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BOARD OF SCIENTIFIC COUNSELORS

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

Final Report

BOSC MID-CYCLE SUBCOMMITTEE ON HUMAN HEALTH RESEARCH

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July 23, 2007

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I. SUMMARY

The U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) enlists its Board of Scientific Counselors (BOSC) to conduct independent expert reviews of ORD's environmental research programs every 4 to 5 years. Mid-cycle reviews, scheduled midway through the review cycle, are a critical step in the process. Narrower in focus than the in-depth technical evaluation that constitutes a full program review, the objectives of a mid-cycle review are to gauge the program's progress and to offer advice and feedback with respect to future directions and performance and accountability.

At a public meeting in early 2005, an eight-member BOSC Subcommittee completed a full review of the Human Health Research Program (HHRP), culminating in a BOSC report submitted to ORD in July 2005. Since that time, the research program has progressed to further define the scope of its long-term goals and to implement research activities within changing Agency resources and priorities. To assess progress in advancing the HHRP in line with BOSC comments, ORD requested that the BOSC conduct a mid-cycle review to assess program activities and plans while adapting to changes in Agency and Human Health Research priorities.

The Human Health Mid-Cycle Subcommittee met by teleconference on January 9 and March 15, 2007, followed by a public meeting, which was held on January 24, 2007. The mid-cycle review focused on ORD's detailed documentation of changes in the HHRP, a revised Multi-Year Plan (MYP), changes in the scope and focus of research activities, and adaptations to budgetary and other programmatic changes. The purpose of the review was to provide general feedback on ORD's efforts to date, and to assist ORD in addressing issues and opportunities surrounding continued development of the HHRP scope. This was accomplished through a set of specific charge questions (Appendix A) used to guide the BOSC Subcommittee through its review of the materials prepared for this review.

The BOSC Human Health Mid-Cycle Subcommittee represents a subset of the 2005 HHRP Subcommittee: the four members (with one exception due to conflict of interest) are the former lead reviewers for each Long-Term Goal (LTG) of the Human Health MYP. The Mid-Cycle Subcommittee members are listed in Appendix B. The Mid-Cycle Subcommittee has developed a number of recommendations for ORD based on the material reviewed and discussions organized as part of this mid-cycle review. Those captured in this Summary are meant to highlight general topics where ORD should focus its efforts. Readers are referred to the full text of this report to understand the context and detail of these comments, additional specific programmatic recommendations, as well as the full scope of the review team efforts and detailed comments.

Program Rating and Recommendations

A rating of Meets Expectations was assessed for work completed to date. As a specific charge question, the BOSC was asked to provide a summary rating of ORD progress in advancing the HHRP consistent with recommendations from the BOSC program review conducted in 2005.

The review team used the rating tool developed through collaboration between the BOSC, the Office of Management and Budget (OMB), and ORD to provide definition to the rating terms. The Subcommittee members thought that, based solely on actions to date, the Agency response and progress meets expectations. In the course of the review, it became apparent that there are many areas where ORD is continuing to work on challenging issues, developing new research plans, and reviewing options for committing additional efforts to enhance various research activities. The Subcommittee agreed that the HHRP has great potential for significant impacts in the future based on planned actions and new initiatives ORD has committed to or is developing, but have not yet been implemented or fully defined.

ORD is encouraged to continue to follow through on the plans and strategies that will make the Human Health Research Program a premier contributor in assessing environmental risks for human populations.

Assessment of HHRP response to recommendations from the 2005 BOSC program review. The Subcommittee noted that ORD invested substantial effort in assessing the BOSC comments and recommendations, revising program scope and direction, and developing point-by-point documentation of programmatic changes in response to BOSC recommendations. This included an initial response letter (http://www.epa.gov/osp/bosc/pdf/hh0509resp.pdf) and then specific actions including revising the MYP and changes in the HHRP scope and activities consistent with the BOSC review. These actions demonstrate ORD's commitment to considering review comments and documenting, point-by-point, programmatic changes in response to BOSC 2005 review comments. This is evidence that ORD takes the BOSC review seriously, is open to changing its approaches, and can add components to the research program to address the concerns of the BOSC and other review committees.

Clarity of the rationale for the revised Human Health Multi-Year Plan, and evaluating the revisions for consistency with advice given in the 2005 BOSC program review. In reviewing the revised Human Health MYP, the BOSC Subcommittee found specific textual passages that provided the rationale for research planning, upgraded illustrations and charts that demonstrated the interconnectedness of various research components, and descriptions of ORD activities that facilitate leveraging and coordination in the planning and execution of the research program. Further, discussion with ORD in the course of the mid-cycle review provided additional insight into ongoing changes and plans to ensure the HHRP moves in clearly defined directions that are also consistent with BOSC advice.

Even though the BOSC Subcommittee was able to document these beneficial changes in the revised MYP, the material discussed during the review makes it clear that the MYP is still a work in progress. ORD presentations informed the reviewers of plans to incorporate a number of new initiatives that will further define the scope and relevancy of the HHRP and enhance communication effectiveness. The Agency is encouraged to proceed with these commitments.

LTG 4, Assessment of Risk Management Decisions, has been refocused to provide a means to tie advancements in human health research and implementation of risk management decisions to overall improvements in the health of the public. Given that this goal is evolving to become a unifying theme for the HHRP, the Subcommittee recommends that ORD broaden the main objective for LTG 4 to reflect the growing emphasis on evaluating and demonstrating the impact of its research on improving environmental health.

Assessment of the performance metrics suggested by the program as indicators of impact. The BOSC Subcommittee reviewed a bibliometric analysis of HHRP research. ORD is commended for having conducted this analysis as it provides a diversity of information that can be used to develop performance metrics commonly used in the research community based on peer-reviewed publications and their impact. From these starting data, basic quantitative evaluations can be developed such as publications per research dollar invested, per FTE, and per year. The Subcommittee recommends that performance-based measures that link directly to publications and their impact be developed to guide ORD in assessing the significance of its research. Further, this information should be stratified by intramural and extramural research activities and included as an integral component of performance metrics for a number of programs. The two performance metrics agreed to with OMB will help the Agency document the progress towards its R&D goals and its contribution toward EPA's mission in protecting public health.

The current HHRP plan is effective in identifying a timeline for achieving research goals, however, it lacks in terms of specifying a plan for evaluation. Given the importance of performance metrics within EPA, ORD is encouraged to further develop an evaluative mechanism that would allow for an assessment of how well goals have been met and appropriately document the plan in future revisions to the MYP. The issue is of sufficient importance that an entire chapter of the MYP might be appropriately dedicated to such a plan.

The BOSC Subcommittee was very enthused about the potential for using environmental health indicators as a metric of performance. This approach has great appeal in that it would consider the full scope of research activities leading to the ultimate goal of protecting human health. For example, the National Center for Environmental Research (NCER) Science To Achieve Results (STAR) Program's Request for Applications EPA-G2007-STAR-A1, *Development of Environmental Health Outcome Indicators,* was issued to support research that uses existing databases of environmental, biological, and/or health-related data to develop indicators that reliably signal changes in environmental conditions, management approaches, or policies on human health. ORD is encouraged to put considerable effort into this and similar new initiatives to compile necessary information and to communicate results regarding efforts to quantify changes in environmental health status.

Recommendations regarding the emerging research area to evaluate risk management decisions, and using LTG 4 (Assessment of Risk Management Decisions) as a unifying theme for the program. The BOSC Subcommittee is enthusiastic about the potential of LTG 4 to serve as a unifying theme for the HHRP. Accomplishments in LTG 4 will provide a means to demonstrate and evaluate ORD's impact and contribution to improving environmental health. As the activities that support LTG 4 evolve and develop, this LTG holds considerable promise as an asset not only for EPA, but as an example for other agencies that have a public health regulatory mandate as well. Given the growing importance of LTG 4 to provide a nucleus by which HHRP's research activities would be both integrated and evaluated, it is recommended that the Program broaden its mission statement to reflect the greater diversity of information and participation necessary to achieve the objectives for LTG 4.

A draft document entitled *A Framework for an Environmental Accountability Research Program* (not to be quoted) was provided to the Subcommittee. In its draft form, it appears to provide a reasonable basis to start defining needs, objectives, and scope for a research program to evaluate

the effectiveness of risk management decisions. What appeared to be missing in that draft document and the other materials that were provided to the Subcommittee was a retrospective analysis. It would be useful to gather information and assess how risk assessments that have relied on the Program's methods, models, and/or data have informed risk management decisions. This is, a critical piece of information needed to address LTG 4. Thus, it is recommended that a plan be developed that would allow the Program's stakeholders and clients to link and track specific risk management decisions with risk assessments and the underlying research supported by ORD.

II. CHARGE QUESTION # 1:

How responsive has the Human Health Research Program been to recommendations from its 2005 program review?

The 2005 BOSC review of the Human Health Research Program offered 27 recommendations based on charge questions covering the topical areas of Relevance, Quality, Performance, and Scientific Leadership. The BOSC report included a number of general, broadly applicable recommendations, as well as specific items relevant to one of the four LTGs that ORD used to organize the HHRP. ORD invested substantial effort in assessing the BOSC comments, revising program scope and direction, and developing point-by-point documentation of programmatic changes in response to BOSC recommendations. This included an initial response letter and then specific actions including revising the MYP and changes in the HHRP scope and activities consistent with the BOSC review. Appendix C of this report provides a detailed listing complied by the Subcommittee to document specific changes observed in the HHRP as ORD responded to the BOSC recommendations; it also includes some additional areas that the Subcommittee believes need more work. The Subcommittee thought that it was important to include its own detailed documentation of ORD's efforts as a courtesy for the efforts ORD made to detail their responsiveness. The full text is included as in Appendix c, and only an abbreviated summary is presented here.

Overall, the Subcommittee noted that HHRP and ORD staff invested substantial effort in changing the HHRP in response to the BOSC's 2005 comments. Responses included revision of the MYP, incorporating broader stakeholder input, organizing ORD researchers and writing teams and formation of a Research Coordination Team, as well as adapting to changes in EPA's budgets and funding projections. ORD revised the MYP by adding outcome-oriented LTGs to the MYP and focused the MYP on addressing extrapolation issues in risk assessment. The revised MYP provides a better conceptual framework, articulates public benefits better, develops strategies to manage risk for new chemicals (computational toxicology, genomics, and proteomics), and broadens the scope of chemicals studied beyond pesticides.

In response to the 2005 BOSC program review, HHRP/ORD developed an extensive, 27-page, bibliometric analysis of scientific publications that presents a persuasive case regarding the scope and impact of the technical accomplishments of the Program. The analysis showed that 1,835 papers were published from l997-2006 by Program researchers. Each paper was cited on average 12.5 times. One quarter of the HHRP papers are highly cited papers. Sixty-four or 3.5% of HHRP papers are highly cited using ESI criteria for the top 2%. More than 50% of HHRP papers are published in high impact journals. Fifty-one percent were published in the top 10% of journals. Fifteen papers qualify as "hot papers." Eighty-one authors of the HHRP papers are included in *ISI Highly Cited.Com*, a database of the world's most influential researchers who have made key contributions to science and technology from l981-l999.

In general, the Mid-Cycle Review Subcommittee was favorably impressed with ORD's response to the previous program review. In total, the tabular and textual response in ORD's letter to the BOSC, the material provided for the review, and discussions during the face-to-face meeting demonstrate ORD's commitment to considering review comments and documenting, point-by-

point, programmatic changes in response to BOSC 2005 review comments. This demonstrates that ORD takes the BOSC review seriously, is open to changing its approaches, and can add components to the research program to address the concerns of the BOSC and other review committees. The re-write of the MYP, the re-cast of the risk management work, and the efforts to document the work with other governmental agencies involved in human health research demonstrate a commitment by ORD to modify the HHRP to meet expectations of outside review organizations.

III. CHARGE QUESTION # 2:

How clear is the rationale for the revised Human Health Multi-Year Plan, and are the revisions consistent with the advice given by the BOSC?

During the initial program review, one of the BOSC comments was that the HHRP needed to be planned and organized using a transparent rationale or conceptual framework, so that the basis for decisions setting priorities and research focus was well understood. In reviewing the revised Human Health MYP, the BOSC Mid-Cycle Subcommittee found specific textual passages that provided the rationale for research planning, upgraded illustrations and charts that demonstrated the interconnectedness of various research components, and descriptions of ORD activities that facilitate leveraging and coordination in the planning and execution of the research program. Further, discussion with ORD in the course of the mid-cycle review provided additional insight into ongoing changes and plans to ensure the HHRP moves in clearly defined directions that are also consistent with BOSC advice. As a matter of process, the BOSC Subcommittee recommends that in future reviews, ORD not only respond to review comments, but also identify the specific changes in documents such as the MYP as a result of review comments. Analogous to authors providing a response to a manuscript review, it is the actual revision to the manuscript that matters more than their comments regarding the reviewer's criticism. The mid-cycle review would have benefited if ORD provided a revised Human Health MYP with annotated changes in response to previous review comments.

As quoted from the revised MYP: "The main objective of the HHRP is to reduce uncertainties in the extrapolations necessary for the risk assessment process by providing a greater understanding of the fundamental determinants of exposure and dose and the basic biological changes that follow exposure to environmental toxicants." The rationale guiding the revised MYP provides a basis to link strategic approaches for research to improvements in the human health risk assessment processes at EPA. This strategic rationale is very clear, and is an obvious, central theme in the HHRP as discussed during this mid-cycle review. The concept that the MYP has been developed by ORD to improve problem-driven risk assessment decisions throughout EPA's program and regional offices also is very clear. The research questions developed in the Summary also are clearly developed and articulated, and the discussions with the BOSC Subcommittee made it clear that the ongoing HHRP can be linked to strategic Agency goals. Given that LTG 4 (Assessment of Risk Management Decisions) may provide a unifying theme for the HHRP, the Subcommittee recommends that ORD broaden its main objective to reflect the growing emphasis on evaluating and demonstrating the impact of its research on improving environmental health.

The revised MYP demonstrates ORD's commitment to make its research planning and prioritization process transparent to the wide diversity of stakeholders involved in human health issues. The revised MYP is much more focused on defining realistic and meaningful outputs and outcomes in human health research. The research strategy is aligned with the risk assessment framework, although it is less clear how the research has influenced risk management decisions made by the Agency. The revised MYP makes it easier to track ORD research programs in terms of their relevance to Agency strategic goals and in relation to research being conducted by other government agencies.

The "wiring diagrams" in the revised MYP (Figures 3-6) are very useful in helping the reader understand where the HHRP fulfills data needs for other ORD research programs. This helps the reader understand that the planning efforts are not conducted in a vacuum, rather ORD management is aware of data needs to address pressing environmental issues driven by a diversity of contaminants and human exposure issues. The regular meetings of ORD staff to determine how general principles derived from human health research can be used for other MYP initiatives shows ORD is responsive to stakeholder concerns that ORD could be vulnerable to potential focus on single programmatic goals and "silo" planning. Further, the MYP shows that ORD has a process to help facilitate big picture leveraging and multiple program cooperation. There are references to several Centers for Disease Control and Prevention (CDC) programs and other institutions conducting epidemiological studies that demonstrate an awareness of the efforts of other government R&D and monitoring programs in this area, and a willingness and commitment of EPA to work collaboratively with or leverage against other agencies in utilizing epidemiological data in human health research. Attachment D of the MYP is very useful in that it helps the reader appreciate the "big picture" in human health research, identifies how the HHRP contributes to these research areas, and allows for the tracking of ORD efforts as they relate to Agency strategic goals and other federal R&D programs.

Even though the BOSC was able to document these beneficial changes in the revised MYP, the material discussed during the review makes it clear that the MYP is still a work in progress. ORD presentations informed the review team of plans to incorporate a number of new initiatives that will further define the scope and relevancy of the HHRP and enhance communication effectiveness. The Agency is encouraged to proceed with these commitments.

IV. CHARGE QUESTION # 3:

How meaningful are the performance metrics suggested by the program as indicators of impact (i.e., scientific accomplishments, effective delivery, use by clients, etc.)?

The HHRP has defined performance metrics via a "wiring diagram" in the MYP that is more effective in defining a plan of research than it is in defining performance metrics. Each LTG within the MYP is supported by and linked to a series of Annual Performance Goals (APGs) (undefined in the report). The linkages, sequence, and timeline for achieving APGs are defined using a "wiring diagram" (e.g., for LTG 1 "Apply Emerging Technologies to Identify Key Changes in Toxicity Pathways"). The project-specific Annual Performance Measures (APMs), or milestones, that underlie and support each APG are defined within Attachment D of the MYP. At the APM level, the year, laboratory, and responsible individual(s) are identified. Accordingly, the current presentation is effective in providing a clear representation of the linkages from the more general LTGs all the way down to specific projects and responsible individuals. The current Human Health MYP is effective in identifying a timeline for achieving research goals; however, it lacks in terms of specifying a plan for evaluation. Given the importance of performance metrics within EPA, ORD is encouraged to further develop an evaluative mechanism that would allow for an assessment of how well goals have been met and appropriately document the plan in future revisions to the MYP (it might be appropriate to dedicate an entire chapter to such a plan).

The reviewed materials provide a systematic and comprehensive plan of research; however, they are less effective in establishing metrics of performance. The HHRP has conducted a comprehensive bibliographic analysis of publications and it is clear that ORD makes substantial contributions to the literature. What is less clear is the degree of consideration that has been given to how such publications would be used to develop performance metrics. Peer reviewed publications are one of the most robust and credible indicators of research performance. They are broadly accepted as a gold standard metric of research productivity. Performance based on publication would offer several advantages. First, it is clearly and objectively linked to research quality and impact. Second, it would provide a common framework of comparison with other academic institutions and federal research organizations. Third, it is compatible with the existing "wiring diagram" research plan such that publications could be linked to APMs. Particular metrics that might be of interest include publications per research dollar invested, per FTE, or per year. Thus, the Subcommittee recommends that performance-based measures that link directly to publications be developed to guide ORD in assessing the impact of its research.

The BOSC Subcommittee reviewed a bibliometric analysis of HHRP research. ORD is to be commended for having conducted this analysis, providing insight in three areas. First, it is responsive to the BOSC Subcommittee review as well as OMB requests to quantify the impact of R&D programs. Second, it shows how truly significant EPA's program of research is in impacting environmental health research. Lastly, it demonstrates how rich these data and analyses are for purposes of quantitative evaluation. ORD is encouraged to expand and strengthen this analysis to consider metrics of research productivity (such as suggested above) and stratified by intramural and extramural research activities and included as an integral

component to performance metrics. The two performance metrics agreed to with OMB will help the Agency document the progress towards its R&D goals and the impact of EPA's research on the scientific research community.

Review articles might be considered separately as a particularly valuable metric of research success and productivity in describing research progress related to a particular topic. Some very visible review articles/white papers on specific topics of significant interest to human health would be excellent technical resources and serve to inform the scientific community and the general public that the HHRP is doing its job of protecting the public health. For instance, a review or problem definition paper on nanoparticles and health issues, or a paper on pesticides and whether they can induce neurodegenerative diseases would go a long way toward showing the scientific community and the public that EPA has achieved, or has come a long way toward achieving, the research goal of settling these important questions. As another example of broad success in accomplishing specific objectives, HHRP scientists could review their contributions in understanding the mechanisms of arsenic toxicity and carcinogenicity, which has allowed EPA to more accurately regulate levels of arsenic in drinking water. Overall, compiling publication data, developing reviews that highlight programmatic impacts, and sharing information in diverse stakeholder venues will help document the productivity of the research programs and demonstrate how these efforts underpin the scientific credibility of the HHRP/ORD/EPA.

An important additional dimension to the HHRP and its implementation is how responsive it is to ORD's client program offices. This is more difficult to evaluate. The current HHRP fails to describe the method or process for evaluation of HHRP in meeting the needs of regions and program offices. It would be important to involve individuals trained and experienced in program evaluation to define this process. A survey might be developed for this purpose. ORD indicated in our face-to-face meeting that such a survey was under development and was being considered for implementation. The BOSC Subcommittee encourages EPA to at least test if not implement this program so that data are available for the next review. Another approach to meet this need might be to catalogue case studies showing how ORD research serves regional and client needs.

The BOSC Subcommittee was very enthused about the potential for plans presented at the face-to-face meeting for using environmental health indicators as a metric of performance. This approach has great appeal in that it would consider the full scope of research activities leading to the ultimate goal of protecting human health. Much of the discussion at the meeting focused on new initiatives the Agency will undertake to compile information and to communicate results. These efforts will enhance our understanding of how the research gets translated into regulatory actions, further documenting the relevancy of the research program. ORD is encouraged to put considerable effort in these areas.

V. CHARGE QUESTION # 4:

What advice can the BOSC provide concerning the emerging research area to evaluate risk management decisions, considering the possibility that this research might serve as a unifying theme for the program in the next 3-5 years?

In the revised MYP Fiscal Years 2006-2013, LTG 4, Assessment of Risk Management Decisions (formerly Evaluation of Public Health Outcomes), shows the fewest number of activities and goals among the four LTGs in the MYP. Nonetheless, the BOSC Subcommittee is enthusiastic about the potential of LTG 4 to serve as a unifying theme for the HHRP, as well as provide a means by which the Program can demonstrate the impact of its research on improving environmental health. As the activities that support LTG 4 evolve and develop, this LTG holds promise in providing an invaluable asset to EPA and other governmental agencies with a public health regulatory mandate.

The currently stated main objective for LTG 4 is "to reduce uncertainties in the extrapolations necessary in the risk assessment process by providing a greater understanding of the fundamental determinants of exposure and dose and the basic biological changes that follow exposure to environmental toxicants" (refer to MYP, page 6). Given the growing importance of LTG 4 to provide a nucleus by which the HHRP's research activities would be both integrated and evaluated, it is recommended that the Program broaden this mission statement to reflect the greater diversity of information and participation necessary to achieve the objectives for LTG 4.

Likewise, it was noted that the description of the research questions and activities that support LTG 4 might be better focused. In the aforementioned MYP, for example, the two key research questions for this goal are: (1) What are the trends in health status in the United States? and (2) What tools are available to determine the impact of regulatory decisions on exposures to environmental stressors that lead to adverse health outcomes? Correspondingly, two research tracks have been identified as: (1) Approaches to Evaluate Risk Management Decisions and (2) Health Chapter for Report on the Environment (ROE). Given that other federal agencies have primary responsibility for collecting mortality and morbidity measures and exposure data (which clearly support the tracking of both health trends and human exposures to environmental contaminants); some consideration might be given to whether question #1 adequately captures a research focus that supports LTG 4. Regarding the second question, it may be worthwhile to consider whether the research question should extend beyond identifying existing tools to assess risk management decisions. For Research Track 2, Approaches to Evaluate Risk Management Decisions, 10 research questions (page 60 of the MYP) were identified. The rationale that supports how those questions were identified should be provided. Also, clarification regarding the linkages between these and other research activities and outputs of the HHRP with LTG 4 would provide some details regarding how this goal might in fact provide a unifying theme for the Program over the next 3 to 5 years.

With respect to the MYP, two additional recommendations are made. First, some, but not all, of the 10 questions that were listed under Research Track 1 appear to support APMs (see Attachment D, Table 4 of the revised MYP). Clarification is requested as to what the expected

outputs might be (in terms of APMs) that derive from each of these activities. Secondly, in describing the synthesis of Research Tracks 1 and 2, it was stated that information derived from the research products will be summarized and communicated to the program and regional offices (revised MYP, page 61). There was no indication, however, of a process by which the program and regional offices can communicate back to the HHRP regarding which products are used and how. Although it was likely intended, a two-way communication mechanism should be explicitly articulated.

There was consensus among the Subcommittee members that the HHRP has responded to the prior recommendation to begin to elaborate a process by which LTG 4 can be carried out, namely, by establishing a Steering Committee comprised of representatives from ORD laboratories and centers, as well as the Office of Environmental Information. The charge to the Steering Committee was to develop a document to "provide a definition, overall objective, and research needs for a research program to evaluate the effectiveness of risk management decisions." A draft document, entitled *A Framework for an Environmental Accountability Research Program* (not to be quoted) was provided to the Subcommittee. What appeared to be missing in that draft document and the other materials that were provided was a plan to gather information and assess how risk assessments relying on the Program's methods, models, and/or data have informed risk management decisions—a critical piece of information needed to address LTG 4. Thus, it is recommended that a plan be developed that would allow the Program's stakeholders and clients to track specific risk management decisions linked to risk assessments that have been supported by the Program's research products. Consideration also should be given to the kinds of interactions that will be needed to allow for the program and regional offices to provide suitable feedback to the HHRP. The BOSC Subcommittee recognized the potential of the 'client-based survey,' which currently is under development to provide a source of 'measurable outcomes' of the HHRP that also might be used to support LTG 4. The utility of the client-based survey should be evaluated for this purpose and, if it is deemed unsuitable, then it is recommended that other mechanisms be identified and evaluated for gathering useful data to assess risk management decisions.

As the *Framework for an Environmental Accountability Research Program* continues to evolve, additional details would be helpful regarding the rationale that will be used to formulate the criteria for prioritizing which risk management decisions to evaluate (once they have been identified). Secondly, it did not appear that the framework included an assessment of resources (human and financial) that will be needed internally to carry out the program once it is delineated. Thus, it is recommended that ORD evaluate the current strengths that can be capitalized on, as well as the additional resources that would be needed to support the program in both the short- and long-term. Notwithstanding the challenges inherent in such an evaluation, it also is recommended that benchmarks of 'effectiveness' of the risk management decisions on improvements in environmental health be developed, which are both measurable and time-delimited.

As part of NCER's STAR Program, a Request for Applications (EPA-G2007-STAR-A1, *Development of Environmental Health Outcome Indicators*) was issued to support research that uses existing databases of environmental, biological, and/or health-related data to develop indicators that reliably signal changes in environmental conditions, management approaches, or policies on human health. This RFA is clearly relevant and supportive of LTG 4; however, no APMs were noted as they relate to the STAR funded research program (Attachment D, Table 4

of the revised MYP) perhaps because the RFA was issued after the MYP was prepared. Once funding decisions are made, it is recommended that APMs be developed as they relate to the funded projects for this and any other relevant programs supported by NCER.

Two collaborative activities were identified in the MYP as supportive of LTG 4. While the Memorandum of Understanding (MOU) established in 2002 with the CDC for an environmental tracking program is clearly relevant, it was not clear how the U.S.-Mexico Border Program (http://www.nmsu.edu/~frontera/old_1996/nov96/1196heal.htm) supports LTG 4; additional clarification would be helpful.

Notwithstanding the budgetary requirements, it is recommended that additional demonstration projects be funded to the extent possible given available resources.

VI. CHARGE QUESTION # 5

Please rate the progress made by the Human Health Research Program in moving the program forward in response to the BOSC review of 2005 as exceptional, exceeds expectations, meets expectations, or not satisfactory.

With respect to specific areas of progress, the BOSC Subcommittee members were not yet clear on the process used to prioritize chemicals for study by the HHRP. The discussions indicated that each program office has its own list of toxic threats ("hit list") that it must deal with, and has rank-ordered these materials. It was explained that these priority lists arise from the program offices, the stakeholders, and the Integrated Risk Information System (IRIS), and then are discussed with HHRP scientists. The BOSC Subcommittee agreed that this is an appropriate process, but also thinks the MYP should explicitly address how specific chemical concerns or toxicity effect issues that may emerge on a short timeframe are addressed. ORD could take leadership here—providing a strong scientific rationale for prioritizing chemicals for study that is complimented by advice and consultation from the program office as opposed to simply being responsive to programmatic needs. This would help stakeholders understand how emerging concerns can become integrated into the overall HHRP. For example, it is not clear in the revised MYP how ORD would quickly address issues such as perfluorooctanoic acid and its derivatives (PFOAs), pesticides that may cause neurodegenerative diseases, or decide to put more focus on studying the toxicities of nanomaterials.

In terms of making progress, it is clear from the bibliometric analysis that ORD authors are publishing scientific papers in good peer-reviewed journals. Many of these papers are being cited to a significant extent. A number of ORD researchers are becoming well known for publishing excellent science, which is enhancing the scientific credibility of the Agency.

The Subcommittee discussion on providing a rating for the progress focused on both the progress to date in responding to the 2005 review comments and the many areas where ORD is continuing

to work on issues, develop plans, and commit additional resources to enhance research activities. The Subcommittee believes that, based solely on actions to date, the Agency response and progress meets expectations.

The plans for additional work in all areas, enhanced efforts to quantify research metrics, and resources dedicated to communicate research results will provide significant progress towards a program with even greater impact. The Subcommittee wholly supports the new vision of greater scope in LTG 4 (Assessment of Risk Management Decisions), efforts to develop LTG 4 research programs at a faster pace, and continued quality science as the driver for all HHRP activities. The Subcommittee agreed that the HHRP is headed in the right direction.

ORD is encouraged to continue to follow through on the plans and strategies that will make the Agency's HHRP a premier contributor in assessing environmental risks for human populations.

VII. APPENDICES

Appendix A: Subcommittee Charge

01-18-07

HUMAN HEALTH MID-CYCLE SUBCOMMITTEE
CHARGE
January 24, 2007
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1.0 Objectives. The objectives of this mid-cycle review are:

- to evaluate the progress made by the Office of Research and Development's (ORD's) Human Health Research Program relative to the commitments it made following its last review (February 28 – March 2, 2005), and
- to obtain advice and feedback on issues related to the future directions of the research program and performance and accountability.

2.0 Background Information. Independent expert review is used extensively in industry, federal agencies, Congressional committees, and academia. The National Academy of Science has recommended this approach for evaluating federal research programs.[1]

For the Agency's environmental research programs, periodic independent reviews are conducted at intervals of four or five years to characterize research progress, to identify when clients are applying research to strengthen environmental decisions, and to evaluate client feedback about the research. Mid-cycle evaluations are an important part of this program review process. Scheduled midway through the review cycle, these independent assessments give ORD an opportunity to gauge the program's progress relative to the commitments it made following its last review.

For the upcoming mid-cycle review, the Human Health Research Program has prepared a progress report that will provide the context for our discussions during the meeting. The report outlines the changes implemented by the program in response to the major recommendations from its 2005 review. The Human Health Research Program also has revised its Multi-Year Plan. The plan lays out the context, and presents a time line, for research on the four long-term goals: 1) use of mechanistic data in risk assessment, 2) cumulative risk, 3) susceptible subpopulations, and 4) evaluation of risk management decisions. These documents are pertinent to the draft charge questions.

1 Evaluating Federal Research under the Government Performance and Results Act (National Research Council, 1999).

This review is not intended to be the in-depth technical evaluation of a full program review. Presentation time will be minimized in favor of discussion.

3.0 Draft Charge Questions for ORD's Human Health Research Program. ORD is interested in receiving feedback concerning the following questions:

- How responsive has the Human Health Research Program been to the recommendations from its 2005 program review?
- How clear is the rationale for the revised Human Health Multi-Year Plan, and are the revisions consistent with the advice given by the BOSC?
- How meaningful are the performance metrics suggested by the program as indicators of impact (i.e., scientific accomplishments, effective delivery, use by clients, etc.)?
- What advice can the BOSC provide concerning the emerging research area to evaluate risk management decisions, considering the possibility that this research might serve as a unifying theme for the program in the next 3-5 years?
- Please rate the progress made by the Human Health Research Program in moving the program forward in response to the BOSC review of 2005 as exceptional, exceeds expectations, meets expectations, or not satisfactory.

For this last question, the BOSC Mid-cycle Subcommittee is being asked to assign a qualitative score that reflects the extent to which the program is making progress in moving the program forward in response to the previous BOSC review. The score should be in the form of one of the adjectives defined below and is 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. For mid-cycle reviews, the rating should be based on the quality, speed, and success of the program's actions in addressing previous BOSC recommendations. The adjectives to describe progress are:

o **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.

o **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.

o **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 its 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.

o **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.

4.0 Potential Subcommittee Approach for Mid-Cycle Review

- Hold one (1) administrative call in the month preceding the face-to-face meeting.
  - allows the subcommittee Chair to make review and writing assignments

- Distribute background materials and documents requested by the subcommittee in advance of the teleconference call.

- Hold one (1) teleconference call in the month preceding the face-to-face meeting.
  - allows the ORD to present background and other relevant materials to the subcommittee
  - allows the subcommittee to ask clarifying questions

- Hold a one-day face-to-face meeting for the mid-cycle review.
  - The meeting will include ORD presentations on program progress and discussions with members of the Human Health Mid-Cycle Subcommittee.
  - The meeting will conclude with the presentation of a draft letter report that addresses all of the charge questions.

If needed, hold one (1) teleconference call within one month following the face-to-face meeting to finalize the draft letter report.

Appendix B: Human Health Mid-Cycle Subcommittee

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Appendix C:
Detailed Answers to Recommendations from the 2005 BOSC Program Review

How responsive has the Human Health Research Program been to recommendations from its 2005 program review?

BOSC Mid-Cycle Review Subcommittee Documentation of ORD's Responses to the 2005 BOSC Review

The 2005 BOSC Human Health Research Program (HHRP) review generated recommendations related to each of the four Long-Term Goals (LTGs) in the HHRP. HHRP/ORD scientists conscientiously responded to the 2005 BOSC program review of the HHRP by identifying 27 recommendations from the review and developing responses for each item. They responded to: (1) general criticisms that spanned more than one LTG, and (2) specific comments relevant to a specific LTG. The HHRP/ORD invested substantial effort in responding to criticisms from the BOSC Subcommittee and were very responsive to the 2005 BOSC program review.

HHRP/ORD Responses to the BOSC's General Comments

HHRP/ORD responded to the BOSC program review of the HHRP in 2005, and revised their Multi-Year Plan (MYP) according to stakeholder input, ORD researchers, and writing teams; a Research Coordination Team (RCT); and changes in EPA's budget for FY 2006-2007. ORD revised the MYP by adding outcome-oriented LTGs to the MYP and focused the plan on addressing extrapolation issues in risk assessment. The MYP also now provides a better conceptual framework, articulates public health benefits better, develops strategies to manage risk for new chemicals (computational toxicology, genomics, and proteomics), and broadens the scope of chemicals studied beyond pesticides. The Subcommittee indicated that ORD needs to articulate a more concrete plan for how the Program will deal with a vast array of chemicals that need to be studied for toxicity and genotoxicity. According to ORD, the National Program Director (NPD) for Human Health will meet with EPA program offices and regions and conduct a customer value analysis of their current and emerging research needs. This list then will be reviewed and prioritized by the RCT and used in the development of the next version of the Human Health MYP. ORD increased stakeholder involvement in planning and prioritization and included community-based participatory research and pharmacodynamic components to source-effect research. ORD also improved: (a) integration between parts of the HHRP, and (b) communication and interactions outside EPA and between intramural and extramural programs. ORD created a Web site for the HHRP to help with these goals. In addition, ORD moved forward with LTG 4, Evaluation of Public Health Outcomes. ORD de-emphasized aggregate risk, increased emphasis on biomarkers, included community risk as a new theme, and focused on life-stage for susceptible subpopulations. ORD de-emphasized the National Children's Study and evolved the theme of evaluating risk management decisions. Further, ORD developed cross-links to stakeholder needs and other MYPs.

There remains a need to develop a formal plan to ensure a smooth transition to new leaders when senior leaders retire. ORD is encouraged to recruit technical leaders from outside and inside EPA, and infuse HHRP with new scientific expertise. EPA should give serious thought to mentoring and developing intramural individuals for leadership positions and recruiting outside scientific leaders. The Subcommittee recommended EPA plan for leadership succession in technical and management areas. ORD responded that they recognize changing demographics, and individual laboratories and centers have developed their own approaches to deal with this challenge. ORD has begun developing new scientific leadership to replace senior scientific leaders who will soon retire. ORD also developed an active postdoctoral program and recruits scientists from the postdoctoral program, and more senior laboratory scientists are being groomed to become scientific leaders and future replacements for the present scientific leadership of ORD. They do this through a Human Resource Plan that involves gradual training of junior scientists to assume leadership positions in ORD. A leadership program also is being developed though the STAR Program.

The Subcommittee asked how easy it is to shift resources to study emerging toxic/ carcinogenic/neurotoxic threats. HHRP/ORD indicated they rapidly mobilized to study bioaccumulation of brominated diphenyl ethers (BDPEs) in human tissue. The BDPE effort arose out of ORD's dioxin studies, so it was quickly initiated among existing staff. ORD indicated they are working to deal with emerging toxicity issues of ozone, and trying to determine how to generate and shift resources to address ozone's toxicity. As a third example, ORD indicated they were working on how to shift resources to study the toxicity of nanoparticles. This effort needs to be accelerated due to the plethora of different types of nanoparticles in commercial use now and large numbers of preparations being developed.

The BOSC Subcommittee requested bibliometric analysis of HHRP publications to better evaluate the quality and performance of the HHRP and show the impact of EPA research. This analysis should differentiate the intramural from the extramural programs to facilitate assessment of Agency capabilities and efforts of funded scientists, as well as assess collaborative efforts. HHRP/ORD provided an extensive, 27-page bibliometric analysis of the Program's scientific publications, which showed that 1,835 papers were published from l997-2006 by the HHRP/ORD. These papers were cited 22,937 times, or 12.5 times/published paper, and 1,561 of these publications (85%) were cited at least once in a journal. One quarter of the HHRP papers are highly cited papers. Sixty-four or 3.5% of HHRP papers are highly cited using ESI criteria for the top 2%. More than 50% of HHRP papers are published in high impact journals; 51% were published in the top 10% of journals. Fifteen papers qualify as "hot papers." Eighty-one of the authors of HHRP papers are included in *ISI Highly Cited.com*, a database of the world's most influential researchers who have made key contributions to science and technology from l981-l999. There was a reasonable distribution of HHRP papers across a broad group of disciplines ranging from mathematics to plant and animal science, geosciences, engineering, chemistry, neuroscience and behavior, immunology, biology and biochemistry, molecular biology and genetics, environment/ecology, pharmacology and toxicology, and clinical medicine.

In future bibliometric analyses, the BOSC Subcommittee recommends separating intramural investigators' publications from extramural investigators' publications for clarity. It was difficult to differentiate among Agency publications, extramural publications, and collaborative intramural-extramural publications. These should be presented as a stick diagram to emphasize

general interactions, then in a separate table with lists of publications, separating intramural from extramural publications, and collaborative publications.

The Subcommittee indicated there is an international leadership opportunity for HHRP/ORD to examine its involvement and potential collaboration with similar HHRP programs in the European Union (EU) and Health Canada. The BOSC indicated that ORD should monitor, engage in, and advise the research efforts of the EU, Health Canada, and other international HHRP agencies with greater intensity and at a significantly higher level within the ORD research organization than has occurred to date. HHRP/ORD should specifically work with other agencies to develop exposure and risk assessment tools needed to study the large number of substances to which humans are exposed. Scientists within the HHRP have considerable skill and knowledge to contribute to EU research planning efforts. Further, issues related to the Food Quality Protection Act (FQPA) have driven much of the work in the HHRP, including the exposure research program. Exposure research does use pesticides as a class of chemicals to facilitate development and validation of models. Exposure research in the 2006 Human Health MYP focuses on developing more generic models that can be applied to any class of chemicals. Emerging issues related to community/cumulative risk and evaluation of risk management decisions, as well as obtaining observational data on susceptible subpopulations, are pertinent to all classes of chemicals.

ORD responded that their scientists participate in many international activities, attended an EU workshop in Italy in 2005, and met with other investigators to identify ways to integrate ORD's HHRP on toxic chemicals with ongoing/planned EU activities. Table 7 in the 2005 documentation package summarized these interactions. ORD also indicated that the NPD for Human Health and key ORD researchers will meet with the Director of the Office of Pollution Prevention and Toxics (OPPT) to develop strategies to engage ORD researchers with the EU and Canadian organizations that are designing related research programs addressing uncertainties for high priority chemicals/classes of chemicals. ORD researchers will actively participate in future EU/Canadian workshops to develop new approaches for addressing risk assessment for chemicals. The Subcommittee thought improvement could be made here by specifying the action taken in the last 2 years, and changes that have been made to the HHRP to ensure desired interactions in the future. For the next review, the documentation package could include a section describing specific research interactions of HHRP scientists with international programs. The BOSC notes that these interactions already occur, but need to be documented better and strengthened. They could be presented in: (1) a stick diagram with HHRP in the middle, and arrows to international agencies with which HHRP/ORD interacts, and (2) a table listing specifics of these interactions.

The BOSC (2005 review) noted that public benefits from doing good science could be enhanced in written materials presented to the Subcommittee. ORD responded that public health benefits of the HHRP are now linked to performance measures developed in collaboration with OMB. The HHRP also will place more emphasis on developing methods, models, and data to assist EPA in evaluating the effectiveness of risk management decisions. Development of biomarkers of effect or exposure to assess changes in human health will have public health benefits. ORD notes that public health benefits of LTG 1, Use of Mechanistic Information in Risk Assessment, were clearly articulated.

BOSC (2005 review) projected that creation of the new National Center for Computational Toxicology (NCCT) may produce challenges regarding teamwork and should be monitored to ensure collaboration continues and is not organizationally impeded. ORD responded that establishment of the NCCT transferred a number of productive HHRP scientists to the computational toxicology program, and now the NPD for Human Health and the Director of NCCT meet on a quarterly basis to discuss coordinating the respective research programs. Several HHRP researchers received funds from the NCCT for research relevant to HHRP themes. Their products are captured in the revised Human Health MYP. In addition, projects underway by some scientists transferred from the HHRP to the NCCT continue. Products from their research programs also are captured in the 2005 Human Health MYP. Finally, as the NCCT has developed its mission and expertise, new projects (developing biologically based models of arsenic toxicity) relating to current HHRP themes have evolved. ORD has been developing data on various chemicals and working to implement computational toxicology solutions to deal with the plethora of chemicals the Agency is charged with regulating, as suggested by the BOSC review.

A list of inter-governmental agency collaborations between HHRP and sister governmental agencies was missing from the 2005 review documents, so the full extent of the Program's partnering could not be judged accurately and given appropriate credit. ORD responded that there were lots of inter-governmental agency collaborations. The Subcommittee recommends that ORD create a one-page stick diagram of these interactions, with EPA at the center and arrows to the agencies with which they collaborate. Additional tables documenting specific interactions should be created for the next review.

BOSC (2005 review) indicated a greater level of interaction between investigators in the externally funded University Centers and in-house researchers could result in more significant research progress, such as in the case of the potential role of SGT polymorphisms in autism. ORD responded they instituted more meetings between intramural investigators and external centers and other externally funded investigators. The Subcommittee compliments ORD for these efforts and recommends they be continued and reinforced.

Regarding program performance, the BOSC Subcommittee (2005 review) noted that the HHRP appeared appropriately directed and focused, but that its scientific basis, justification, and conceptualization could be further developed. The presentation of the justification of research priorities appeared to the Subcommittee to be defined by external advisory bodies, such as the National Research Council (NRC). Advice from such advisory groups provides an important element of justification, but further clarification of the role of HHRP scientists in defining and setting these priorities is suggested. The process by which broad research themes (use of mechanistic information in risk assessment, cumulative risk, susceptible subpopulations, and evaluating risk management decisions) are transformed into a research program was not clearly articulated during the 2005 review. ORD replied that once broad research themes have been identified by external bodies, such as the NRC or Science Advisory Board (SAB), and recognized as high priority needs by EPA, they are pursued. ORD relies on discussion with its clients (program/regional offices) and the scientific community to determine what research needs to be addressed, from programmatic and scientific points of view. Meetings are held with program and regional offices to understand their regulatory science priorities and confirm that HHRP research addresses these needs. Results of discussions with program and regional office clients are summarized in Attachment B of the 2006 Human Health MYP. Emerging HHRP

science needs are identified through ORD scientists attending scientific symposia, conferences, workshops, and scientist-to-scientist meetings. Programmatic and science needs are compiled and prioritized based on science and resources. Scientific meetings are used to develop approaches to address these questions from scientific points of view. Scientific meetings related to the HHRP since June 2005, are found in Table 2.

Programmatic Changes in Response to BOSC's Specific Comments in 2005

LTG 1: Use of Mechanistic Information in Risk Assessment

In 2005, the BOSC Subcommittee thought the HHRP lacks a specific plan that articulates strategies that will be used to manage risks from the thousands of new chemicals being synthesized and put into the environment. ORD responded that the NCCT is developing computational approaches to identify and manage risks for large numbers of new chemicals, including approaches to improve prioritization for screening and testing. One research theme in the HHRP is developing emerging methods and models that can be used with computational methods. Other MYPs (Safe Pesticides/Safe Products, Drinking Water, and Endocrine Disruptors) also support research to develop approaches for prioritization of chemicals for screening and testing relative to their specific problem-driven areas. A new research area in LTG 2 will develop tools to identify communities at risk from cumulative exposure to chemicals/non-chemical stressors.

LTG 2: Aggregate Cumulative Risk Assessment

The BOSC (2005 review) indicated the current level of involvement of program offices, regional offices, and other stakeholders strengthens the HHRP, and should be sustained and upgraded. It is important to expand EPA expertise to include community-based participatory research (CBPR). ORD responded that much of the research supported by the STAR Program includes CBPR. The Children's Environmental Health Research Center Requests for Applications (RFAs) required CBPR from the program's inception. Children's Center investigators are experts in CBPR in environmental health research. They published on CBPR and organized scientific sessions at meetings on CBPR in environmental health research. Additionally, the newly developing intramural research program related to community risk will require CBPR. Initial steps of the extramural program include: (1) inventorying available tools; (2) establishing collaborations with groups conducting CBPR to gain expertise and test these tools; and (3) revising the tools to address future needs.

The BOSC (2005 review) commented that the one dimensional model presented in the HHRP MYP did not represent the dynamic, multidimensional HHRP. ORD's focus on children as a susceptible population subgroup is justified, but the justification can be strengthened by EPA's scientific assessment of the public health benefit to be achieved through research focused on children as a specific subpopulation. ORD responded to this through the revised MYP and responses to the PART review.

The BOSC (2005 review) found a strong effort to provide coordination and integration across HHRP's research themes, but little integration of exposure assessment across themes that deal with health effects. ORD recognizes that some fundamental research in the HHRP is laboratory/center-specific, such as research on toxicity pathways or modes of action. Multidisciplinary research projects are emphasized to a greater degree in the 2006 MYP. Pharmacodynamic/pharmacokinetic (PD/PK) model development, biomarker development, community risk, susceptible populations, and risk management decisions depend on multidisciplinary integration.

The BOSC (2005 review) commented that criteria and framework for decisions regarding why specific elements are included in the HHRP were not clear. ORD responded that it receives broad strategic direction from EPA, influenced by external advisory bodies/public health concerns, and generates strategic approaches to address broad goals. ORD scientists generate research needed to address those goals in collaboration with input from program/regional office stakeholders. Articulation of annual products is derived from discussions by the RCT, including ORD scientists/EPA stakeholders.

The BOSC (2005 review) indicated HHRP source-to-effect research should include pharmacodynamic issues. ORD responded that biomarker research in LTG 2 is developing state-of-the-art mathematical and statistical modeling techniques to estimate target tissue doses and individual exposure, and apportion these to sources (Table 3). Once such models are evaluated, they will be linked to studies that focus on pharmacodynamic issues. Research on developing linkages between PK and PD models also is covered in LTG 1, where PK/PD models for pyrethroid pesticides and As are being developed. NCCT is leading development of systems biology approaches to investigate differences in tissue responses.

LTG 3: Evaluation of Risk to Susceptible Subpopulations

The BOSC (2005 review) noted that a listing of intergovernmental agency collaborations between ORD's HHRP and sister governmental agencies was not provided during the review. Hence, the full extent of this partnering could not be judged accurately and given appropriate credit. ORD responded that ORD scientists collaborate extensively with scientists from other federal agencies. The documentation package provided for the 2005 program review attempted to capture these collaborations in biosketches and posters, but this underestimated the extent of these interactions. For the next review, it would be beneficial if the documentation package included a section detailing specific interactions of HHRP researchers with scientists from other federal agencies. The Subcommittee thinks the HHRP could improve information transfer here, for example, by providing a stick diagram with linkages from HHRP to sister agencies with which ORD collaborates, and/or a table listing joint publications between ORD/HHRP researchers and sister agencies, listed under area of scientific interest (e.g., carcinogenesis) and agency.

The BOSC (2005 review) observed less evidence of interactions between intramural scientists and the extramural Children's Environmental Health Research Centers. The BOSC noted that greater interaction between investigators in externally funded University Centers and in-house researchers could yield more significant research progress. ORD responded that it recognizes the need to better coordinate intramural research with the STAR grants program. The NPD for Human Health has had discussions with the Director of NCER concerning this issue. Interaction

between NCER and other ORD laboratories has increased, through enhanced participation by NCER representatives on the HHRP RCT, more inclusive review of new RFAs for future extramural research, review of products from the grants program by ORD staff, and hosting scientist-to-scientist meetings between intramural and extramural scientists. NCER routinely relies on scientists from ORD laboratories to serve on internal programmatic review teams to offer advice on final funding decisions on STAR grants. NCER also initiated "initial investigator meetings," where newly funded grantees meet with EPA scientists to discuss their research plans to encourage communication between extramural and intramural researchers. Products from extramural research also are more integrated into the 2005 Human Health MYP. The relationship of these products to the intramural program is clearly articulated.

The BOSC (2005 review) recommended the HHRP MYP be updated. ORD responded that a revised Human Health MYP was accepted by the ORD Science Council in 2005 and is the road map for the HHRP for FY 2006-2013. Products (APMs) in the MYP will be updated annually. The plan will be revised in 2009. Recent scientific meetings provide opportunity to refine research approaches relevant to HHRP research themes and deal with emerging issues.

The BOSC (2005 review) noticed discrepancies between specific projects and performance measures listed in LTG 1 of 2003 and the current projects in today's HHRP, deliverables, and APMs. ORD indicated that this had been addressed in the revised MYP.

The BOSC (2005 review) noted EPA's conceptual framework for the core HHRP representing the LTGs and their interaction needs to be more clearly and fully developed. Conceptual models provided in EPA's Human Health Research Strategy (Figures 1-3, 1-4, and 1-5) do not clearly represent its risk assessment context, the LTGs, or the importance of their interactions. ORD responded that the revised HHRP MYP outlines the main objectives of the program, which is to provide methods, models, and data that will reduce reliance on default assumptions and uncertainties in risk assessment. This will be accomplished by providing a greater understanding of determinants of exposure, dose, and basic biological changes that follow exposure to environmental agents. The main research themes of the HHRP remain the same as those from the 2005 program review (use of mechanistic data in risk assessment, cumulative risk, susceptible subpopulations, and approaches to evaluate risk management decisions). In 2005, OMB reviewed the HHRP, supported its strategic direction, and agreed that performance measures need to focus on reducing reliance on default assumptions in risk assessment.

In 2005, the BOSC indicated ORD needed to articulate and provide a clearer health rationale. ORD has done this in the revised MYP. The BOSC also noted that interactions between ORD and regional/program offices in the HHRP vary across program offices. ORD is working to make these uniform through a client questionnaire.

The BOSC (2005 review) suggested broadening the stakeholder list. ORD agreed that many research projects described at the 2005 program review were relevant to needs of the l995 FQPA. Issues raised by FQPA were a significant driver for the HHRP. Hence, much of the research described at the 2005 review involved pesticides. Research related to other stakeholders had a lower priority. Significant progress was made since the 2005 program review to ensure the HHRP is balanced. ORD prepared a table (Table 3) of ORD research by stakeholder for each research theme that gives an inclusive picture of the current research portfolio related to stakeholders.

The BOSC (2005 review) observed that future peer reviews of the HHRP will be enhanced by providing critiques from previous reviews. ORD responded that the ORD Human Health Research Strategy document was externally reviewed in 2003 by the SAB. The HHRP, however, was not reviewed prior to 2005. At the next review of the HHRP, in 2008, comments from the 2005 review, ORD's response, and results from the 2007 Mid-Cycle Review, will be included. ORD laboratories/centers supporting human health research also have periodic reviews at the divisional and/or programmatic level. Results of those reviews are available.

LTG 4: Evaluation of Public Health Outcomes

The BOSC (2005 review) recommended the goals of LTG 4 be further focused to guide future activities and that a process be formalized to make decisions about which actions to evaluate, endpoints to study, and environmental indicators to apply. Long-term success of LTG 4 depends on the ability to develop strong interactions with other EPA programs and utilize research from other LTGs. The BOSC recommended a mechanism be created with formal and informal components to promote dialogue among investigators involved in different LTGs and assess research outputs. The BOSC also recommended more specific research priorities be listed in future BOSC reviews as this program develops. HHRP should add overarching themes to LTG 4; LTG 4 is a pilot effort at this point (2005). The BOSC strongly supports its continued development, and will assess this program as it develops from its current nascent effort into a well-funded, productive effort. ORD formed a steering committee of members from ORD's laboratories, centers, and steering groups, to set specific research priorities for LTG 4 and focus work on approaches to evaluate risk management decisions, and that the research effort is being planned. ORD realizes additional resources (expertise/extramural support) will be needed to support research in LTG 4, which is only supported by 2 full-time equivalents (FTEs). They are developing a strategic framework to identify knowledge gaps and limitations to serve as a starting point to develop an implementation plan. Once concrete research approaches have been identified, issues related to obtaining necessary resources will be addressed. ORD noted this program is new and utilizes a small proportion of ORD's budget; 7% of the FY 2004 budget earmarked for the HHRP was allocated for public health outcomes research. The program will require additional expertise outside ORD, such as biostatistical support and environmental epidemiology expertise. ORD also is considering having scientists associated with LTGs 1-3 conduct research for LTG 4, and to have intramural and extramural scientists contribute equally to this program. ORD plans to have a Workgroup review of LTG 4, peer review, workshops with other federal agencies, an implementation plan, and future initiatives.

The BOSC (2005 review) indicated that goals and a process for decision-making need to be established for LTG 4. ORD responded that, once a strategic framework for research in LTG 4 is developed, ORD will sponsor scientific meetings and develop an implementation plan with goals and mechanisms for determining priorities of research under LTG 4. ORD provided an update on their progress on LTG 4—Research to Evaluate Risk Management Decisions. ORD formed a Steering Committee on October 16, 2006, and a Working Group to develop a framework for LTG 4. ORD planned a scientific meeting for spring 2007, and is working on and will finalize an Implementation Plan by fall 2007.

The BOSC (2005 review) suggested LTG 4 should be periodically reviewed externally. ORD responded that scientist-to-scientist meetings involving multiple stakeholders will provide the basis for implementation for LTG 4. Research will be evaluated by the RCT during the prioritization phase of the budget cycle. Research to develop approaches to evaluate risk management decisions will undergo periodic external peer review by the BOSC.

The 2005 BOSC Subcommittee indicated that materials presented by HHRP/ORD lacked detail on specific program elements to enable the BOSC to determine whether the focus is consistent with stated goals. Details such as how the work will be planned and processed are critical, and were not presented in pre-meeting materials, but were clearly articulated during the meeting. ORD responded that it now has two proof-of-concept studies in progress and a framework in development; ORD provided an outline for the program.

The BOSC (2005 review) recommended that criteria for the Memorandum of Understanding (MOU) Demonstration Project between EPA and CDC be made explicit and communicated to program and regional offices so projects are selected and developed with the greatest potential for success. ORD responded that proposals for demonstration projects were evaluated by a panel of regional office/ORD scientists using five criteria: clarity of objectives, scientific merit, qualifications/competency of staff, strengths/weaknesses of project, and recommendations for improvement.

The BOSC (2005 review) recommended the Asthma Program have regular group meetings. In response, ORD appointed a coordinator for asthma research (Dr. Hillel Koren), and formed an Asthma Research Team, which sponsors a seminar series that invites senior asthma researchers to ORD to share their research. The BOSC also recommended that HHRP create a pilot group to begin thinking about whether pesticide exposure contributes to the incidence of neurodegenerative diseases in humans. This issue requires further thought and/or study, by HHRP/ORD, or by HHRP/ORD in collaboration with external partners, i.e., National Institutes of Health (NIH), CDC, and/or National Institute of Environmental Health Sciences (NIEHS). If HHRP/ORD determines this issue is worth studying, the Subcommittee recommends that ORD begin pilot studies, alone or with collaborators.

Appendix D: List of Acronyms

APG	Annual Performance Goal
APM	Annual Performance Measure
BDPE	Brominated Diphenyl Ether
BOSC	Board of Scientific Counselors
CBPR	Community-Based Participatory Research
CDC	Centers for Disease Control and Prevention
EPA	Environmental Protection Agency
EU	European Union
FACA	Federal Advisory Committee Act
FQPA	Food Quality Protection Act
FTE	Full-Time Equivalent
HHRP	Human Health Research Program
IRIS	Integrated Risk Information System
LTG	Long-Term Goal
MOU	Memorandum of Understanding
MYP	Multi-Year Plan
NCCT	National Center for Computational Toxicology
NCER	National Center for Environmental Research
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NPD	National Program Director
NRC	National Research Council
OMB	Office of Management and Budget
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
PD/PK	Pharmacodynamic/Pharmacokinetic
PFOA	Perfluorooctanoic Acid
RCT	Research Coordination Team
RFA	Request for Application
ROE	Report on the Environment
SAB	Science Advisory Board
STAR	Science To Achieve Results