and the EPA, the Subcommittee did not discuss nor comment on the extent to which this research should be pursued further. Better integration of MOA with the quantitative risk assessment generated by the epidemiology studies is needed. In particular, it is important to demonstrate the value and impact of the basic mechanistic studies of MOA on the Agency's quantitative risk assessments.

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Summary Assessment of LTG 2: Meets Expectations

The leadership and scientists of this LTG are commended for their accomplishments. They recognized the need and demonstrated the ability to move from a single chemical with multiple routes of exposures to multiple chemicals with similar modes/mechanisms of action. They have successfully incorporated sophisticated modeling concepts into N-methyl carbamate risk assessments and have done so in partnership with the program offices. The effort supporting this LTG has remained true to the two major research goals on cumulative risk and susceptible populations as described in the MYP. The Subcommittee believes, however, that even though the planning and organization has been logical, this LTG could achieve greater benefits from more cross-LTG planning. The coordination and communication effort with program offices is laudable but the Subcommittee believes that more attention should be given to the needs of regional offices. Overall, there is substantial evidence that LTG 2 scientists are providing thought leadership through participation in a variety of boards, panels, and workshops, and by making presentations at conferences. The bibliometric data indicate that they are creating new knowledge, transferring this knowledge to the public domain, and adroitly applying it to environmental health issues.

Summary Assessment of LTG 3: Meets Expectations

LTG 3 was assessed as meeting program expectations based on the inarguable population health and public policy relevance of this area of research. The coordination and communication efforts with EPA program offices are commendable. The excellent to outstanding scientific quality of the specific endeavors and the high level of productivity within the areas in which LTG 3 has focused are the result of strong leadership. The programmatic structure was assessed as over-weighting childhood health within its life-stage construct of vulnerability, additionally treating asthma, one of its major foci, as little more than a surrogate of childhood risk. Absent this serious limitation, this LTG would have been assessed as "exceeding expectations."

Summary Assessment of LTG 4: Exceeds Expectations

LTG 4 was assessed as being an integral part of closing the loop created when a hazard is identified and decisions related to that hazard then are developed/implemented by working to develop the tools necessary to determine if the management decisions were warranted, effective, and should be continued. Many times, this critical aspect of environmental health decision-making is overlooked and programs are implemented that are unnecessary or no longer effective. Having the tools to evaluate risk management decisions must be a priority, and the Subcommittee is pleased this is being undertaken with regard to the long-term impacts on human health. Specifically, the Subcommittee found that this LTG: was designed to capture and communicate advances made by EPA and use this information to effectively improve future programs; was creating databases that, while not yet sufficient, were the genesis for a comprehensive approach to program review; was considering a broad array of means to estimate the amount of morbidity and mortality imposed by our environment and prevented through EPA's efforts; and had developed a number of products that were extremely useful in understanding the issues associated with assessing the effectiveness of EPA's decisions. Even though the program is rather new, we see enthusiasm in the staff involved, early successes in the

approaches chosen, and the beginnings of a very successful activity for the Agency. The Subcommittee members believe that the projects in this LTG have advanced more than was expected since the last evaluation and should be continued and supported.

Recommendations for the Long-Term Goals

LTG 1

1. The BOSC recommends that, through close collaborations with the Integrated Risk Information System (IRIS) staff, examples be developed in which the MOA for a chemical actually changes or influences the quantitative risk estimates IRIS makes for the chemical.

2. The BOSC recommends more integration of the MOA science with the quantitative risk assessment generated by the epidemiology studies.

3. Increased interactions (data sharing and research planning) among the researchers in LTG 1 with those in LTGs 2 and 3 are recommended.

LTG 2

1. The BOSC recommends that the Human Health Research MYP include a concerted educational outreach effort to the program offices, regional offices, and states regarding the use of sophisticated models and new knowledge developed through its research.

2. The BOSC recommends that goals or guidelines be defined that describe the threshold of acceptable accuracy for source-to-dose-to-health models and methods used in making assessments. Further characterization of the uncertainty of models similar to that described in the source-to-dose paper by Ozkaynak, *et al.*,[1] is highly endorsed.

3. As part of future BOSC reviews and as an accountability goal, the BOSC recommends that evidence (in summary narrative form) be provided on the use of completed research products in cumulative risk assessments.

4. The BOSC recommends the continuation of the general framework for planning with the inclusion of greater planning efforts and knowledge sharing among LTG 1, LTG 2, and LTG 3, and with other agencies.

5. The BOSC recommends that researchers who have extensive experience in "non-chemical stressors" be included in the overall plan for community-based research.

[1] Ozkaynak H, Frey HC, Burke J, Pinder RW. Analysis of coupled model uncertainties in source-to-dose modeling of human exposures to ambient air pollution: a $PM_{2.5}$ case study. *Atmospheric Environment* 2009;43(9):1641-1649.

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6. As a future goal, the BOSC recommends more engagement of the regional offices in planning and identifying areas in which they need tools, methods, and data from ORD.

7. The BOSC suggests an added influx of resources into developing the science in cumulative risk assessments if such assessments are to be effective in a reasonable timeframe.

LTG 3

1. The BOSC recommends developing a more fully elucidated conceptual framework for vulnerability and susceptibility.

2. The BOSC recommends redressing program imbalance within the life-stage arm of LTG 3 such that the strengths of the childhood susceptibility research thrust are matched with an expanded research program addressing the elderly as well as potential subgroups across the entire age range.

3. Rethinking the approach to asthma as a target condition so that it is not simply approached as a surrogate of childhood susceptibility to new disease onset, but rather considered across the entire age range and considered also in terms of vulnerability in pre-existing disease, is recommended.

4. In addressing preexisting conditions, the BOSC recommends the program consider expansion beyond asthma to encompass other airway disease (in particular chronic obstructive pulmonary disease [COPD]) and, beyond lung diseases, consider other classes of disease such as neurological and endocrine disorders.

5. The BOSC recommends better integration of LTG 3 across the other LTGs, in particular with LTG 2 in terms of cumulative exposure.

6. The BOSC recommends using successful intra-agency collaborations with the National Institute of Environmental Health Sciences (NIEHS) and the Centers for Disease Control and Prevention (CDC) in regard to childhood asthma as a model to address other vulnerable subpopulations, for example, collaboration with the National Institute on Aging (NIA) to address the potential susceptibility of the elderly to selected environmental exposures, such as those linked to neurodegenerative disease.

LTG 4

1. The BOSC recommends improving interaction and linkage with other federal agencies and state agencies.

2. Developing a means to capture and preserve institutional memory to improve long-term assessment of programs is recommended.

3. The BOSC suggests making the ROE more prominent and influential in the Agency.

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4. The BOSC recommends expanding the use of health databases used to evaluate improvements in human health related to improvements in the environment, remaining cautious in interpreting these types of ecological analyses.

5. The BOSC recommends expanding the use of direct estimates of the health implications of environmental interventions by calculating burden of disease or similar appropriate measures of risk.

6. The BOSC recommends incorporating additional case studies into LTG 4 and attempting to extrapolate from existing case studies to other examples.

Recommendations for the Overall Program

The BOSC identified seven needs that the Program should address:

1. The BOSC recommends that the partner survey be improved so that it is informative, or it should be abandoned.

2. The BOSC recommends an increase in the expertise and integration of epidemiology and biostatistics throughout the LTGs.

3. The BOSC recommends a reevaluation and reassessment of LTG groupings with the goal of increasing communication within and among the various LTGs and decreasing silos.

4. Development of a systematic process of prioritization and selection for determining which agents will be prioritized will create needed transparency and is recommended.

5. The BOSC recommends that a communication plan be implemented with the intent to disseminate the impact of Program research throughout the Agency, clients, and the general public.

6. The BOSC recommends that the HHRP explore more opportunities to collaborate with other agencies and with academia to strengthen the program, save resources, and leverage external expertise.

7. The BOSC recommends that susceptibility factors examined in children's health be expanded to all life stages and across all LTGs.

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Recommendations for the Review Process

1. There appears to be a good scientific impact of the Program, but the bibliometric analysis is difficult to interpret and understand, especially with the co-mingling of intramural and extramural publications. The BOSC recommends that this analysis be modified and improved or discontinued.

2. The Subcommittee members found it challenging to navigate the Program evaluation materials, not only in terms of quantity but in how the material was presented. The BOSC recommends adding one poster at the beginning of each session that highlights all work done to date under each LTG to enhance each poster session. Inclusion of posters presented at national scientific meetings during the previous 2 years, or an abstract book detailing such posters, also would be helpful to the reviewers.

3. Additionally, the Subcommittee would have benefitted from hearing about more specific partner interactions. The BOSC recommends that in future reviews, program partners and clients be included in the review, and that they justify how they use program products. One suggestion is to include partner testimonials in the poster sessions so that there can be more interaction between Subcommittee members and partners and clients.

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II. INTRODUCTION

ORD's Human Health Research Program and Its Long-Term Goals

The overall goal of the HHRP, as defined in the current MYP (June 2006), is to characterize and ultimately reduce uncertainties in extrapolations inherent in the risk assessment process by providing a greater understanding of the fundamental determinants of exposure and dose and the basic biological changes that result from exposures to environmental toxicants. An overarching theme is to improve understanding of the linkages in the exposure-to-dose-to-effect continuum. It is, of necessity, an interdisciplinary research program that develops the methods, models, and data needed to characterize uncertainties in each of these linkages and apply the information to the real world to elucidate exposures and risks in communities. Research projects are integrated across the intramural and extramural grants programs and currently are organized around four LTGs. The four goals are interrelated by design.

Long Term Goal 1 (LTG 1): Risk assessors and risk managers use ORD's methods, models or data to reduce uncertainty in risk assessment using mechanistic (or mode of action) information. *Fundamental research in this goal elucidates mechanisms of action of priority environmental contaminants and related families of contaminants, explores toxicity pathways that are perturbed by these contaminants, and uses this information to develop and link pharmacokinetic and pharmacodynamic models for use in risk assessment. These models are applied to reducing uncertainties associated with extrapolating from high to low dose, from test species to humans, from* in vitro *data to* in vivo *exposures, and between cancer and non-cancer effects. Progress is measured by the extent to which this information is being used in Agency risk assessments and rulings. A new direction in this goal is to develop a systems biology approach and apply novel models such as a virtual liver to predict toxicity and estimate risk.*

Long Term Goal 2 (LTG 2): Risk assessors and risk managers use ORD's methods, models, and data to characterize aggregate exposure and cumulative risk in order to inform risk management for humans exposed to multiple environmental stressors. *Research in this goal develops and applies biomarkers to assess cumulative exposure and risk; develops and applies source-to-dose models for cumulative risk assessment and dose reconstruction; and creates tools for community-based exposure and risk assessments of complex mixtures. The long-term objective is to produce a research framework outlining tools and approaches to characterize and assess aggregate exposures and cumulative risks, especially for vulnerable populations, based on a full range of both chemical and non-chemical stressors.*

Long Term Goal 3 (LTG 3): Risk assessors and risk managers will use ORD's methods, models, and data to characterize and provide adequate protection for susceptible populations. *This goal focuses on susceptibility as a function of life stage with a strong emphasis on children and older Americans as potentially vulnerable populations. Fundamental research characterizes real-world exposures and the key exposure factors for these populations. Research is designed to examine how developmental exposures during pregnancy and early*

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childhood may impact health later in life, and how life stage affects responsiveness to environmental contaminants, particularly in children and older adults. Tools and methods for longitudinal epidemiology studies developed in this research are applied in STAR-funded Children's Environmental Health Centers and translated to other national longitudinal studies on children's health. A specific strategy is being applied to understand the predisposing factors for asthma as a function of life stage, considering interactions with contaminants in both outdoor (e.g., diesel particles) and indoor air (e.g., mold) environments.

Long Term Goal 4 (LTG 4): Evaluation of the impact on human health of risk management decisions. *Research in this goal develops and tests indicators for gauging the effectiveness of risk management decisions and pollution mitigation efforts. This research makes use of fundamental information generated by the other three goals. Current efforts focus on real world scenarios and include projects developed in collaboration with EPA regional offices and by National Center for Environmental Research (NCER) grantees. These projects test the hypothesis that measured changes in community and personal exposures result in improvements in human health that can be measured and confirmed by using appropriate environmental health indicators. This research both contributes to and draws from issues raised in EPA's Report on the Environment.*

Research products typically are not program office- or media-specific. Rather, HHRP research is designed to produce knowledge and tools that are generalizable to the needs of multiple program offices, regions, other parts of ORD including the National Center for Environmental Assessment (NCEA) and the National Center for Computational Toxicology (NCCT), and other federal agencies (e.g., National Institutes of Health [NIH]/National Institute of Child Health and Human Development [NICHD]) and international groups (e.g., Organisation for Economic Co-operation and Development [OECD]) to further their goals.

Human Health Research Program Subcommittee

For this program review, a nine-member Subcommittee was formed, the members of which are listed in Appendix A. The charge to the Subcommittee is provided in Appendix B and includes questions that originate with and relate to the Office of Management and Budget (OMB) Program Assessment Rating Tool (PART). The Subcommittee was provided with a number of documents related to the HHRP as well as several presentations that were made during public teleconferences and the face-to-face meeting (see Table 1 for the dates of these events).

Table 1. Summary of BOSC Human Health Subcommittee Meetings

DATE	TYPE OF MEETING
October 10, 2008	Administrative Call
October 10, 2008	Conference Call
December 1, 2008	Conference Call
January 7, 2009	Administrative Call
January 13-15, 2009	Face-to-Face Meeting

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DATE	TYPE OF MEETING
February 27, 2009	Conference Call
April 21, 2009	Conference Call

The responses of the Subcommittee to the charge questions are organized by the Program's LTGs and each response addresses the major topics of program relevance, structure, quality, coordination and communication, program performance, and scientific leadership.

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

Program Relevance

The current program objectives are essential for the Agency to improve its current risk assessment methodologies. The challenge is to successfully integrate MOA results into the quantitative risk assessments. The choice of scientific techniques and methodologies used to define MOA and to integrate those results into quantitative risk assessment is appropriate. The computational toxicology and reproductive effects were particularly well received by the Subcommittee. Further, it was recognized that it has been an important shift to a "pathways orientation" instead of traditional single-target analyses. Additional scientific areas should be incorporated into the program, namely, population studies addressing the role of epigenetics and genetic polymorphisms in human susceptibility. Regarding "asking the right questions," the Subcommittee has some specific comments:

a. Epidemiology is being used to generate more dose-response curves for risk assessment, a trend that is likely to continue. The studies of MOA and biologically based dose response (BBDR) need to integrate more with this trend. Specifically, there is a need to provide biological plausibility to the epidemiology studies (e.g., potential mechanisms), but more importantly, use differences in the top-down and bottom-up approaches to generating dose-response curves to generate hypotheses that further our understanding. Moreover, epidemiologic studies often will have poor power at low dose, suggesting that an emphasis on low-dose modeling, including innovative use of biomarkers, would be most useful for risk assessment.

b. The algorithm behind the choice of chemicals to study is not clear, and should be made explicit. What approaches will be used to adjust this over time? How can this process be reviewed?

The Program staff understands the importance of the MOA approach to risk assessment. It is not clear to the Subcommittee, however, that the HHRP has shown to its stakeholders specific examples of how the incorporation of MOA considerations can benefit quantitative risk estimates, and the BOSC would like to see such examples in future reviews. Also, the program needs to establish the validation of its models through the use of human data (e.g., NHANES and pharmacological data). How to evaluate uncertainty is an additional important issue, and attention needs to be paid to modeling the variance as well as the mean.

The program is responsive to both the stakeholders and their issues, but leads in establishing emerging issues in risk assessment. The Subcommittee notes that with increasing use of dose-response estimates in epidemiology, there is a greater need to interface with MOA. The use of the pharmacological literature of human data also should be explored.

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The Subcommittee would have liked to see a specific example of a risk assessment with results that have changed as a result of this work. The Subcommittee is concerned that program offices may not be utilizing these tools optimally and that training programs may be needed to allow this technology transfer.

Program Structure

The structure of the program is good. It has a large number of parts, and the level of effort on the individual parts is not clear to the Subcommittee. It was not possible to evaluate whether the distribution of skills among the personnel was appropriate. There was some concern with the small number of investigators with experience in epidemiology and biostatistics. These skills are important for integration and assessment of risk assessment improvements in human populations, and for improving approaches for modeling. Although milestones were provided, there was not a clear way to evaluate their success. Again, it was not possible for the Subcommittee to evaluate the use of the MYP in guiding the program's research.

Program Quality

The scientific quality of the program for LTG 1 is high, as expected by the Subcommittee. The publication quality also is good, but the Subcommittee cannot answer questions about competitive funding. It is very important that the HHRP is leading the entire field of toxicology in the areas of reproductive and developmental toxicology, computational toxicology, and respiratory toxicology.

Coordination and Communication

There is good evidence of interactions between ORD and program staff. The Subcommittee assumes that this also applies to issues of planning. Better interactions among groups within ORD (e.g., the people in LTG 1 with those in LTG 2 and LTG 3) would be beneficial. There is critical help through the recently sponsored National Research Council (NRC) studies. Specific projects often involve collaboration with outside scientists. The level of their effort in the individual studies is not known. Generally, with a few exceptions, the quality of the outside collaborations has been very good. The Subcommittee believes that better translation of the potential impact of MOA on quantitative risk estimation and management should be made to the program offices. Basically, an advocacy approach should be considered.

Program Performance

Considerable scientific progress has been made since the previous review. Measures of outcome were not evaluated by the Subcommittee. The use of program results by decision makers is very

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important, but the Subcommittee does not have specific examples of this at this time. Further, without a clear understanding of the resources involved, resource efficiency is difficult to evaluate.

Scientific Leadership

The program's scientific leadership is outstanding, and the quality of the staff is generally first-rate. The program is providing scientific leadership to the entire field of toxicology in areas such as reproductive and developmental toxicology, computational toxicology, and, to some extent, respiratory toxicology.

Summary Assessment

The scientific quality of the program and its outstanding leadership make it an essential component of the Agency's HHRP. The program is at the forefront in computational biology as well as the traditional areas of developmental and inhalation toxicology. What is needed is better integration of MOA with the quantitative risk assessment generated by the epidemiology studies. In particular, it is important to demonstrate the value and impact of the basic mechanistic studies of MOA on the Agency's quantitative risk assessments.

With respect to LTG 1, the program meets expectations.

Recommendations

1. The BOSC recommends that, through close collaborations with the IRIS staff, examples be developed where the MOA for a chemical actually changes or influences the quantitative risk estimates IRIS makes for the chemical.

2. The BOSC recommends more integration of the MOA science with the quantitative risk assessment generated by the epidemiology studies.

3. Increased interactions (data sharing and research planning) among the researchers in LTG 1 with those in LTGs 2 and 3 are recommended.

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IV. LONG-TERM GOAL 2: CUMULATIVE RISK

Program Relevance

In general, the goals of LTG 2 address research on cumulative risk assessments and susceptible populations as set forth in the MYP. These goals are grounded in and are responsive to several key legislative mandates (the Safe Drinking Water Act, Food Quality Protection Act, etc.).

The research program clearly is aware of the evolving nature of risk assessment and the enlarging responsibility of the Agency for these tools—from single chemical to complex exposure patterns and complex exposures. The research team has demonstrated the ability to move from a single chemical with multiple routes of exposures to multiple chemicals with similar modes/mechanisms of action. There is clear evidence of attempts to enhance the risk assessment methods to include susceptibility and the role of other types of stressors (e.g. social class, economic factors, age, sex, and disease presence in the individual).

The program objectives are appropriate. They address improving risk assessment methods by incorporating multiple interacting chemicals and non-chemical exposures that influence risk, and are in line with objectives of the Agency. With the exception of one example (public health tools provided by CDC), however, the extent to which approaches are translated to the regional offices and states was not apparent to the Subcommittee.

ORD's long-range research objective on forward and reverse prediction of source-to-dose-to-health effects paradigm through development and performance evaluation of models and methods is a laudable one. This vision has great potential for impacting the basis for Agency decision making, and elements from it will be very useful to LTG 4's goal where indicators are identified within this paradigm for EPA's Report on the Environment. Selecting stochastic and physiologically based pharmacokinetic (PBPK) models to integrate the source-to-health paradigm at this time appears to be relevant, while there are some concerns regarding the specific models and approaches selected. The goal to reduce the uncertainty in exposure assessments used for assessing risk is an appropriate one. Estimating distributions of human exposure is difficult with models, particularly when estimating the tails of the distribution.

The models and methods that are being developed are sophisticated, and perhaps even esoteric. The utility of the models and methods for use by the various partners throughout EPA remains to be fully appreciated. Future products potentially will be very useful and will align with the needs of ORD and the program offices; however, these products are of less interest and benefit to the regional offices or Office of Homeland Security, where the latter often respond to emergencies or acute issues.

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In summary, the research conducted under this LTG is staying true to the two major research goals on cumulative risk and susceptible populations as described in the 2006-2013 MYP. The MYP is heavily influenced by the needs of the program offices.

Program Structure

It is evident that the planning and organization of research to accomplish the goals of LTG 2 is guided by the MYP. The planning and organization is logical from this perspective, but it is not as comprehensive as it could be because it appears that the cross-LTG planning is minimal or non-existent in some cases. As such, optimal value of the program's accomplishments is less than it could be.

The framework of the proposed research and the sequencing of related activities, for example, the modeling from source-to-dose-to-health effect and the development of new models and tools for cumulative exposure assessments, appear to be properly structured so that new knowledge will inform corollary research activities occurring within this LTG in a timely fashion. Research planning has been guided by the MYP and thus, has been highly vertical-centric. The Subcommittee believes that the science developed in LTGs 1 and 3 could benefit even more from the research conducted in LTG 2 if there were greater planning efforts and knowledge sharing among them. For example, knowledge about modes of action and corresponding modulators of action would benefit LTG 3 in the development of exposure-to-dose models with more accurate predictability. Such knowledge also would facilitate interpretation of biomonitoring data and designing the biomonitoring strategies in epidemiological studies.

ORD's research in support of the N-methyl carbamate cumulative risk assessment has been timely for the Office of Pesticide Programs (OPP). Using similarly linked human exposure and dose models developed and applied for carbamates, it has been nicely dovetailed and logically extended to informing the cumulative risk assessment of pyrethroid insecticides.

While the MYP has provided the overarching LTG of addressing cumulative risk and susceptibility assessments, the APG has provided the specific work product to the program offices in a highly successful manner.

Program Quality

The research in LTG 2 was divided into two basic areas: cumulative risk assessment and community-based exposure and risk screening. The cumulative risk assessment also was subdivided into methods and statistical models for dose-additivity, full cumulative risk assessments for high-priority environmental exposures, and methods development addressing a variety of questions.

Overall, the Subcommittee finds that the research that already has been conducted has mixed quality. There were a number of projects either using outdated statistical methods or trying to create tools that already have been developed elsewhere. This especially is true for the statistical

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models for dose-additivity for which there is a rich statistical literature that appears to have been ignored in favor of a linear models approach. This issue also is apparent for the community-based research where there is a tremendous literature on non-chemical stressors, and the inclusion of researchers with experience in these areas should be included in the overall plan. There also is extensive expertise on the uses and limitations of ecologic health studies that does not appear to have been tapped fully.

The examples in which cumulative risk assessments have been completed or are being conducted for OPP (organophosphate pesticides [OPs], carbamates and pyrethrins) appear to be well-conducted and at an appropriate level of complexity for the question at hand. The use of the SHEDS model to drive the exposure scenarios is a good example of cooperation across multiple labs and of using regulatory-validated models as part of the assessment. There is a tendency to think that every issue requires a PBPK model, but this is a highly specialized modeling form that requires an expertise that may not be available in other programs for an extended period of time. The quality of the research could be improved if a broader array of models, and in some cases simpler ones, are included in the arsenal of tools being used for the analyses.

Coordination and Communication

The program's scientific leaders are commended for their coordination and communication efforts with program offices. There is evidence that scientists in this LTG are responsive to the Office of Water (OW) and OPP. The needs of these offices are clearly part of the fabric of the research thrust that is undertaken in this LTG. OPP has expressed great satisfaction with the research products provided by ORD. These observations are to some extent reinforced in the results of the Partner Survey.

Based on testimonials, planning occurs between OPP and ORD. For example, ORD is taking a systems biology approach in defining underlying biological mechanisms of chemical mixtures and understanding the effect of dose and mixture composition on chemical interactions and joint toxic action of mixtures.

Even though ORD is providing some tools for examining community exposures that may be useful to the regional offices, there is less apparent interaction and thus coordination of research efforts that serve these offices. The very low satisfaction exhibited in the Partner Survey seems to support this observation.

Based on discussions with the poster presenters, training and communication through outreach efforts with the stakeholders of models, methods, and data are evident but somewhat rudimentary. Training and outreach efforts will become even more important as ORD scientists develop comprehensive, complicated, and even esoteric models and methods for use by the stakeholders (see Recommendation 1).

Program scientists are very much engaged in communicating knowledge developed from their research endeavors to the national and international scientific community. This occurs through

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publications; presentations at national and international conferences, briefings, and seminars; and preparation of reference compendiums (e.g., pesticide exposure factors for children).

Program Performance

Overall, program performance was coherent within a somewhat bifurcated programmatic context. This division was mandated by the focus on cumulative pesticide exposure-effect studies driven by OPP needs that accounted for one major component of the output. In contrast, other considerations of cumulative exposure-response appeared to be either theoretical/ conceptual (or to some extent, hypothesis generating) or, on the other hand, service oriented. The latter, a programmatic approach to risk mapping at the local level, appears to be popular with field offices. With regard to performance, the program's success in the "response" component of the exposure-response dyad may require considerably more evolution, given the difficulties in quantifying such outcomes. Program performance, in terms of intramural-extramural balance, was thought to be meritorious, as was peer-review publication productivity.

This LTG has become more focused and organized during the past few years. It is gaining traction where it seemed to be lacking before.

Scientific Leadership

In examining scientific leadership, the Subcommittee addressed the question of the overall role of the HHRP in promoting the improved use of science in cumulative risk assessment. In examining this issue, the main questions are: What should have been done 5 years ago? What should be the state of the use of the science today? What will be used in 5 years?

The Subcommittee is pleased that ORD leadership is moving this issue to the forefront and has made great strides during the past 4 years by completing some very high-profile and clear cumulative risk assessments for pesticides. The Subcommittee believes, however, that this issue is still behind where it could be, and it will continue to lag if EPA does not invest the necessary resources in both dollars and skills that are necessary to move this issue forward. The work, both intramural and extramural, on the interpretation and use of biomarkers of exposure is needed and shows good scientific leadership by the HHRP. Finally, the community-based tools and Websites being developed are good steps forward in providing tools that local communities can use to make local decisions. This activity also can move more rapidly than it has and begin to incorporate a broader community of scientists to aid in the program.

Substantial evidence exists that researchers are providing intellectual leadership by participating in a variety of boards, panels, and workshops; by presenting at conferences; and through publications.

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Summary Assessment

The leadership and scientists of this LTG are commended for their accomplishments. They recognized the need and demonstrated the ability to move from a single chemical with multiple routes of exposures to multiple chemicals with similar modes/mechanisms of action. They have successfully incorporated sophisticated modeling concepts into N-methyl carbamate risk assessments and have done so in partnership with the program offices. The effort in this LTG has remained true to the two major research goals on cumulative risk and susceptible populations as described in the MYP. The Subcommittee believes, however, that even though the planning and organization has been logical, this LTG could achieve greater benefits from more cross-LTG planning. The coordination and communication effort with program offices is laudable but the Subcommittee members think that more attention should be given to the needs of regional offices. Overall there is substantial evidence that LTG 2 scientists are providing thought leadership through participation in a variety of boards, panels, and workshops, and in presentations at conferences. The bibliometric data indicate that they are creating new knowledge, transferring this knowledge to the public domain, and adroitly applying it to environmental health issues.

With respect to LTG 2, the program meets expectations.

Recommendations

1. The BOSC recommends that the MYP include a concerted educational outreach effort to the program offices, regional offices, and states regarding the use of sophisticated models and new knowledge developed through its research.

2. The BOSC recommends that goals or guidelines be defined that describe the threshold of acceptable accuracy for source-to-dose-to-health models and methods used in making assessments. Further characterization of the uncertainty of models similar to that described in the source-to-dose paper by Ozkaynak, *et al*.,[2] is highly endorsed.

3. As part of future BOSC reviews and as an accountability goal, the BOSC recommends that evidence (in summary narrative form) is provided on the use of completed research products in cumulative risk assessments.

4. The BOSC recommends the continuation of the general framework for planning with the inclusion of greater planning efforts and knowledge sharing among LTG 1, LTG 2, and LTG 3, and with other agencies.

[2] Ozkaynak H, Frey HC, Burke J, Pinder RW. Analysis of coupled model uncertainties in source-to-dose modeling of human exposures to ambient air pollution: a $PM_{2.5}$ case study. *Atmospheric Environment* 2009;43(9):1641-1649.

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5. The BOSC recommends that researchers who have extensive experience in non-chemical stressors be included in the overall plan for community-based research.

6. As a future goal, the BOSC recommends more engagement of the regional offices in planning and identifying areas in which they need tools, methods, and data from ORD.

7. The BOSC suggests an added influx of resources into developing the science in cumulative risk assessments if such assessments are to be effective in a reasonable timeframe.

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V. LONG-TERM GOAL 3: SUSCEPTIBLE AND VULNERABLE POPULATIONS

Program Relevance

There was consensus among the Subcommittee members that the subject area of susceptible and vulnerable subpopulations is highly relevant to the HHRP. The previous BOSC review (conducted in 2005) specifically commented positively on the relevance of assessing the effects of low-level environmental exposures among susceptible subpopulations insofar as such effects might be manifest only within those subpopulations, and that for that reason such groups should be a priority for study. Although this is one argument in favor of this research focus, its rationale is more broadly based. For example, a higher frequency of responses in susceptible subpopulations provides more statistical power to epidemiological investigations and controlled human exposure studies, allowing detection of effects with enrollment of smaller numbers of subjects. Therefore, such studies are more feasible to carry out and more likely to provide data relevant to risk assessors seeking to protect both more- and less-susceptible groups. Moreover, the responses of one susceptible subpopulation may provide insights into mechanisms of action and cumulative exposure effects relevant to other subgroups and to the population as a whole. One example of insights into mechanism of action derived from studying vulnerable subpopulations may be found in genetic polymorphisms associated with increased risk of disease onset or worsening.

Program Structure

The program structure in relation to LTG 3 raised a series of questions within the Subcommittee. These questions related principally to the relative weighting of the research priorities, in particular the programmatic dominance of children as a vulnerable subpopulation within the "life-stage" research track, and, beyond that, the life-stage track in relation to the two other structural components of program: track two, methods for longitudinal research (which is, in effect, an extension of childhood life-stage activities) and track three, asthma (which, as will be discussed below, is approached by the HHRP as a surrogate measure of childhood vulnerability).

Confusion as to the underpinning for the programmatic structure may stem in part from a lack of clarity in the Agency's scientific justifications, as elucidated. In that regard, the comments of the 2005 BOSC review on this aspect of LTG 3 are noteworthy: "Although the Agency's focus on children as a susceptible population subgroup appears well justified, the justification was based on a consensus of recommendations across external advisory bodies (e.g., Office of Pollution Prevention and Toxics, National Research Council). 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 potential subpopulation research foci that may be less obvious*

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than children" (p. 32 of BOSC review report, emphasis added). At the face-to-face review meeting held in January 2009, Dr. Devon Payne-Sturges, from the ORD/NCER, commented that, "the definitions of vulnerability and susceptibility do not come from the Multi-Year Plan, but from clients, including EPA's National Environmental Justice Advisory Council and Risk Assessment Forum." These comments further underscore the need for EPA to re-examine internally (within the Agency itself) how it views the definition and scope of "susceptible and vulnerable" populations.

This is particularly relevant to the need for a better thought-out scientific justification for the selection of asthma as a disease of primary study interest for the Agency. Operationally, this appears to be viewed as little more than a surrogate measure of childhood-associated life-stage vulnerability. Indeed, by way of background (Human Health Research MYP, p. 55), after describing the prevalence of asthma in children (as of 1995), it is stated: "Although children appear to be the population most at risk, there is growing concern that new cases are also arising in adults." This conceptual weakness fails to recognize fully the importance of asthma across various life stages, does not appear to separately concern itself with asthma exacerbation or recrudescence as opposed to initiation, or take into account the potential vulnerability of the high-risk subpopulations of adults of working age as well as the elderly (those no longer in the labor force). An outgrowth of such conceptual shortcomings is a missed opportunity to consider asthma and COPD within a spectrum of airway disease, particularly insofar as this may be relevant to susceptibility of exacerbation (not causation). For example, it is well established that persons with increased non-specific airway responsiveness are more susceptible to broncho-constriction following exposure to certain air pollutants (e.g., sulfur dioxide), thus constituting a subpopulation that should be of great interest across a range of ages. In addition, susceptibility to environmentally related disease worsening or complications is not limited to pre-existing asthma. Diabetes has been demonstrated to convey susceptibility to the effects of air pollution, for example.[3,4] Also, there now are well established genetic risk factors for neurocognitive effects of lead.[5,6] The choice of ages and predisposing conditions examined does not appear to be consistent with Agency risk assessments, such as the "812" studies required by the Clean Air Act to examine the health benefits gained through legislation, for example, insofar as the burden of air pollution health effects appears to fall disproportionately on the elderly rather than children.

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[3] Liu L, Ruddy TD, Dalipaj M, *et al*. Influence of personal exposure to particulate air population on cardiovascular physiology and biomarkers of inflammation and oxidative stress in subjects with diabetes. *Journal of Occupational and Environmental Medicine* 2007;49:258-265.

[4] Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? *American Journal of Respiratory and Critical Care Medicine* 2001;164:831-833.

[5] Wang FT, Hu H, Schwartz J, Weuve J, Spiro AS III, Sparrow D, Nie H, Silverman EK, Weiss ST, Wright RO. Modifying effects of the HFE polymorphisms on the association between lead burden and cognitive decline. *Environmental Health Perspectives* 2007;115:1210-1215.

[6] Rajan P, Kelsey KT, Schwartz JD, Bellinger DC, Sparrow D, Spiro III A, Smith TJ, Wright R, Nieh H and Hu H. Lead burden and psychiatric symptoms and the modifying influence of the δ-aminolevulinic acid dehydratase (ALAD) polymorphism: the VA Normative Aging Study. *American Journal of Epidemiology* 2007;166:1400-1408.

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It is interesting to note that the introduction to the posters subsumed under LTG 3 took a far broader conceptual view of the criteria upon which subpopulation vulnerability might be defined and seemed to contextualize asthma as an example of a preexisting condition that could impart vulnerability. This was not reflected, however, in the content of the poster presentation itself nor by the portfolio of research upon which it was based.

Program Quality

The program quality within LTG 3 on a project-by-project basis is excellent to outstanding. For example, among the extramurally funded projects there is a level of epidemiological sophistication that represents an impressive gathering of resources. Exemplars of this can be found in the Duke Center for Children's Environmental Health Research and the University of Southern California's Children's Health Study. Innovation and creativity is not limited to the extramural projects, but also is evident within the intramural components. Indeed, it is likely that additional resources directed at areas that currently are understudied (e.g., aging human populations) also would result in high-quality outputs.

Although the quality of the individual parts is not at issue, the programmatic quality as a whole is compromised to the extent that susceptibility/vulnerability has been defined in an overly narrow sense to virtually exclude rigorous investigation beyond the childhood life-stage aspect of such risk. This issue has been addressed elsewhere in this review and will not be revisited in greater detail as a quality issue *per se*.

Coordination and Communication

As with other LTGs, the scientific leaders are is to be commended for their coordination and communication efforts with program offices and, beyond that, in terms of interagency collaborations with NIEHS and CDC. Such coordination has been particularly relevant to the development and funding of Requests for Applications (RFAs) for extramural research and to the complexities of the National Children's Study.

LTG 3 was particularly noteworthy for combined strengths on both the intramural and extramural fronts. Coordination among the various and diverse research projects that fall within the scope of LTG 3, particularly interactions between intramural and extramural undertakings, would present challenges to any organization. The general recommendation made previously in regard to strengthening internal EPA epidemiological resources is particularly relevant to this specific point.

Although the within-LTG coordination indicated programmatic coherence, questions arose in regard to interactions across goals, specifically in regard to the "cumulative exposure" focus of LTG 2. Despite that fact that this component of LTG 2, on its face, seems directly related to the core of LTG 3, there did not appear to be much in the way of additive, let alone synergistic, interactions between the two working groups. This may point more to the aspects of the LTG structure that are inherently artificial, rather than reflecting on the content of the work involved.

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Program Performance

The childhood and the asthma components of LTG 3 have been highly productive, with particular note of the extramurally funded (jointly with NIEHS) Children's Centers and the intramurally based research program on the developmental (pre-natal and early childhood) origins of adult diseases. This successful performance can be measured in peer-reviewed journal and governmental publications, as well as in practicable applications, such as the "Relative Moldiness Index." Although the National Children's Study, by design, will not have endpoint data for analysis, methods-related research and documentation also have reflected excellent performance.

The aging component of the life-stage track, by contrast to the childhood-asthma components, has been a relatively weak performer. In scope, a similar program of work was described in the last BOSC review 5 years ago. In particular, there appears to be very little epidemiological or controlled human exposure activity within this track, either currently or planned for the immediate future. Paralleling this, the commendable interagency communications alluded to above in regard to NIEHS and CDC do not seem to have extended from childhood susceptibility (including asthma) to the aging, nor is there evidence of active coordination with other NIH agencies that could have a role (in particular, NIA). This may reflect the priorities of those outside bodies as much or more than those of EPA.

It is difficult to evaluate how program performance in LTG 3 more narrowly translates into risk assessment activities. This may be an artifact of the current structure of the four LTGs as formulated, given that programmatic outcomes are more clearly addressed in LTG 4. Also, the "partner testimony" as presented was not particularly germane in this regard. Nonetheless, the trajectory of the program performance of LTG 3 indicates that risk assessment, as it touches on childhood as a susceptibility factor, will benefit from this work.

Scientific Leadership

EPA is inarguably a scientific leader in regard to the National Children's Study. Its role is formidable in the extramural funding of childhood vulnerability in general and in terms of childhood asthma in particular. This includes both independent leadership and coordination with NIEHS and CDC. EPA's role in extramural epidemiological research in this arena represents an area of substantive maturation within the HHRP. At the same time, intramural laboratory-based scientific leadership for the same foci has not been compromised.

Summary Assessment

LTG 3 was assessed as meeting program expectations based on the inarguable population health and public policy relevance of this area of research. The coordination and communication efforts with EPA program offices are commendable. The excellent to outstanding scientific quality of the specific endeavors and the high level of productivity within the areas in which

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LTG 3 has focused are the result of strong leadership. The programmatic structure was assessed as over-weighting childhood health within its life-stage construct of vulnerability, additionally treating asthma, one of its major foci, as little more than a surrogate of childhood risk. Absent this serious limitation, this LTG would have been assessed as "exceeding expectations."

With respect to LTG 3, the program meets expectations.

Recommendations

1. The Subcommittee recommends developing a more fully elucidated conceptual framework for vulnerability and susceptibility.

2. The Subcommittee recommends redressing program imbalance within the life-stage arm of LTG 3 such that the strengths of the childhood susceptibility research thrust are matched with an expanded research program addressing the elderly as well as potential subgroups across the entire age range.

3. Rethinking the approach to asthma as a target condition so that it is not simply approached as a surrogate of childhood susceptibility to new disease onset, but rather considered across the entire age range and considered also in terms of vulnerability in pre-existing disease, is recommended.

4. In addressing preexisting conditions, the Subcommittee recommends that the program consider expansion beyond asthma to encompass other airway disease, in particular COPD, and, beyond lung diseases consider other classes of disease such as neurological and endocrine disorders.

5. The Subcommittee recommends better integration across LTGs, in particular with LTG 2 in terms of cumulative exposure.

6. The Subcommittee recommends using successful intra-agency collaborations with the NIEHS and the CDC in regard to childhood asthma as a model to address other vulnerable subpopulations, for example, collaboration with the National Institute on Aging to address the potential susceptibility of the elderly to selected environmental exposures, such as those linked to neurodegenerative disease.

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VI. LONG-TERM GOAL 4: DEVELOPING TOOLS TO EVALUATE RISK MANAGEMENT DECISIONS

Program Relevance

Evaluation is core to understanding the strengths, benefits, and consequences of any public health intervention. The consequences of risk management decisions are seldom revisited, making it difficult to judge the effectiveness of these decisions. While improvement of the environment over the life of EPA has been studied and is apparent in many areas, what has not received as much attention is whether these improvements have resulted from risk management decisions and, of critical importance, how these environmental improvements, through management decisions, have reduced disease and premature death in the United States. For example, EPA, CDC, and others have clearly demonstrated declining lead levels in the atmosphere and in human biomonitoring programs, but have found it very difficult to demonstrate an improvement in health from these declines, although there are estimates that can be made. The BOSC Subcommittee believes there needs to be a concerted effort in quantifying and communicating improvements in human health resulting from risk management decisions. The programs within LTG 4 are structured around three themes: the development of means and methods to measure impacts, research studies of impact measurements, and finally, the ROE. All three of these areas are directly relevant to the need to evaluate the health impact of risk management decisions and are strongly supported by the BOSC as relevant to the HHRP.

Program Structure

The leadership of the HHRP has done an excellent job in bringing these groups together, including the regional offices, and moving forward on the overall objectives of LTG 4. Hence, the Subcommittee finds they have done a good job in linking these various activities into a single long-term project that holds great promise for addressing the utility of EPA's programs to improve health and the environment.

There are some activities that can be developed to strengthen the structure of this LTG. The BOSC Subcommittee believes that the HHRP could do a better job of interaction and linkage with other federal agencies. Although this program uses quite a bit of information generated by the CDC and the U.S. Geological Survey (USGS), there is a need to work closely with these agencies to improve their products so that they have greater utility for the needs of the HHRP. In addition, the HHRP should partner with other granting agencies such as the NIH, the National Science Foundation (NSF), and the CMS, monitoring their activities and taking advantage of opportunities to partner and leverage resources. In this specific area in which an attempt to evaluate risk management decisions is being made, testing new technologies or procedures in

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concert with epidemiology or laboratory studies that are just beginning could both improve the activities and extend the resources.

There was some concern that, in this specific area where long-term trends are being evaluated over extended periods of time, loss of institutional memory could lead to unexpected problems in completing research or errors in the interpretation. The HHRP is encouraged to look into this issue and find ways to limit its impact on the program.

Finally, the BOSC Subcommittee sees the location of the ROE within EPA bureaucracy as a critical component of LTG 4 and, indeed, the management and evaluation of the entire EPA. This activity serves a critical role for summarizing the long-term trends in environmental quality and as a communication tool to highlight the successes and areas for improvement of EPA. As such, the BOSC believes that the ROE should be more prominent and influential in the Agency.

Program Quality

The program is in its early stages, but the signs of quality are very encouraging. The ROE was an excellent effort to track trends in exposure and health and begin to provide a framework for closing the loop. The program is cognizant of the potentials for confounding and methodological issues in ecological analyses. The BOSC recommends explicit incorporation of these understandings into documents to ensure that inappropriate pressure to examine the concordance or discordance of simple time trends is resisted more easily. The Subcommittee members think that there is room to expand the set of data sources for examining health trends, including CMS data on Medicare and Medicaid, Homeland Security monitoring networks for emergency room visits, state databases on all hospital admissions, NIH databases, etc. It is not clear how other efforts, such as the Section 812 study, the OMB study of benefits of government regulations, and so on, interact with this. The incorporation of more information from these centers, networks, and databases would be useful.

The Subcommittee was particularly impressed with the early results of community-based studies that close the loop (e.g., the exposure modeling in New Haven, the New York City study of pesticide exposure that resulted in a regulatory change in New York, etc.). These examples combine good science in the original study with appropriate interactions of community leaders, resulting in policy-relevant information being transferred, and demonstrations of the benefits of interactions. In part, these examples made use of studies that were funded under other rubrics (e.g., Children's Centers) that subsequently were integrated into the LTG. The study of the impact of changes in drinking water disinfection on health, however, seemed to be closer to a *de novo* exercise of this goal. The approach combined innovative science (developing a new approach for measuring antibodies to multiple infectious agents using a noninvasive approach) with an opportunistic intervention trial that the Subcommittee thinks could be a model study for this LTG. As in comments on other products, however, the Subcommittee would like to see better evidence of a commitment by the program office to take the results of this research and use it more widely for regulatory purposes.

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Coordination and Communication

This LTG appears to be very well coordinated and, certainly through the ROE, communicated to the public, other scientists, and the regulatory community at EPA. The one concern of the Subcommittee is whether the tools being developed that allow for the evaluation are being developed in a way that will allow them to be shared with other groups that would want to use them to expand these activities. It would be appropriate and useful to have detailed, publicly available databases providing the underlying facts supporting the ROE and the other evaluations. By making these widely available, the Agency is allowing others to not only review their scientific interpretations of these data, but also to suggest alternative evaluations and interpretations that may better address the goals of LTG 4.

Program Performance

This is a relatively new LTG that has gained considerable traction and has achieved several fine accomplishments in a short period of time. Overall, the program performance was considered exceptional.

As indicated above, there are three themes of research. The Subcommittee believes that the ROE is asking the right set of science questions. Nineteen indicators have been identified to evaluate and answer questions related to exposure and effects of environmental contaminants as they are represented in the environmental public health paradigm consisting of source to transport/transformation, to exposure, to dose, to altered structure/function, and to adverse health. Indicators are being used to help evaluate trends in human exposure to environmental contaminants in the general health status of a population and in human disease and conditions, and, thus, the impact of regulations.

In addition, excellent progress has been made to demonstrate the performance of the formulated concepts and approaches, one of which is how trends in human exposure to an environmental contaminant can be assessed by measuring an indicator through biomonitoring. For example, the impact of public education on smoking and ETS exposure in the human population has been determined by measuring and observing decreasing levels of cotinine, a nicotine metabolite, in urine. Another example is the decreasing levels of lead in blood subsequent to implementing lead regulations.

Trends in increased life expectancy, decreases in infant mortality, and increases in asthma prevalence in adults and children are indicators that are being used to assess health status. The ORD scientists are cognizant of the difficulties of relating trends in human exposure and body burdens to stressors with changes in a health status indicator. Burden of disease or some type of calculated national and global risk is useful and should be included with caveats. For example, correlating decreasing blood lead levels and changes in cognitive abilities in children is fraught with problems. Some are concerned that when doing these evaluations of risk management decisions, they could be forced into doing simple ecological evaluations of disease incidence or mortality rates that do not really describe that improvements have occurred. Nevertheless, there is a need to be direct in the estimate of the human health impact of environmental interventions,

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and the Agency is encouraged to partner with national and global agencies attempting to do the same thing, and use uniform measures such as Disability Adjusted Life Years (DALYs). Overall, the indicators selected for monitoring exposures or adverse effects have been selected on solid scientific principles developed in LTGs 2 and 3.

The HHRP is strongly encouraged to continue "thinking outside of the box" regarding how to evaluate the impact of policy and regulations on human health and thus bring accountability to the decisions made about environmental issues. There are many different means available to evaluate programmatic performance, and these should be studied and applied where appropriate. Expanding beyond case studies to broader evaluations also is encouraged.

Scientific Leadership

The framework developed for assessing the public health impacts of risk management is a necessary means to move forward in this LTG, and it shows good leadership on the part of the HHRP. The nascent research studies of public health impact are timely and could be effective in advising the Agency on how this can be done. The example studies are well positioned to address problems that will undoubtedly arise in these types of studies, such as stakeholder involvement, scientific quality, statistical power and linkage to future utility. Finally, the ROE is well done and is presented in such a way that it is likely to have the expected impact on the Agency that evaluations like this should. The leadership of the ROE has planned for changes to the report over time that mimic some of the recommendations of the BOSC, such as a broader use of other databases, online tools for understanding environmental impacts at the local level, and better indices of the health implications of risk management decisions displaying sound scientific leadership in this area.

Summary Assessment

LTG 4 was assessed as being an integral part of closing the loop created when a hazard is identified, decisions related to that hazard are developed and implemented, and management decisions are examined to determine if they were warranted, effective, and should be continued. Many times, this critical aspect of environmental health decision-making is overlooked and programs are implemented that are unnecessary or no longer effective. Having the tools to evaluate risk management decisions must be a priority, and the Subcommittee is pleased that this is being undertaken with regard to the long-term impacts on human health. Specifically, the Subcommittee found this LTG: was designed to capture and communicate advances made by EPA and use this information to effectively improve future programs; was creating databases that, while not yet sufficient, were the genesis for a comprehensive approach to program review; was considering a broad array of means to estimate the amount of morbidity and mortality imposed by the environment and prevented through EPA's efforts; and had developed a number of products that were extremely useful in understanding the issues associated with assessing the effectiveness of EPA's decisions. Even though the program is rather new, the Subcommittee observed the enthusiasm in the staff involved, early successes in the approaches chosen, and the beginnings of a very successful activity for the Agency. The Subcommittee believes that the

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projects in this LTG have advanced more than was expected since the last evaluation and should be continued and supported.

With respect to LTG 4, the program exceeds expectations.

Recommendations

1. The BOSC recommends improving interaction and linkage with other federal agencies and state agencies.

2. Developing a means to capture and preserve institutional memory to improve long-term assessment of programs is recommended.

3. The BOSC recommends making the ROE more prominent and influential in the Agency.

4. The BOSC recommends expanding the use of health databases used to evaluate improvements in human health related to improvements in the environment, remaining cautious in interpreting these types of ecological analyses.

5. The BOSC recommends expanding the use of direct estimates of the health implications of environmental interventions by calculating burden of disease or similar appropriate measures of risk.

6. The BOSC recommends incorporating additional case studies into the LTG and attempting to extrapolate from existing case studies to other examples.

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VII. APPENDICES

Appendix A: Human Health Subcommittee Members

Board of Scientific Counselors (BOSC)
2009 Human Health Subcommittee

Chair:
James E. Klaunig, Ph.D.
School of Medicine
Indiana University

Vice Chair:
Henry Falk, M.D., M.P.H.
Director, Coordinating Center for Environmental Health and Injury Prevention
Centers for Disease Control and Prevention

Subcommittee Members:
Paul D. Blanc, M.D., MSPH
Chief, Division of Occupational and Environmental Medicine
Department of Medicine
University of California San Francisco

George P. Daston, Ph.D.
Miami Valley Laboratories
The Proctor & Gamble Company

David G. Hoel, Ph.D.
Medical University of South Carolina

Donald Mattison, M.D.
Senior Advisor to the Directors of the National Institute of Child Health and Human Development, and the Center for Research for Mothers and Children
National Institutes of Health

Edo Pellizzari, Ph.D.
Senior Fellow
RTI International

Christopher J. Portier, Ph.D.
Associate Director, National Institute of Environmental Health Sciences
National Institutes of Health

Joel Schwartz, Ph.D.
Professor, Department of Environmental Health
Harvard University School of Public Health

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Appendix B: Charge to the Subcommittee

Program Review Charge
Human Health Research Program Subcommittee

1.0 Objective. The BOSC Human Health Research Program Subcommittee will conduct a retrospective and prospective review of ORD's Human Health Research Program and evaluate the program's relevance, quality, performance, and scientific leadership. The BOSC's evaluation and recommendations will provide guidance to the Office of Research and Development to help:

- plan, implement, and strengthen the program;
- compare the program with programs designed to achieve similar outcomes in other parts of EPA and in other federal agencies;
- make research investment decisions over the next 5 years;
- prepare EPA's performance and accountability reports to Congress under the Government Performance and Results Act; and
- respond to assessments of federal research programs such as those conducted by the Office of Management and Budget (OMB 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 possible 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 especially 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, especially in a research program like the Human Health Research Program that is specifically designed to address longer term, relatively intractable problems. Indeed, decades may be required for some research outcomes to be realized and measurable in terms of public health outcomes.

Most of ORD'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 environmental outcomes. In interdisciplinary 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 studies.

In designing and managing its research programs, ORD emphasizes the importance of identifying priority research questions or topics to guide its research. Similarly, ORD

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recommends that its research 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 Agency partners, e.g., to strengthen environmental decisions. These decisions and resulting actions (e.g., the reduction of contaminant emissions or restoration of ecosystems) ultimately contribute to improved environmental quality and health.

In a comprehensive evaluation of science and research at EPA, the National Research Council[9] recommended that the Agency substantially increase its efforts to both 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 coordination teams. These teams help identify research contributions with significant decision-making value and help plan for their transfer and application.

For ORD's environmental research programs, periodic retrospective analysis at intervals of 4 or 5 years is needed to characterize research progress, to assess how clients/partners are applying research to strengthen environmental decisions, and to evaluate their feedback about the usefulness of the research. Conducting program evaluations at this interval enables assessment of: research progress toward long term goals and the ability of the program to adjust its approaches and plans according to unanticipated results; the overall scientific quality and decision-making value of the research; and, to what extent the research progress has resulted in short-term outcomes for specific clients/partners.

As guidance for these periodic program evaluations and consistent with the recent NAS report "Evaluating Research Efficiency in the U.S. Environmental Protection Agency", ORD follows the OSTP/OMB *Research and Development Investment Criteria* appended to this document.

3.0 Background for ORD's Human Health Program and Draft Charge Questions

Background

The overall goal of the HHRP, as defined in the current MYP (June 2006), is to characterize and ultimately reduce uncertainties in extrapolations inherent in the risk assessment process by providing a greater understanding of the fundamental determinants of exposure and dose and the basic biological changes that result from exposures to environmental toxicants. This research supports risk assessment activities conducted under the ORD Human Health Risk Assessment (HHRA) MYP and by Agency program and regional offices. An overarching theme is to improve our understanding of the linkages in the exposure-to-dose-to-effect continuum. It is of necessity an interdisciplinary research program that develops the methods, models and data needed to characterize uncertainties in each of these linkages and apply the information to the real world to elucidate exposures and risks in our communities. Research projects are integrated across the intramural and extramural grants programs and currently are organized around four LTGs. The relative effort and specific projects under each goal are adjusted on an annual basis in response to research findings as they become apparent and based on available resources.

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Long Term Goal 1 (LTG 1): Risk assessors and risk managers use ORD's methods, models or data to reduce uncertainty in risk assessment using mechanistic (or mode of action) information. *Fundamental research in this goal elucidates mechanisms of action of priority environmental contaminants and related families of contaminants, explores toxicity pathways that are perturbed by these contaminants, and uses this information to develop and link pharmacokinetic and pharmacodynamic models for use in risk assessment. These models are applied to reducing uncertainties associated with extrapolating from high to low dose, from test species to humans, from* in vitro *data to* in vivo *exposures, and between cancer and non-cancer effects. Progress is measured by the extent to which this information is being used in Agency risk assessments and rulings. A new direction in this goal is to develop a systems biology approach and apply novel models such as a virtual liver to predict toxicity and estimate risk.*

Long Term Goal 2 (LTG 2): Risk assessors and risk managers use ORD's methods, models, and data to characterize aggregate exposure and cumulative risk in order to inform risk management for humans exposed to multiple environmental stressors. *Research in this goal develops and applies biomarkers to assess cumulative exposure and risk; develops and applies source-to-dose models for cumulative risk assessment and dose reconstruction; and creates tools for community-based exposure and risk assessments of complex mixtures. The long-term objective is to produce a research framework outlining tools and approaches to characterize and assess aggregate exposures and cumulative risks, especially for vulnerable populations, based on a full range of both chemical and non-chemical stressors.*

Long Term Goal 3 (LTG 3): Risk assessors and risk managers will use ORD's methods, models and data to characterize and provide adequate protection for susceptible populations. *This goal focuses on susceptibility as a function of life stage with a strong emphasis on children and older Americans as potentially vulnerable populations. Fundamental research characterizes real-world exposures and the key exposure factors for these populations. Research is designed to examine how developmental exposures during pregnancy and early childhood may impact health later in life, and how life stage affects responsiveness to environmental contaminants, particularly in children and older adults. Tools and methods for longitudinal epidemiology studies developed in this research are applied in STAR-funded Children's Environmental Health Centers and translated to other national longitudinal studies on children's health. A specific strategy is being applied to understand the predisposing factors for asthma as a function of life stage, considering interactions with contaminants in both outdoor (e.g., diesel particles) and indoor air (e.g., mold) environments.*

Long Term Goal 4 (LTG 4): Evaluation of the Impact on Human Health of Risk Management Decisions. *Research in this goal develops and tests indicators for gauging the effectiveness of risk management decisions and pollution mitigation efforts. This research makes use of fundamental information generated by the other three goals. Current efforts focus on real world scenarios and include projects developed in collaboration with EPA regional offices and by NCER grantees. These projects test the hypothesis that measured changes in community and personal exposures result in improvements in human health that can be measured and confirmed by using appropriate environmental health indicators. This research both contributes to and draws from issues raised in EPA's Report on the Environment.*

These four goals are interrelated by design. Findings in each goal continually enable progress in and adjustments to research in one or more of the others. For example, new biomarkers

developed in LTG 2 may be used as indicators of children's exposures and health in LTG 3 and as measures of the impact of risk management decisions in LTG 4. Modes of action elucidated in LTG 1 are used to develop models for evaluating cumulative risk in LTG 2. Also, research products are typically not program office or media-specific. Rather, HHRP research is designed to produce knowledge and tools that are generalizable to the needs of multiple program offices, regions, other parts of ORD including the National Center for Environmental Assessment (NCEA) and the National Center for Computation Toxicology (NCCT), and other federal agencies (e.g., NIH/NICHD) and international groups (e.g., OECD) to further their goals.

Draft Charge

(A) Program Assessment (evaluate entire research program): The responses to the program assessment charge questions below should be in a narrative format, and should capture the performance for the entire research program and all the activities in support of the program's LTGs.

Program Relevance

1. How appropriate are the current HHRP objectives for achieving the Agency's strategic plan (Safe Communities) and providing a clear public benefit?
2. How appropriate is the science used to achieve each LTG, i.e., is the program asking the right questions, and using the most appropriate methods?
3. How effectively does the program identify and respond to the needs of its stakeholders, i.e. EPA partners in the program offices, regions, and ORD, and other partners outside EPA, and how effectively does it adjust to their changing needs?
4. How effectively does the program identify emerging issues relevant to its objectives and adjust its research strategy accordingly?

Factors to consider: the degree to which the research is driven by EPA priorities; the degree to which this research program has had (or is likely to have) an impact on Agency decision making; the appropriateness of the key science questions; the responsiveness of the research to the needs of EPA programs, regions, and other stakeholders within ORD (e.g., risk assessors); the responsiveness of the research plan to recommendations from outside advisory boards and stakeholders; the extent to which research program scientists participate on and contribute to Agency workgroups engaged in identifying and addressing research needs.

Program Structure

1. How clear a logical framework do the LTGs provide for organizing and planning the research, with clearly identified priorities and program outcomes?
2. Does the MYP describe an appropriate flow of work (i.e., the sequencing of related activities) that reasonably reflects the anticipated pace of scientific progress and timing of client needs?
3. Does the program use the MYP to help guide and manage its research? And is the program responsive to changing results and priorities as the science progresses?

Factors to consider: the scope of the LTGs in providing a logical framework for organizing the Human Health program to best meet its overall goals; the degree of clarity in the pathway to the performance goals specified for accomplishing the LTGs; the appropriateness of the LTG and

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associated Annual Performance Goals (APGs) identified in the MYP as the means to meet the overall objectives of the program.

Program Quality

1. How high is the scientific quality of the program's research products?
2. Are the means the program employs to ensure quality research (including peer review, competitive funding, etc.) sufficient?

Factors to consider: the scientific soundness of the research approaches used; the impact and use of research results by EPA program and regional offices and other organizations; the regularity with which papers on common themes are synthesized into documents more useful to decision-making; the degree to which peer reviewed publications from this program are cited in other peer reviewed publications, the immediacy with which they are cited, and their impact factor; the processes used to peer review intramural research designs and products (e.g., division-level or product-level reviews by independent panels); and the processes used in the competitive extramural grants program.

Coordination and Communication

1. How effectively does the program engage scientists and managers from ORD and relevant program offices in its planning?
2. How effectively does the program engage outside organizations, both within and outside government, to promote collaboration, obtain input on program goals and research, leverage the use of its resources with other organizations to achieve higher efficiency and avoid duplication of effort?
3. How effective are the mechanisms that the program uses for communicating research results both internally and externally?

Factors to consider: the extent to which program/regional office scientists/managers are involved in planning the research; the degree of collaboration and coordination with other federal agencies, academic institutions, industry partners, and/or other countries; the timeliness and means for making quality (peer-reviewed) information available to the Agency and scientific community (e.g., through peer reviewed publications, briefings, scientific meetings, and seminars); the extent to which research reports are synthesized into review documents and/or guidance documents and made available to Agency partners.

Program Performance

1. How much progress is the program making on each LTG based on clearly stated and appropriate milestones?
2. How well defined are the program's measures of outcomes?
3. To what extent are the program results being used by environmental decision makers to inform decisions and achieve results?
4. How efficiently has the program invested and managed resources to achieve the LTGs?

Factors to consider: the degree to which scientific understanding of the problem has been advanced; the degree to which scientific uncertainty has been reduced; the extent to which the program demonstrates impact and its products are used by EPA program and regional offices, ORD partners, and other organizations; the effectiveness of the program in identifying and

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investing in the most promising lines of research to achieve the LTGs; the relative prioritization and allocation of resources and scientific staff among the LTGs; and the investment of resources in short-term versus long-term research priorities.

Scientific Leadership

1. Please comment on the leadership role the research program and its staff have in contributing to advancing the current state of the science and solving important environmental health research problems.

Factors to consider: the degree to which this program is identified as a leader in the field; the degree to which peer reviewed publications from this program are cited in other peer reviewed publications, the immediacy with which they are cited, and their impact factor; the degree to which Human Health scientists serve/are asked to serve on national/international workgroups and advisory groups, as officers in professional societies, and on publication boards; the degree to which Human Health scientists lead national/international collaborative efforts, organize national/international conferences/symposia, and are awarded for their contributions/leadership; and benchmarking of scientific leadership relative to other programs, agencies, and countries.

(B) Summary Assessment (rate program performance by LTG): A summary assessment and narrative should be provided for each LTG. The assessment should be based primarily on three of the questions included above, which are:

1. How appropriate is the science used to achieve each LTG, i.e., is the program asking the right questions, with the most appropriate methods?
2. How high is the scientific quality of the program's research products?
3. To what extent are the program results being used by environmental decision makers to inform decisions and achieve results?

Elements to include for Long-Term Goal 1:

The appropriateness, quality, and use of ORD science by program and regional offices, ORD partners, and other organizations to characterize or reduce uncertainty in risk assessment by incorporating mode of action information and/or by taking a systems biology approach to model the dose to effect continuum and to enhance predictive toxicology.

Elements to include for Long-Term Goal 2:

The appropriateness, quality, and use of ORD science by program and regional offices, ORD partners, and other organizations to accurately measure and assess the risks associated with complex exposures to individuals, populations, and communities and relate these exposures to internal dose.

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Elements to include for Long-Term Goal 3:

The appropriateness, quality, and use of ORD science by program and regional offices, ORD partners, and other organizations to characterize susceptibility as a function of life stage and thereby contribute to protecting the health and well being of children and older Americans. The extent to which Human Health research informs activities of the Office of Children's Health Protection and the Office of Radiation and Indoor Air.

Elements to include for Long-Term Goal 4:

The extent to which "accountability" projects succeed in measuring exposures in communities at risk, before and after remediation, and relate those changes to indicators of public health impact, and the degree to which research addresses gaps and needs identified in EPA's Report on the Environment.

In developing the summary assessment for each LTG, the BOSC Human Health Subcommittee will assign a qualitative score that reflects the quality and significance of the research as well as the extent to which the program is meeting or making measurable progress toward the goal—relative to the evidence provided to the BOSC. The scores should be in the form of the adjectives that are defined below and intended to promote consistency among BOSC program reviews. The adjectives should be used as part of a narrative summary of the review, so that the context of the rating and the rationale for selecting a particular rating will be transparent. The rating may reflect considerations beyond the summary assessment questions, and will be explained in the narrative. The adjectives to describe progress are:

- Exceptional: indicates that the program is meeting all and exceeding some of its goals, both in the quality of the science being produced and the speed at which research result tools and methods are being produced. An exceptional rating also indicates that the program is addressing the right questions to achieve its goals. The review should be specific as to which aspects of the program's performance have been exceptional.
- Exceeds Expectations: indicates that the program is meeting all of its goals. It addresses the appropriate scientific questions to meet its goals and the science is competent or better. It exceeds expectations for either the high quality of the science or for the speed at which work products are being produced and milestones met.
- Meets Expectations: indicates that the program is meeting most of its goals. Programs meet expectations in terms of addressing the appropriate scientific questions to meet their goals, and work products are being produced and milestones are being reached in a timely manner. The quality of the science being done is competent or better.
- Not Satisfactory: indicates that the program is failing to meet a substantial fraction of its goals, or if meeting them, that the achievement of milestones is significantly delayed, or that the questions being addressed are inappropriate or insufficient to meet the intended purpose. Questionable science is also a reason for rating a program as unsatisfactory for a particular long term goal. The review should be specific as to which aspects of a program's performance have been inadequate.

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Appendix C: OSTP/OMB Research and Development Criteria

The Relevance, Quality, and Performance criteria apply to all R&D programs. Industry-relevant applied R&D must meet additional criteria. Together, these criteria can be used to assess the need, relevance, appropriateness, quality, and performance of federal R&D programs.

I. Relevance

R&D investments must have clear plans, must be relevant to national priorities, agency missions, relevant fields, and "customer" needs, and must justify their claim on taxpayer resources. Review committees should assess program objectives and goals on their relevance to national needs, "customer" needs, agency missions, and the field(s) of study the program strives to address. For example, the Joint DOE/NSF Nuclear Sciences Advisory Committee's Long Range Plan and the Astronomy Decadal Surveys are the products of good planning processes because they articulate goals and priorities for research opportunities within and across their respective fields. Programs that directly address Presidential priorities may receive special consideration for support, with adequate documentation of their relevance to those priorities.

OMB will work with some programs to identify quantitative metrics to estimate and compare potential benefits across programs with similar goals. Such comparisons may be within an agency or among agencies.

A. **Programs must have complete plans, with clear goals and priorities.** Programs must provide complete plans, which include explicit statements of: specific issues motivating the program; broad goals and more specific tasks meant to address the issues; priorities among goals and activities within the program; human and capital resources anticipated; and intended program outcomes, against which success may later be assessed.

B. **Programs must articulate the potential public benefits of the program.** Programs must identify potential benefits, including added benefits beyond those of any similar efforts that have been or are being funded by the government or others. R&D benefits may include technologies and methods that could provide new options in the future, if the landscape of today's needs and capabilities changes dramatically. Some programs and sub-program units may be required to quantitatively estimate expected benefits, which would include metrics to permit meaningful comparisons among programs that promise similar benefits. While all programs should try to articulate potential benefits, OMB and OSTP recognize the difficulty in predicting the outcomes of basic research. Discovery is a legitimate object of basic research, and some basic research investments may be justified on external judgments of the opportunity for discovery.

C. **Programs must document their relevance to specific Presidential priorities to receive special consideration.** Many areas of research warrant some level of federal funding. Nonetheless, the President has identified a few specific areas of research that are particularly important. To the extent a proposed project can document how it directly addresses one of these areas, it may be given preferential treatment.

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D. Program relevance to the needs of the Nation, of fields of science and technology, and of program "customers" must be assessed through prospective external review. Programs must be assessed on their relevance to agency missions, fields of science or technology, or other "customer" needs. A customer may be another program at the same or another agency, an interagency initiative or partnership, or a firm or other organization from another sector or country. As appropriate, programs must define a plan for regular reviews by primary customers of the program's relevance to their needs. These programs must provide a plan for addressing the conclusions of external reviews.

E. Program relevance to the needs of the Nation, of fields of science and technology, and of program "customers" must be assessed periodically through retrospective external review. Programs must periodically assess the need for the program and its relevance to customers against the original justifications. Programs must provide a plan for addressing the conclusions of external reviews.

II. Quality

Programs should maximize the quality of the R&D they fund through the use of a clearly stated, defensible method for awarding a significant majority of their funding. A customary method for promoting R&D quality is the use of a competitive, merit-based process. NSF's process for the peer-reviewed, competitive award of its R&D grants is a good example. Justifications for processes other than competitive merit review may include "outside-the-box" thinking, a need for timeliness (e.g., R&D grants for rapid studies in response to an emergency), unique skills or facilities, or a proven record of outstanding performance (e.g., performance-based renewals).

Programs must assess and report on the quality of current and past R&D. For example, NSF's use of Committees of Visitors, which review NSF directorates, is an example of a good quality-assessment tool. OMB and OSTP encourage agencies to provide the means by which their programs may be benchmarked internationally or across agencies, which provides one indicator of program quality.

A. Programs allocating funds through means other than a competitive, merit-based process must justify funding methods and document how quality is maintained. Programs must clearly describe how much of the requested funding will be broadly competitive based on merit, providing compelling justifications for R&D funding allocated through other means. (See OMB Circular A-11 for definitions of competitive merit review and other means of allocating federal research funding.) All program funds allocated through means other than unlimited competition must document the processes they will use to distribute funds to each type of R&D performer (e.g., federal laboratories, federally funded R&D centers, universities). Programs are encouraged to use external assessment of the methods they use to allocate R&D and maintain program quality.

B. Program quality must be assessed periodically through retrospective expert review. Programs must institute a plan for regular, external reviews of the quality of the program's research and research performers, including a plan to use the results from these reviews to guide future program decisions. Rolling reviews performed every 3-5 years by advisory committees can satisfy this requirement. Benchmarking of scientific leadership and other

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factors provides an effective means of assessing program quality relative to other programs, other agencies, and other countries.

III. Performance

R&D programs should maintain a set of high priority, multi-year R&D objectives with annual performance measures and milestones that show how one or more outcomes will be reached. Metrics should be defined not only to encourage individual program performance but also to promote, as appropriate, broader goals, such as innovation, cooperation, education, and dissemination of knowledge, applications, or tools.

OMB encourages agencies to make the processes they use to satisfy the Government Performance and Results Act (GPRA) consistent with the goals and metrics they use to satisfy these R&D criteria. Satisfying the R&D performance criteria for a given program should serve to set and evaluate R&D performance goals for the purposes of GPRA. OMB expects goals and performance measures that satisfy the R&D criteria to be reflected in agency performance plans.

Programs must demonstrate an ability to manage in a manner that produces identifiable results. At the same time, taking risks and working towards difficult-to-attain goals are important aspects of good research management, especially for basic research. The intent of the investment criteria is not to drive basic research programs to pursue less risky research that has a greater chance of success. Instead, the Administration will focus on improving the management of basic research programs.

OMB will work with some programs to identify quantitative metrics to compare performance across programs with similar goals. Such comparisons may be within an agency or among agencies.

Construction projects and facility operations will require additional performance metrics. Cost and schedule earned-value metrics for the construction of R&D facilities must be tracked and reported. Within DOE, the Office of Science's formalized independent reviews of technical cost, scope, and schedule baselines and project management of construction projects ("Lehman Reviews") are widely recognized as an effective practice for discovering and correcting problems involved with complex, one-of-a-kind construction projects.

A. Programs may be required to track and report relevant program inputs annually. Programs may be expected to report relevant program inputs, which could include statistics on overhead, intramural/extramural spending, infrastructure, and human capital. These inputs should be discussed with OMB.

B. Programs must define appropriate output and outcome measures, schedules, and decision points. Programs must provide single-and multi-year R&D objectives, with annual performance measures, to track how the program will improve scientific understanding and its application. Programs must provide schedules with annual milestones for future competitions, decisions, and termination points, highlighting changes from previous schedules. Program proposals must define what would be a minimally effective program and a successful program. Agencies should define appropriate output and outcome measures for

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all R&D programs, but agencies should not expect fundamental basic research to be able to identify outcomes and measure performance in the same way that applied research or development are able to. Highlighting the results of basic research is important, but it should not come at the expense of risk-taking and innovation. For some basic research programs, OMB may accept the use of qualitative outcome measures and quantitative process metrics. Facilities programs must define metrics and methods (e.g., earned-value reporting) to track development costs and to assess the use and needs of operational facilities over time. If leadership in a particular field is a goal for a program or agency, OMB and OSTP encourage the use of benchmarks to assess the processes and outcomes of the program with respect to leadership. OMB encourages agencies to make the processes they use to satisfy GPRA consistent with the goals and metrics they use to satisfy these R&D criteria.

C. **Program performance must be retrospectively documented annually.** Programs must document performance against previously defined output and outcome metrics, including progress towards objectives, decisions, and termination points or other transitions. Programs with similar goals may be compared on the basis of their performance. OMB will work with agencies to identify such programs and appropriate metrics to enable such comparisons.

IV. Criteria for R&D Programs Developing Technologies That Address Industry Issues

The purpose of some R&D and technology demonstration programs and projects is to introduce some product or concept into the marketplace. However, some of these efforts engage in activities that industry is capable of doing and may discourage or even displace industry investment that would occur otherwise. Programs should avoid duplicating research in areas that are receiving funding from the private sector, especially for evolutionary advances and incremental improvements. For the purposes of assessing federal R&D investments, the following criteria should be used to assess industry-relevant R&D and demonstration projects, including, at OMB discretion, associated construction activities.

OMB will work with programs to identify appropriate measures to compare potential benefits and performance across programs with similar goals, as well as ways to assess market relevance.

A. **Programs and projects must articulate public benefits of the program using uniform benefit indicators across programs and projects with similar goals.** In addition to the public benefits required in the general criteria, all industry-relevant programs and projects must identify and use uniform benefit indicators (including benefit-cost ratios) to enable comparisons of expected benefits across programs and projects. OMB will work with agencies to identify these indicators.

B. **Programs and projects must justify the appropriateness of federal investment.** Programs and projects must demonstrate that industry investment is sub-optimal to develop a technology or system and explain why the development or acceleration of that technology or system is necessary to meet a federal mission or goals.

C. **Programs and projects must demonstrate that investment in R&D and demonstration activities is a more effective way to support the federal goals than other policy alternatives.** When the federal government chooses to intervene to address market failures,

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there may be many policy alternatives to address those failures. Among other tools available to the government are legislation, tax policy, regulatory and enforcement efforts, and an integrated combination of these approaches. Agencies should consider that the legislation, tax policy or regulatory or enforcement mechanisms may already be in place to achieve a reasonable expectation of advancing the desired end.

D. **Programs and projects must document industry or market relevance, including readiness of the market to adopt technologies or other outputs.** Programs must assess the likelihood that the target industry will be able to adopt the technology or other program outputs. The level of industry cost sharing or enforceable recoupment commitments in contracts are indicators of industry relevance. Agencies must be able to justify any demonstration activities with an economic analysis of the public and private returns on the public investment.

E. **Program performance plans and reports must include "off ramps" and transition points.** In addition to the schedules and decision points defined in the general criteria, program plans should also identify whether, when, and how aspects of the program may be shifted to the private sector.

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Appendix D: List of Acronyms

ALAD	δ-Aminolevulinic Acid Dehydratase
BBDR	Biologically Based Dose Response
BOSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
DALYs	Disability Adjusted Life Years
DOE	Department of Energy
EPA	Environmental Protection Agency
ETS	Environmental Tobacco Smoke
FACA	Federal Advisory Committee Act
GPRA	Government Performance and Results Act
HHRA	Human Health Risk Assessment
HHRP	Human Health Research Program
IRIS	Integrated Risk Information System
LTG	Long-Term Goal
MOA	Mode of Action
MYP	Multi-Year Plan
NCCT	National Center for Computational Toxicology
NCEA	National Center for Environmental Assessment
NCER	National Center for Environmental Research
NHANES	National Health and Human Examination Survey
NIA	National Institute on Aging
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIEHS	National Institute of Environmental Health Sciences
NSF	National Science Foundation
OECD	Organisation for Economic Co-operation and Development
OMB	Office of Management and Budget
OPs	Organophosphate Pesticides
OPP	Office of Pesticide Programs
ORD	Office of Research and Development
OSTP	Office of Science and Technology Policy
OW	Office of Water
PART	Program Assessment Rating Tool
PBPK	Physiologically Based Pharmacokinetic
R&D	Research and Development
RFA	Request for Applications
ROE	Report on the Environment
SHEDS	Stochastic Human Exposure and Dose Simulation
STAR	Science To Achieve Results
USGS	United States Geological Survey

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