HUMAN HEALTH SUBCOMMITTEE

Face-to-Face Meeting Summary
U.S. Environmental Protection Agency
Office of Research and Development
109 TW Alexander Drive, Building C
Research Triangle Park, NC
January 13 - 15, 2009

TUESDAY, JANUARY 13, 2009

Welcome and Opening Remarks

Dr. James Klaunig, Indiana University School of Medicine, Subcommittee Chair

Dr. James Klaunig, Chair of the Board of Scientific Counselors (BOSC) Human Health Subcommittee, welcomed Subcommittee members and other participants. He asked all Subcommittee members to introduce themselves and provide background information and relevant experience. Following introductions, Dr. Klaunig reviewed the agenda.

BOSC DFO Remarks

Ms. Virginia Houk, U.S. Environmental Protection Agency (EPA)/Office of Research and Development (ORD), Subcommittee Designated Federal Officer (DFO)

Ms. Virginia Houk, Subcommittee DFO, reviewed the Federal Advisory Committee Act (FACA) procedures that are required for all BOSC Subcommittee meetings. She noted that Dr. Henry Falk was unable to attend the face-to-face meeting.

The BOSC is a Federal Advisory Committee that provides independent, scientific peer review and advice to EPA's ORD. The Human Health Subcommittee was established to review ORD's Human Health Research Program (HHRP). The first review was held in 2005, and a mid-cycle review has been completed since that time. The Subcommittee is tasked with responding to a series of charge questions and providing a report to the BOSC Executive Committee. This face-to-face meeting was preceded by two conference calls on October 10, 2008, and December 1, 2008; a third follow-up conference call likely will be scheduled in February or March 2009.

As the DFO for the Subcommittee, Ms. Houk serves as the liaison between the Subcommittee and ORD. It is her responsibility as the DFO to ensure that the Subcommittee's conference calls and meetings comply with all FACA rules. BOSC meetings are public, per FACA rules. All background information provided to the Subcommittee is available to the public on the BOSC Web Site. The minutes of the meeting are being taken by a contractor and will be available on the BOSC Web Site after they have been certified by the Chair. Notice of this meeting was published in the *Federal Register*, and an electronic public docket was established.

To ensure that all ethics requirements were satisfied, each Subcommittee member signed the standard government confidentiality disclosure form, which was reviewed by the Office of Science Policy's

Deputy Ethics Officer in consultation with EPA's Office of General Counsel. One conflict of interest was discovered within Long-Term Goal (LTG) 1; the Subcommittee member will recuse himself from the review of LTG 1.

No requests for public comment have been received, but there will be time for public comment on Day 1 of the meeting at 1:40 p.m. Each comment must be limited to 3 minutes. Audience members may only respond to questions asked by the BOSC Subcommittee members and only after being recognized by the Chair.

ORD Welcome and Brief Overview of the Human Health Research Program

Dr. Sally Perreault Darney, EPA/ORD, National Program Director (NPD), HHRP

Dr. Sally Perreault Darney welcomed the Subcommittee members to the EPA facility in Research Triangle Park, North Carolina, and extended her appreciation for their efforts in reviewing HHRP. She also thanked the HHRP LTG leads, poster presenters and contributors, partners, laboratory and center directors, and Research Coordination Team for their efforts in preparing for the BOSC review. Drs. Kevin Teichman (ORD's Deputy Assistant Administrator for Science), Hugh Tilson (former HHRP NPD), and Rebecca Calderon also were recognized for their contributions.

Dr. Darney explained that the Program is designed to address cross-program issues, and the research has broad applications and implications for multiple EPA offices. HHRP: (1) addresses persistent scientific issues that underlie uncertainties in risk assessment, (2) develops and applies new models and tools and provides innovative approaches to address long-standing issues, and (3) increases the value of its research by selecting specific contaminants or groups of contaminants to address issues that also inform program-targeted efforts. HHRP data and models—drawn from three EPA laboratories and complementary extramural research—are used directly and indirectly by ORD and other partners within EPA to achieve the Agency's mission.

The overall goal of the Program is to understand the linkages in the source-to-dose-to-effect continuum. The research develops methods, models, and data to characterize and reduce uncertainty in the critical links across the continuum and explores fundamental determinants of exposure, dose, and effects of environmental contaminant exposures that lead to adverse health outcomes. This is done in the context of the four LTGs, and risk assessors and managers use ORD's methods to: (1) understand and reduce uncertainty in risk assessment using mechanistic (mode of action) information (LTG 1); (2) characterize aggregate and cumulative risk to manage risks to humans exposed to multiple environmental stressors (LTG 2); (3) characterize and provide adequate protection for susceptible populations (LTG 3); and (4) evaluate the effectiveness of risk management decisions (LTG 4). LTGs 1 and 2 are interrelated, and HHRP is an integrated, multidisciplinary research program. As such, the Program requires the cooperation of scientists from a wide range of areas of expertise (e.g., biologists, physiologists, environmental and exposure scientists, toxicologists, chemists, epidemiologists, engineers, microbiologists); many of these scientists also contribute to other EPA research areas (e.g., air, safety and pollution prevention, drinking water). The Program is driven by various EPA, National Institutes of Heath (NIH), National Research Council (NRC), and National Academy of Sciences (NAS) reports. The HHRP Multi-Year Plan (MYP) was formally established in 2003, but the Program began informally in the 1990s. Since the 2007 mid-cycle review, the HHRP has developed a white paper, *Framework for Assessing the Public Health Impacts of Risk Management Decisions*, in response to the first full BOSC review; produced recommendations from two 2007 workshops; and released three 2009 Requests for Applications (RFAs).

Dr. Darney reminded Subcommittee members that they are charged with a retrospective and prospective review that evaluates HHRP on relevance, quality, performance, and leadership. The Subcommittee will provide an overall rating for the Program and a rating for each LTG, while recognizing that the LTGs are increasingly overlapping and interdependent; for example, research on children's health combines LTGs

2 and 3. In terms of the prospective review, time has been reserved on the final day of the meeting to recap the highlights of future needs and plans, revisit the new science drivers, consider the realities of workforce planning and budget, and comment on the straw proposal for restructuring the Program into two integrated LTGs, one focusing on toxicity and the other on public health.

Dr. George Daston commented that the Program was designed so that broad lessons are learned no matter which chemicals and modes of action are being studied, and the MYP mentions developing and maintaining core expertise; these are commendable actions. He asked to what extent HHRP scientists are involved in helping out in crises/unexpected events and how any such involvement was reflected in the Annual Performance Measures. Dr. Darney responded that the scientists who often respond to emerging contaminants and crises also perform the research, and these scientists and the Program must remain nimble and responsive. The leadership reports highlight examples of HHRP researchers working on workgroups and committees with other program offices and international organizations. The challenge is to be nimble when resources are limited. Additionally, EPA regions also have acute problems that require the assistance of HHRP scientists, who are expected by EPA management to be responsive and dedicate time to provide assistance.

Dr. Daston asked how HHRP scientists relate to outside groups. Dr. Darney responded that components of this are captured in the partner survey that the Program administers, which asks about the quality of assistance and the usefulness of scientific products. The leadership reports also explain participation in workgroups, committees, advisory panels, and so forth.

Dr. Joel Schwartz commented that being provided with the workforce distribution was useful and asked whether the distribution of expertise within HHRP was ideal or needed to be adjusted. Dr. Darney explained that the provided distribution did not include grantees, and most epidemiological work was done externally. Dr. Schwartz responded that internal epidemiological expertise is necessary to use epidemiology for risk assessment. Dr. Darney explained that the Program partners with the National Center for Environmental Assessment (NCEA), which provides EPA's internal epidemiological expertise.

LTG 1: Poster Session Overview

Dr. R. Julian Preston, EPA/ORD/National Health and Environmental Effects Research Laboratory (NHEERL)

Dr. Julian Preston explained that ORD's research plan for LTG 1 is defined in the *Human Health Research Plan (2006–2013)* as addressing the requirement for risk assessors and managers to use ORD's methods, models, or data to address uncertainty in risk assessment using mechanistic (or mode of action) information. The umbrella of the LTG 1 research is work that involves methods and models needed to identify modes or mechanisms of action that can be used for risk assessment. Several other key research questions also guide LTG 1 research. The research is cohesive within the LTG and integrated across HHRP, and the aims are addressed by a framework that utilizes a set of key events to describe a mode of action (usually in rodents) for any particular exposure scenario and then assesses the feasibility of this mode of action in humans. This feasibility assessment considers toxicokinetic and toxicodynamic characteristics of the system, and the key events are used for selecting biomarkers of exposure and early biological response and bioindicators of disease outcome. Ten posters describe the development of key input data for specific chemicals or exposure conditions that can be incorporated into this framework. All of the data inputs, which fall under four broad categories, can be used in a quantitative risk assessment when required. Out of the modes of action and key events, biomarkers and bioindicators can be developed under LTG 1 mechanism-based research, which can provide a linkage between LTG 1 and other HHRP LTGs. Dr. Preston explained that 10 of the 14 posters describe current LTG 1 research projects, and these were divided into four themes that address different aspects of the development of models and approaches for incorporating mechanistic data into risk assessments.

In terms of future directions, LTG 1 researchers are initiating an integrated toxicology–systems approach to respond to the challenges presented by EPA and NAS reports (*Futures of Toxicity Testing Strategic Plan* and *The Future of Toxicity Testing and Improving Risk Analysis Approaches Used by the U.S. EPA,* respectively). The research has maintained the mode of action and human relevance framework but is moving toward a whole genome approach. Four posters highlight the future work directed toward establishing systems-based models for use in risk assessments. Dr. Preston described how systems approaches fit into the traditional parallelogram for risk assessment; the approaches are used to predict human responses via a mixture of *in vitro* and *in vivo* models based on networks, bioindicators, and biomarkers. Network analyses will be used to provide input into assessments at the population level.

Dr. Christopher Portier commented that the partner survey indicated a weak response to pharmacokinetic and pharmacodynamic (PKPD) modeling and asked how the Program is going to address the lack of utility of PKPD data and analyses. Dr. Preston responded that this was a question of short- versus long-term thinking. It is difficult to envision how PKPD modeling can be used in the immediate term, and the Program is evaluating whether it should heavily invest in this modeling. In the meantime, the Program is performing biologically based dose response (BBDR) modeling, a component of PKPD modeling, and it will ask the users whether there will be a utility in developing this type of model. He was unsure why users perceived PKPD modeling as unusable, but the Program must be alert to this perception.

Dr. David Hoel commented that molecular network research is basic environmental health research and asked what research in this area is being performed at the National Institute of Environmental Health Sciences (NIEHS) and how HHRP is working with the NIEHS. Dr. Preston replied that HHRP has several collaborations with the NIEHS, and LTG 1 has an emphasis on basic science. The aim is for HHRP and NIEHS collaborative research to be complementary, with any overlap being informative rather than duplicative. Additionally, EPA has a memorandum of understanding with the National Toxicology Program and NIH's Chemical Genomics Center to address toxicology testing in the 21st century. The Program is alert to similar research being performed elsewhere.

Dr. Schwartz discussed physiologically based pharmacokinetics (PBPK) models versus epidemiological models and their lack of similar results. The PBPK lead model has only been validated in small and nonrepresentative samples, which creates a concern for using this model for risk assessment. The epidemiologic studies incorporate genetic variations and other factors that need to be incorporated into the PBPK models, as these models tend to underestimate the important issue of variance. He asked how the models are going to be validated in a larger population sample that captures variations. Dr. Preston acknowledged that this is an important consideration and has been the most significant problem to date. There are very few human data, so it is necessary to extrapolate from other systems. Dr. Schwartz mentioned the human data available via the National Health and Nutrition Examination Survey (NHANES) and stated that there were many opportunities to grasp human data. Dr. Preston agreed and stated that this would be addressed in the posters; there is a significant effort underway to develop an approach for linking the exposure models to the response models.

LTG 1: Poster Session

This poster session was held in the Atrium. The Subcommittee reviewed 14 posters in this session. During the 140-minute poster session, each Subcommittee member also had the opportunity to ask questions about the research or clarify specific points with the presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

LTG 1: Subcommittee Discussion

BOSC Human Health Subcommittee

Dr. Daston thought that many aspects of LTG 1 research were commendable. Human health research covers a broad area and cannot be covered by one program. HHRP is making a good effort to develop

modeling systems that convey the complexity of biologically variable populations; the Program is moving forward and taking advantage of sophisticated technologies.

Dr. Hoel was most interested in seeing the impact on current quantitative risk estimation and how close the studies are to having an impact on point and uncertainty estimates for decision-makers elsewhere in the Agency.

Dr. Schwartz commented that there is good science addressing relevant issues and Agency needs. The ability of models to predict appears to be a long way off, but the models are providing other useful information. He thought that there was insufficient integration of the bottom-up approach with the top-down approach in terms of epidemiology. Validation is occurring in the human population, but he would like to hear more about this topic. Additionally, epigenetics is lacking in the models and must be considered.

Dr. Klaunig saw improvements made since the last full BOSC review; the research shows a more logical, mechanistic, mode-of-action approach and generally is addressing pathways instead of specific compounds. Hypothesis-driven research is occurring, which is important, although the modeling group still is in development. Modeling may be important in identifying data gaps, specifically key events and pathways that need to be examined further. Human application is being addressed in the research, which was not the case during the last full review.

Dr. Paul Blanc wanted clarification regarding the deprioritization of arsenic-related research and how the decision was made. He also was unclear as to why there was such an emphasis on BBDR. Oxidative stress is understood as a model toxic mechanism, but it would be more useful as an example of a pathway and in applying the same method to other toxic pathways. Virtual liver toxicity modeling is acceptable, but a virtual cardiopulmonary model is overreaching. The previous BOSC mid-cycle review also brought up the same concerns regarding the systematic basis for prioritizing the toxic substances that are evaluated.

Dr. Donald Mattison commented that he was pleased with the researchers' responses when they were confronted with surprising observations during the course of their work.

Dr. Preston attempted to answer the concerns brought up during the discussion. He explained that there has been a fairly extensive program regarding toxicology of inorganic arsenic and its metabolites. The question became how this research could be integrated and could address the most significant issues for the program offices, which generally were most concerned about carcinogenic risk at environmental exposure levels. The decision made was to approach this problem by developing a BBDR model and presenting it to EPA's Office of Pesticide Programs (OPP) and Office of Water (OW) to determine whether the program offices would find it useful; the response was that BBDR on mode of action would not be useful, especially within the short timeframe necessary. Additionally, an external group of arsenic experts reviewed the plan and said that it was not a viable approach. The experts and the program offices, however, did indicate that dose metrics related to the arsenic metabolites would be useful. With limited resources and such a broad area, it was necessary to determine in which area to concentrate efforts, and dose metrics was ascertained to have the greatest use within the Agency.

In terms of the emphasis on BBDR, Dr. Preston explained that this was thought to represent the "gold standard" in dose-response characterization; it has exposure dose and response components linked together in a dose-response framework. This is considered a sophisticated approach to fully utilize mechanistic data for extrapolation. Dr. Blanc asked whether this has any implications for default values. Dr. Preston responded that it did; the aim of examining the mode-of-action and human relevance frameworks is to reduce the uncertainty. Dr. Blanc asked for clarification regarding the uncertainty parameters of BBDR. Dr. Preston responded that BBDR is designed to provide parameter values for

factors that have been characterized as defaults; it reduces the reliance on defaults and therefore should address and reduce the uncertainty in the low-dose estimation.

Dr. Preston addressed the oxidative stress issue by explaining that the Program was unsure what emphasis to place on oxidative stress in the context of key events along the pathway to mode of action and adverse outcomes. Researchers are trying to determine where oxidative stress fits into the framework and how important it is; they are addressing the issue of where to incorporate oxidative stress as a key event in different adverse outcomes in different exposure scenarios. He explained that the Program is undertaking some epigenetic work, but the work is limited at this time. Future work will address epigenetic responses in a more comprehensive manner. HHRP is making a conscious effort to provide the umbrella framework of its plan to point to human data. Dr. Klaunig stated that one method to find human data and apply it environmentally is to examine pharmaceutical data. Additionally, having advisors who are familiar with such studies would enhance the Program. Dr. Schwartz added that NHANES was another source of human data to validate models. Dr. Preston responded that the Program has made efforts in this direction, but other LTGs have a more direct link.

In terms of prioritizing and selecting agents for study, HHRP receives input from program and regional offices regarding chemicals and chemical classes that are of priority to them. Additionally, there may be a need to understand a specific mode of action, so agents may be chosen based on their mode of action. Dr. Schwartz asked whether there was a formal mechanism to select toxins that may not be of priority to program or regional offices but have the potential to impact public health. Dr. Preston explained that the MYP covers a 5-year period, and planned research focuses on the longer term. There is no formula, but the Program needs to be responsive to emerging issues while not being over-responsive at the expense of long-term research. Dr. Schwartz cautioned that there may be programmatic reasons (e.g., federal mandates) to address certain chemicals, but other chemicals may be just as important from a public health standpoint. Dr. Preston explained that the MYP has criteria regarding level of importance; program and regional offices are involved in the process. Dr. Darney added that HHRP is engaged in long-term research, and some of the issues that have been brought up may fall under pesticide or drinking water research. In these cases, HHRP is involved in the planning discussions with the appropriate research programs.

Subcommittee Discussion

BOSC Human Health Subcommittee

During a working lunch on Tuesday afternoon, the Subcommittee discussed details and strategies for completing their evaluation and shared their initial impressions of the Program.

Dr. Blanc was still unclear about the decision-making regarding the arsenic research and the scientific basis for the arsenic threshold in drinking water; it is a matter of debate whether it is public health protective. Dr. Schwartz thought that this might be a result of the bottom-up approach of risk assessment that was applied. The lack of data at low levels and the linear response seen with available data caused the threshold to be set based on extrapolation. Dr. Daston commented that there is too much "noise" (i.e., individual variability) at lower levels, and therefore there is a great need to understand the mode of action and develop a reliable model. This would have been the advantage to continuing the arsenic research. Dr. Schwartz noted that collecting more epidemiological data at lower doses would reduce the noise. There is a lack of recognition that the dose-response relationships of an increasing number of substances will be derived from epidemiology; HHRP should focus on validation and consider how its future research will be adjusted to better serve that role and integrate epidemiology.

Dr. Schwartz also remarked that there is an issue with program office priorities differing from HHRP priorities. Additionally, with the information available, it currently is difficult to assess whether, if the intra- and extramural research were approached in a different manner, the research would be more efficient.

Dr. Portier wanted clarification regarding the bibliometric analysis and how it was performed, including the method by which papers were identified as highly cited. The analysis needs to be improved to be useful; adjusting by discipline would be a better measure of impact.

Public Comment Period

Ms. Houk called for public comment at 1:40 p.m. No comments were offered.

LTG 2: Poster Session Overview

Dr. Linda Sheldon, EPA/ORD/National Exposure Research Laboratory

Dr. Linda Sheldon explained that LTG 2 does not deal exclusively with exposure nor perform risk assessments; it combines exposure to health effects and cumulative risk and provides tools and scientific understanding to risk assessors so that they may perform risk assessments. The overall goal of LTG 2 research is to develop the scientific knowledge and tools to understand and predict cumulative risks that reflect real-world situations. LTG 2 addresses two types of cumulative risk: (1) legislatively mandated cumulative risk assessments associated with aggregate exposures to chemicals with a common mechanism of action; and (2) the broader health perspective. The first examines substrates, and the latter examines the population and receptors. LTG 2 research is part of a well-integrated MYP and is organized under three research tracks that develop the science and tools for: (1) conducting legislatively mandated cumulative risk assessments, (2) using biomonitoring data to improve risk assessments, and (3) assessing cumulative risks to chemical and nonchemical stressors. Each of these tracks asks a series of science questions. The approach to the first track is to examine the fundamental science that is needed on the health effects side and the exposure side. This systems approach brings together aggregate and cumulative exposure, kinetic modeling, and effects modeling to determine cumulative risk. The approach to the second track is to determine exposure biomarkers and understand linkages between exposure, biomarker measures, and indicators of effect. The approach for the third track focuses on community, evaluates the state of the science, and develops and applies tools.

LTG 2 cumulative risk assessment research is directly used by OPP in pesticide cumulative risk assessments. Enhanced cumulative risk assessment science and methods are used by other Agency risk assessors, and tools for using biomonitoring in cumulative risk assessments will be used directly by EPA program offices in future risk assessments. The guidance for collecting and using biomarkers will be used to improve future exposure and epidemiological studies, and methods for assessing cumulative exposures in communities will be used by researchers in future epidemiological studies, Community Action for a Renewed Environment Program partners for community risk assessments, and regions and local communities to assess risk management options.

Dr. Schwartz asked whether HHRP would be expanding its research to include complex diseases that can be impacted by more than one mechanism of action. Dr. Sheldon replied that it would; the value of developing a modeling system was that different factors (e.g., enzymes, metabolisms, pathways, endpoints) could be examined.

Dr. Portier asked why cumulative risk assessments were done separately on organophosphates and carbamates despite their identical modes of action. Dr. Sheldon responded that when the work was being performed, the program office required results within a certain timeframe, and the Program provided the science immediately available for the organophosphates and then used what it learned to improve the next assessment, which was on carbamates. The Program was responding to OPP needs.

Dr. Portier asked how ORD planned to guide OPP into reassessment in a broader sense. Dr. Sheldon explained that the Program is integrating the data in an improved manner and increasing the understanding of the science and linkages to inform future assessments.

Dr. Portier asked what happened to the aggregate portion of the work. Dr. Sheldon replied that the exposure models that were used comprised the aggregate work, which was a building block for the cumulative risk assessment in which the data and exposure models were developed and evaluated. Aggregate and cumulative research address how to examine aggregate exposure for single chemicals and how these can be combined to develop cumulative risk.

Dr. Edo Pellizzari commented that the linkage from source to health effects had been discussed and visualized the development of a "super model" that would allow examination of source to prediction and vice versa. He asked whether the Program has thought about optimizing the interplay between the tracks and how they inform each other to minimize uncertainty. Dr. Sheldon responded that the pyrethroid work was explicitly designed to link across components; the data have been and will continue to be very informative. The Program has considered optimization and realizes that it must be performed, but optimization has not been completed yet.

LTG 2: Poster Session

This poster session was held in the Atrium. The Subcommittee reviewed 11 posters in this session. During the 110-minute poster session, each Subcommittee member also had the opportunity to ask questions about the research or clarify specific points with the presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

LTG 2: Subcommittee Discussion

BOSC Human Health Subcommittee

Dr. Pellizzari commented that the organization of the research topics, the integration, and the approach to examine cumulative risk assessments in the population were well conceived, which speaks well of the scientific leadership. It is evident that there is cross-talk occurring among HHRP scientists and with clients and users. The source-to-outcome approach is necessary, and the modeling aspect is very important. One question regarding modeling, however, is whether uncertainty accumulates to the point that the model is not useful. He would like the researchers to make a concerted effort to define the uncertainty of each of the steps and be explicit about where the major uncertainties lie. In addition to examining biomarkers of exposure, health effects, and susceptibility, researchers should consider markers of modulation processes on modes of action; this type of research could be a means to reduce some of the variability or uncertainty in the model. Additionally, the Program has shown considerable thought and action regarding transfer of knowledge and turning research into practice.

Dr. Mattison thought that the development of skills was very well expressed; however, building in a broad array of environmental and chemical stressors will be a challenge. He suggested that the Program attempt to link extramural funding activities to intramural products in a meaningful manner.

Dr. Portier overall was impressed with LTG 2 research; it was difficult to link the papers in the program evaluation materials with activities, and this session provided a clearer picture. The scientific paradigm that the research is being conducted under is good, and he approved of the systems approach. He reminded LTG 2 personnel that PBPK models are excellent tools, but they are not the only tool. EPA must examine when use of the two-compartment model is sufficient. It must be determined whether the use of sophisticated tools is sustainable for the Agency, and if so, this must be communicated to EPA leadership. In addition to providing risk assessments, global mortality must be studied; following this it is necessary to determine how the environment can be changed to reduce mortality and morbidity. He cautioned that in using two different mixture approaches, the researchers must determine how these approaches are going to be brought together and how other groups are going to be informed. He suggested that HHRP examine standards documents and determine how many times the Program has guided the Agency. There is good linkage to OPP, but the carbamate and organophosphate research need to be put together. LTG 2 research is where it should be—it is not at the extreme cutting edge, but it is

not lagging, either; this indicates good scientific leadership. Additionally, there was good extramural linkage within this LTG.

Dr. Blanc commented that the series of projects driven by OPP regulatory needs for combined exposure assessments were concrete and data driven; the remainder of the projects were mainly theoretical. In going forward, there should be data that correspond to the theoretical ideas. He was optimistic about the community mapping project and what it will potentially yield. He noted that EPA terminology differs from that used by the outside research community (e.g., "chemical exposure"). In terms of the LTG in the more general sense, the combined effect of multiple exposures is an important question; epidemiology may be more informative in this area than theoretical modeling. Examining pathways that have anticipated synergism but are not well predicted by additive models may be a future research direction.

Dr. Schwartz thought that overall LTG 2 was well coordinated, but in some cases the information is available elsewhere; it is not efficient for EPA to recreate what is already available. This is where additional internal expertise, such as in biostatistics, would be helpful. In terms of the community work, a large body of knowledge is available regarding social epidemiology, and researchers should explore available data in this area. Dr. Hoel added that a large amount of literature is available regarding radon. Program researchers and leadership also should consider talking to Dr. Bernard Cohen, Professor Emeritus at the University of Pittsburgh, and Jerry [NEED SCTE MBR TO PROVIDE LAST NAME] of EPA's Office of Air and Radiation (OAR). Dr. Schwartz noted that there did not appear to be sufficient knowledge of work being done elsewhere.

Dr. Pellizzari noted that the MYP emphasizes that LTG 2 research should focus on cumulative risk and susceptible populations. The products developed under LTG 2 will be beneficial to the program offices, but how will EPA regions benefit? Dr. Sheldon responded that although work with cumulative risk is directed toward program offices and NCEA, some tools have been simplified (e.g., the Stochastic Human Exposure and Dose Simulation [SHEDS] Model) so that they can be used by regional risk assessors; community-based risk assessment resonates with the regions.

LTGs 1 and 2: Partner Testimonials

Dr. Vicki Dellarco, EPA/OPP/Office of Prevention, Pesticides, and Toxic Substances; and Dr. Ed Ohanian, EPA/OW

Dr. Vicki Dellarco provided background about OPP, which is the gateway to the $11 billion/year pesticide market. There are more than 1,000 active ingredients contained within 19,000 pesticide products. OPP evaluates new pesticides and regularly re-evaluates existing pesticides based on statutory schedules. With finite resources, OPP makes more than 5,000 regulatory decisions annually. Efficiency is important because of public expectations for timeliness, scientific soundness, and transparency, and new risk assessment and management challenges often arise. OPP performs many types of risk assessments, including dietary, residential, occupational, route, time frame, probabilistic, deterministic, and single and multiple chemical. The amount and quality of the data vary among pesticide products, and OPP looks to ORD for PKPD models to perform risk assessments. One common risk management question that OPP uses data, methods, and models to address is: How will risk change with different use/exposure assumptions? There are many risk assessment and management issues and challenges, which are not specific to OPP. OPP prioritizes which chemicals it will examine to improve its ability to carry out the mission of protecting public health and the environment.

HHRP's LTGs are aligned with OPP's high-priority research needs for advancing methods, models, and data. HHRP's mechanistic research helps OPP move toward an efficient Integrated Testing and Assessment Program that provides an improved capacity to prioritize, screen, and characterize risk based on a hypothesis-driven effort. Integrated testing and assessment combine *in vitro* testing and computational modeling to make predictions for *in vivo* outcomes and guide more targeted animal testing. The integrated testing and assessment paradigm is consistent with the NAS report, *Toxicity Testing in the*

21st Century: A Vision and Strategy. HHRP has provided mechanistic data in risk assessment that demonstrate the use of "omic" technologies to efficiently identify toxicity pathways, and provides data on specific chemical classes that directly support ongoing risk assessment decisions. HHRP's cumulative risk work is valuable because it provides data and models on specific chemical classes that directly support cumulative risk assessment decisions and lays the foundation for the pyrethroid cumulative risk assessment. HHRP's exposure research will benefit OPP's overall risk assessment program by providing procedures for using the SHEDS Model, child-specific exposure factor data, residential standard operating procedures, and improvement of the use and interpretation of biomarkers. HHRP researchers also plan to develop a systems biology approach in defining underlying biological mechanisms of chemical mixtures and increase understanding of the influence of dose and mixture composition on chemical interactions and the joint toxic action of mixtures. Dr. Dellarco stressed the importance of ORD and program office partnerships, stating that ORD has contributed greatly to regulatory acceptance and applications. It is critical to enter the regulatory framework via transferable methods such as staff training, stakeholder engagement, peer review, and science policy development.

Dr. Blanc asked whether research areas were selected and prioritized via negotiation between OPP and ORD or specifically mandated. Dr. Dellarco responded that it was a combined policy and scientific decision. Dr. Blanc asked, in terms of cumulative risk assessment, what pesticide classes would be studied in the future. Dr. Dellarco explained that Dr. Peter Preuss would discuss this topic in more depth during his presentation, but phthalates and endocrine disruptors are two research areas that OPP is examining.

Dr. Portier asked how many risk assessments OPP had completed and whether they always were in conjunction with ORD. Dr. Dellarco responded that four had been completed, and all of them had some degree of ORD involvement.

Dr. Portier asked whether OPP runs the SHEDS Model itself or must rely on ORD support. Dr. Dellarco replied that SHEDS has been used by OPP for risk assessment, and OPP has exposure scientists who work with the model.

Dr. Pellizzari commented that, in terms of identifying long-term emerging issues of a cumulative nature, LTG 1 scientists may uncover new cumulative issues or chemicals/classes of chemicals that have a cumulative effect, which in turn would inform LTG 2 research about what to include in models for prediction. He asked whether OPP scientists are communicating with LTG 1 and 2 researchers. Dr. Dellarco responded that she believed so. Within her office there is a growing concern about multiple stressors, and OPP's first priority is to carry out regulatory mandates; HHRP research can inform OPP on how best to carry out these mandates.

Dr. Schwartz asked for clarification about the prioritization process. Dr. Dellarco explained that some areas are data rich, whereas others have very little data. OPP looks to ORD to develop models that will bridge the data gap, which in turn will allow OPP to prioritize what it must examine. Dr. Schwartz asked whether this approach might inadvertently de-prioritize medium-risk chemicals that have larger exposure populations. Dr. Dellarco clarified that these types of chemicals would not be ignored. Dr. Darney added that OPP has a Science Advisory Panel that prioritizes chemicals; this does not fall under ORD's scope.

Dr. Schwartz asked whether, when delisting certain chemicals, OPP reassessments considered whether one chemical has a higher risk than other chemicals that provide the same agricultural utility. Dr. Dellarco replied that to her knowledge this was not done.

Dr. Ed Ohanian provided background on OW's structure and explained that the office works with other ORD research programs (e.g., the Drinking Water Research Program) to meet its statutory requirements under the Safe Drinking Water Act and Clean Water Act. If a contaminant: (1) adversely affects human health, (2) is known or likely to occur in public water systems with a frequency and at levels posing a

public health threat, and/or (3) can be regulated to provide a meaningful opportunity for health risk reduction, then it will be regulated via the National Primary Drinking Water Regulations. The NRC made an interesting recommendation to EPA that strengthened the role of scoping, planning, and problem formulation stages of risk assessment and stressed the need to communicate and understand some of the key risk management options and questions. OW and ORD have engaged in this type of communication for some time. Examples of HHRP research areas that have been extremely important to OW include arsenic, triazines, disinfection byproducts, and microbial contaminants. This research has provided information on modes of action, metabolism, PBPK models, application to cumulative risk assessments, health effects, and bioindicators. ORD has been a tremendous help to OW, visiting the program office and ensuring that OW personnel have the knowledge and understanding that they require. OW is eager to continue its partnership with ORD to ensure informed regulatory decision-making.

Dr. Pellizzari noted that most of the HHRP LTGs deal with chemical contaminants and asked whether OW has a need for microbial research. Dr. Ohanian explained that this effort is being conducted under the Drinking Water Research Program MYP for drinking water and the Water Quality Research Program MYP for recreational waters.

Dr. Blanc asked for clarification regarding whether it was OW that indicated that no further arsenic research was needed. Dr. Ohanian responded that the timeliness of the data availability was a factor in the decision. Dr. Preston added that the mode of action that was being examined was for cancer, and it was clear that research needed to focus on noncancer endpoints. Currently, the dose metric side of arsenic is being investigated.

Dr. Klaunig thanked the presenters for their time and efforts and recessed the meeting at 5:46 p.m.

WEDNESDAY, JANUARY 14, 2009

Review of Yesterday's Activities and Overview of Today's Agenda

Dr. Klaunig, Subcommittee Chair

Dr. Klaunig reconvened the meeting at 8:34 a.m. and reviewed the day's agenda.

LTG 3: Poster Session Overview

Dr. Devon Payne-Sturges, EPA/ORD/National Center for Environmental Research (NCER)

Dr. Payne-Sturges explained that ORD's research plan for LTG 3 is defined in the *Human Health Research Plan (2006–2013)* as addressing the requirements for risk assessors and managers to use ORD's methods, models, and data to characterize and provide adequate protection for susceptible and vulnerable populations. Several executive orders and statutory requirements call for EPA to set standards to protect vulnerable populations, and internal EPA policies also are in place. Key research questions under this LTG include: Is there differential life-stage responsiveness or exposure to environmental contaminants? Which methods and models are appropriate for longitudinal research with children? What are the predisposing factors for diseases such as asthma, and how does the indoor air environment affect susceptible populations? The current environmental public health paradigm is too linear, and it may be time to develop a new paradigm that addresses the area in which the largest data gap exists, human susceptibility and vulnerability. The definitions of vulnerability and susceptibility do not come from the MYP but from clients, including EPA's National Environmental Justice Advisory Council and Risk Assessment Forum.

Dr. Payne-Sturges explained that the LTG 3 posters were grouped in four clusters: (1) children's environmental health research, (2) tools and methods for understanding vulnerability and susceptibility of children, (3) linking susceptibility during early and later lifestages, and (4) asthma and lifestage susceptibility. In terms of children's environmental health research, HHRP is interested in a variety of

exposures and health outcomes and has developed tools. The major consideration is whether research results can be used to benefit children's health. LTG 3 research has entered Agency toxicity assessments, exposure assessment guidelines, and regulatory and criteria documents, and has informed policies and prevention at the local level. LTG 3 intra- and extramural research have been integrated, via the sharing of knowledge and tools, in several research areas. In summary, LTG 3 research: (1) is multidisciplinary and builds on the strengths of intramural and extramural research expertise, (2) provides research findings that inform and use results of other LTGs, and (3) is forward thinking and leading toward a holistic framework. Establishing a multilevel and holistic framework for environmental health is useful for assessing disparities and vulnerabilities.

Dr. Daston commented that, from a broad public health standpoint, a critical piece of vulnerability and susceptibility is knowing the range of vulnerability. In examining LTG 3 research, he saw some activity in this area but not quantitation. It is necessary to ensure that risk assessment and management are protective. He asked whether there are projects that identify quantitation of vulnerabilities. Dr. Payne-Sturges answered that one example of this was the *PON1* research.

Dr. Schwartz commented that the research focused on a very narrow portion of vulnerability, namely children. Genetics contribute to risk in vulnerable populations, and this does not appear to be receiving quite enough attention in terms of thinking about the distribution of risk in the population (versus lifestages). Additionally, pre-existing disease is important in understanding the interaction of other disease states and socioeconomic stress. Are there plans to change the distribution of research to include underrepresented vulnerable populations? Dr. Darney explained that the focus must be on areas in which EPA can accomplish something. Some of the items that Dr. Schwartz mentioned are performed in partnership with internal and external partners. A genomic partnership will help identify susceptible genes. LTG 3 focuses on priorities and first steps. Dr. Schwartz asked why children are a priority, and Dr. Darney responded that this was a result of the coordination with the EPA Air Program.

Dr. Portier asked how the joint funding with NIEHS worked, especially in terms of acknowledging NIEHS contributions. Dr. Darney acknowledged that NIEHS was a contributor to the children's health research, but ORD work needed to be highlighted for accountability during the BOSC review. The Children's Environmental Health Research Program is a joint EPA-NIEHS program, independent of funding.

Dr. Mattison commented about scientists choosing research topics that may be beyond EPA's mandate but may help the Agency address the mandate in a more thoughtful manner, such as developing tools to identify the most susceptible population instead of focusing on children as a hypothetical most susceptible population. There may be issues that transcend the mandate but would put ORD in a position to better support the Agency.

LTG 3: Poster Session

This poster session was held in the Atrium. The Subcommittee reviewed 13 posters in this session. During the 135-minute poster session, each Subcommittee member also had the opportunity to ask questions about the research or clarify specific points with the presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

LTG 3: Subcommittee Discussion

BOSC Human Health Subcommittee

Dr. Blanc noted that the epidemiology component in LTG 3 research is not only evident but dominant; the earlier observation that epidemiological methods were less integrated may reflect the balance of how the research themes are structured. This may speak to the artificial manner of dividing certain components into certain LTGs and shows the weakness of this method. There is a dominance of

childhood issues regarding susceptibility that does inform the research agenda somewhat. For example, asthma is a health condition of interest, but it should not be studied because of childhood susceptibility; instead it should be studied because of the prevalence of the disease and the fact that asthmatics are more susceptible to inhalants. Examining asthma risk is good, but what happens after a person is asthmatic also must be considered. Asthma and chronic obstructive pulmonary disease (COPD) research could be the bridge between the childhood and senior lifestages, but COPD research was not presented. This is not a shortcoming of the Program but is noted as an opportunity for a heightened research agenda.

Dr. Klaunig commented that polymorphisms also can affect multiple diseases, and Dr. Blanc added that polymorphisms in children could affect the adult onset of disease. There is an under-representation of neurodegenerative research regarding pesticides; researchers should examine the effects of combined exposure to pesticides on neurodegenerative diseases.

Dr. Daston commented that this research displayed a nice integration of molecular and cellular biology, epidemiology, and clinical components. The intra- and extramural research programs are well integrated, and leveraging with the National Children's Study (NCS) is strong. EPA will be able to meet many data needs with the NCS, and its input into the study design will ensure data are generated that are useful to EPA. Quantitative variability was addressed in some of the projects. Prioritization decisions are good but are being driven by many outside forces (e.g., focusing on children as a result of leveraging with the NCS) and are not always programmatically explained. He also noted the artificial division of the LTGs and suggested that in the future HHRP may want to determine how to matrix accounting and projects more tightly among the LTGs. There was a missed opportunity to utilize the expertise of researchers thinking very quantitatively and applying sophisticated modeling.

Dr. Schwartz commented that good research is being accomplished under the LTG, but he is concerned with the focus on children and thought that more focus needed to be on the elderly. Increased thinking about pre-existing diseases as important modifier also is necessary. There was increased epidemiology under this LTG, but he was unsure whether there was enough integration. Roles should be examined to optimize the research and improve coordination.

Dr. Blanc commented that researchers must further consider conceptually how they want to approach susceptibility and the areas of overlap and nonoverlap with age-specific lifestages. The approach should be rethought so that the research agenda is informed differently. Additionally, the relationship between asthma and other airway diseases should be explored.

Dr. Mattison noted that there is a good deal of long-term benefit of merging LTGs 2 and 3, as they inform each other and are parallel in many ways. There is potentially a stronger set of tools for merging social and nontraditional environmental factors into susceptibility and risk assessment methodology that would come from LTG 3 activities and benefit those in LTG 2.

Dr. Portier noted a cross-cutting issue. Three major groups—ORD, NIEHS, and the Centers for Disease Control and Prevention's (CDC) National Center for Environmental Health (NCEH)—are performing federally funded environmental health research. How are these groups interacting and contributing to each other's work? What is EPA doing to bring together all of the information? Translation of this research must be used in public health decision-making. What is HHRP's overall role as compared to other agencies performing federally funded environmental health research? Dr. Darney responded that Dr. Preuss had more information on this, but HHRP is partnering with other agencies and strategically completing research plans. Dr. Portier suggested that it would be a good idea for the new ORD leader to evaluate strategically what ORD's role is in the larger picture and meet with the leaders of NIEHS and NCEH to determine how to work together.

Subcommittee Discussion

BOSC Human Health Subcommittee

During a working lunch on Wednesday afternoon, the Subcommittee members continued to discuss their strategy for completing their evaluation.

The Subcommittee members agreed that the integration of the LTGs was a general issue that needed to be addressed. There were several instances in which, if the researchers had been communicating between LTGs, the outcomes would have been different and more efficient. It is necessary to have an MYP and goals, but this type of structure should not silo researchers. The science of LTGs 1 and 2 would have been improved if the epidemiologists in LTG 3 had communicated with researchers within these two LTGs. Also, researchers in LTGs 1 and 3 are not taking advantage of new knowledge produced under LTG 2.

The Subcommittee members also agreed that more epidemiological expertise is needed, possibly through cooperative agreements or extramural research. If the overarching goal is to understand and integrate all of the knowledge received from all of the LTGs, this is necessary.

Dr. Blanc noted that LTG 2 research is separated by a large dichotomy: there is the work for OPP, and then there is "everything else." Dr. Pellizzari noted that the researchers working on cumulative issues have aligned themselves vertically.

The Subcommittee members noted that the prioritization and selection decision-making process is not transparent. Additionally, the reasoning behind the decisions to place certain research areas within certain LTGs also was not apparent. Dr. Blanc noted that the MYP and LTG structure is imposed on HHRP by the Agency, and it is doing its best to conform to that structure. Within this framework, however, the Program should evaluate the current structure of the MYP and determine whether it is serving the needs of HHRP. Perhaps the LTGs need to be realigned or abandoned for a more organic method that responds to the shifting nature of collaborations. Dr. Daston added that the Program should consider the questions: Are these the right LTGs? If so, are the projects arranged correctly? Is there a way to matrix them to reduce silos?

Dr. Klaunig noted that the Program has several strengths. It has matured since the last full BOSC review and made good progress. Additionally, it is much less siloed than in the past. Dr. Mattison agreed; during the previous full review most of the strengths were individual laboratory strengths. Dr. Blanc added that the Program is responsive to emerging issues.

Dr. Portier commented that it is difficult to determine whether the grants are related to the issues. He also would like to know specifically what the internal research contributes to the overall picture. Internal NIH reviews examine why research should be done internally if it can be done at a university; EPA should consider this as well. It is necessary to examine feasibility; how does ORD drive the national agenda? Dr. Daston remarked that most research programs struggle with how to quantify this without devoting too many resources to this issue. Dr. Portier would like a list of HHRP research and how this research translated to tools that can be used by regulators.

Dr. Pellizzari noted that it is impossible to determine, under the current BOSC review structure, why a client or end-user may not use tools that are provided to them; the program offices would have the answer to this question, rather than HHRP. Drs. Schwartz and Klaunig agreed that it would improve future reviews to have end-users be a part of the review and provide evidence of why tools are or are not being used. The Program can benefit from knowing why tools are not being used and can address these issues and remove any barriers.

Dr. Blanc commented that the bibliometric analysis as provided indicated scientific strength in terms of the number of publications and citations, but the commingling of the intra- and extramural work made it impossible to understand fully. Some of the metrics were completely irrelevant to actual EPA performance. Dr. Hoel remarked that it would be helpful to list the important papers and their impact, and Dr. Klaunig added that information on how the papers influence the research also would be beneficial. Dr. Schwartz thought that knowing whether the papers do not impact risk assessment or are not relevant would be useful as well. Dr. Blanc did not think the current bibliometric analysis represents the true body of work and did not find it useful. Dr. Schwartz agreed and stated that he would prefer a list of 10 to 20 papers that ORD thinks are seminal and show how the Program is meeting its goals; the Subcommittee members agreed that this would be very useful in evaluating the Program.

Dr. Blanc reiterated that there is not a systematic process for how priorities are set for determining which substances will flow into the research of the LTGs; this was noted at the previous BOSC mid-cycle review. Some decisions are investigator driven and some by other mechanisms, but it is not systematically clear. He wondered how emerging issues are addressed in a systematic manner. Dr. Pellizzari noted that the process is described in the program evaluation materials, but he was unsure whether HHRP was following the process.

The Subcommittee members discussed the logistics of the BOSC review, particularly the poster sessions. Dr. Blanc commented that the poster sessions are not what the scientific community considers to be a poster session. It would be more useful for researchers to present posters that they have presented at national scientific meetings during the previous 2 years; an abstract book would be helpful too. He suggested that new Subcommittee members be briefed about the nature of the sessions so that they know what to expect. He also suggested that an extra 30 minutes be built into the first conference call for the members to get to know each other. Dr. Klaunig agreed with the assessment regarding the poster sessions but added that the interaction with the researchers still is very beneficial. Dr. Daston stated that an inventory of each individual project under each LTG that included a project-specific bibliography would be helpful.

LTG 4: Poster Session Overview

Dr. Andrew Geller, EPA/ORD/NHEERL

Dr. Andrew Geller explained that EPA is a regulatory agency with a public health mission. Because the connection between the Agency's regulations, regulatory science, and public health outcome can be difficult to elucidate, risk assessors and managers use ORD's methods and models to evaluate risk management decisions. In response to the previous BOSC reviews, HHRP has developed the framework for research under LTG 4, developed pilot projects, and provided significant resources to intramural and extramural research under this LTG, which comprises two research tracks: (1) trends in exposure and health status and (2) development of tools to identify indicators. Evaluating risk management decisions includes developing, evaluating, and linking indicators that can be used to demonstrate the effectiveness of risk reduction and risk management decisions. Research is needed to develop and evaluate robust indicators that describe the linkages across the source-to-effects continuum. The LTG 4 posters address the questions: Are there direct indicators or surrogates for public health measures? How can additional indicators be identified? Can existing databases be used to address this?

Dr. Geller provided background information about each of the six posters devoted to LTG 4 activities. The chapter on human exposure and health in the *Report on the Environment* presents biomonitoring and health outcome indicators to address trends in: human exposure to environmental contaminants, health status in the United States, and human diseases and conditions for which environmental contaminants may be a risk factor. In addition to providing data from existing indicators, the *Report on the Environment* identified a set of challenges to: (1) develop an integrated set of health indicators for use at all spatial scales and that could be assessed over time, (2) develop indicators that would provide risk assessors and managers with the capability to distinguish acceptable from unacceptable conditions, and

(3) establish the link between an indicator of exposure and the change in risk of a public health measure. These challenges set the stage for the further development of the research framework to define how researchers can implement research to develop tools for evaluating the outcomes of risk management decisions. The *Framework for Assessing the Public Health Impacts of Risk Management Decisions* and the risk assessment workshop were the initial steps needed to move toward full implementation of ORD research efforts to address LTG 4. The framework document emphasizes that assessing the impact of a risk management decision is seen as an integral part of the risk assessment and risk management paradigm, and understanding linkages in the source-to-exposure-to-outcome paradigm is essential to developing valid indicators of health outcomes. Linkage of indicators to the source-to-outcome continuum must be considered when answering the question of how to develop additional indicators. The five RFAs within LTG 4 taken as an ensemble are arrayed across the source-to-outcome continuum. Research from the EPA and NIEHS Children's Environmental Health Research Centers also is highlighted on one of the posters. EPA's approach to framing the current research is one that treats understanding linkages in the source-to-exposure-to-outcome paradigm as essential to developing valid indicators of health outcomes. Researchers must consider whether arraying research along the source-to-outcome continuum provides the tools to address proper accountability data in the absence of overt health effects to determine whether regulations have a positive impact.

In summary, HHRP has moved forward on LTG 4 since the 2005 and 2007 BOSC reviews, including drafting the framework document and dedicating intramural and extramural resources to build the elements required to make the necessary linkages through source-to-outcome or population-based modeling. There are great challenges to this charge, including the gap between federal regulatory decisions, the implementation of these decisions at local levels, the multiple determinants of disease, and temporal lags between exposure and ultimate outcomes. The Program retains the potential to serve as a unifying theme and provide the Agency with invaluable tools for assessing the impacts of its actions.

Partner Testimonial

Dr. Peter Preuss, EPA/ORD/NCEA

Dr. Preuss explained that risk assessment is the single most important basis for many of the Agency's decisions. Currently, there is a changing risk assessment landscape, with several bills in Congress that, if passed, will result in the generation of large amounts of data. Additionally, the NAS report *Science and Decisions: Advancing Risk Assessment* offers a new framework for risk-based decision-making. Despite this, there still are major recurring science issues. Within ORD, NCEA occupies a critical position between HHRP researchers and program office and regional regulators; these entities all work together with HHRP and are dependent on HHRP outcomes. Primary research from HHRP and other ORD programs (e.g., air toxics, computational toxicology, ozone, particulate matter, and drinking water) is applied to risk management decisions. Additionally, HHRP informs Integrated Risk Management Information System (IRIS) human health assessments, including IRIS assessments on dichloroacetic acid, toluene, and naphthalene. HHRP also informs high-profile assessments, such as that of the neurotoxic effects of tetrachloroethylene; human health risk assessment approaches, including collaboration on susceptible populations and lifestages; and NCEA's Integrated Science Assessments (ISAs) on air quality, which include asthma research that informs the nitrogen oxide, sulfur oxide, carbon monoxide, and particulate matter ISAs.

In terms of arsenic research and setting priorities, human arsenic data indicate that there is a high risk of cancer and other noncancer health effects from arsenic exposure, but there also are questions about what occurs at lower doses than are seen in human populations. The goal of the arsenic research was to determine what was occurring at low arsenic doses, especially as arsenic regulation is expensive to the U.S. economy. Program offices and regions turn to HHRP for help with increasing the clarity and definitiveness of assessments; the HHRP is a very important program for NCEA and its human health risk assessments. HHRP research is critical to the development of state-of-the-science human health assessments, which in turn are critical to EPA's regulatory and policy decision-making process.

Dr. Portier expected to see more of a translational role for the HHRP (i.e., using established research more often in future work) and asked whether there are emerging HHRP outcomes that will be routine for NCEA in the future. Dr. Preuss responded that this would be the case. Risk assessment has become increasingly complex, and being able to articulate what is occurring has become more important, as has developing models and acquiring data for these models. The current focus is on examining issues from a combined approach (e.g., combined chemicals, combined effects) and determining what influences the endpoint (versus examining the mode of action). In doing so, information will be more generalizable than it has been previously.

Inter-Relationships Between Human Health and Clean Air Research Programs

Dr. Dan Costa, EPA/ORD, National Program Director, Air Research

Dr. Dan Costa explained that three words/phrases have come to represent what all of the NPDs and research programs are attempting to accomplish: multidiscipline research, integrate, and leverage. The Clean Air Research Program works with HHRP in such a manner that scientists divide their work between both programs, which allows flexibility, integration, and use of models and approaches that serve clients with multiple objectives. Many HHRP asthma models use air pollutants as a study paradigm; this allows air and human health expertise to be exchanged and connectivity between the two programs to be maintained. Many issues are being examined in terms of the unifying hypothesis of oxidative stress, including human health research on underlying diseases, such as diabetes. As a result of mandates, OAR is extremely interested in the issue of accountability. Because of the billions of dollars at stake, it is necessary to be able to evaluate the public and environmental health benefits of decisions; ORD research and data help with this evaluation. Both programs have a source-to-outcome approach and attempt to design studies so that they have measurable benefits. Because HHRP, the Clean Air Research Program, and OAR are interested in this, they can move forward together, and HHRP helps the Clean Air Research Program and OAR meet the mission of protecting public health with regard to air-related issues.

Dr. Blanc asked whether there are specific projects and/or research that the Clean Air Research Program requests from HHRP, comparable to how OPP operates. Dr. Costa explained that because the Clean Air Research Program is a research program and OPP is a program office, their relationships with HHRP differ. His research program has set priorities and looks to other research programs to determine how they can support these priorities and have the greatest collaborative impact; the joint research evolves in parallel. Dr. Blanc asked whether OAR requests specific projects and/or research from the Clean Air Research Program. Dr. Costa responded that this was not the case; the two communicate frequently, and OAR can raise problem areas. The research program uses this as input for planning research to fit these problems.

Dr. Daston asked how specific projects are allotted to HHRP or the Clean Air Research Program and whether there was cross-talk for accountability. Dr. Costa answered that some is organizational for accounting purposes. For example, the asthma work started in the Clean Air Research Program, and as it started to grow the susceptibility issue became involved, and the research was moved to HHRP, which was in a better position to apply the susceptibility data more broadly.

LTG 4: Poster Session

This poster session was held in the Atrium. The Subcommittee reviewed six posters in this session. During the 90-minute poster session, each Subcommittee member also had the opportunity to ask questions about the research or clarify specific points with the presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

LTG 4: Subcommittee Discussion

BOSC Human Health Subcommittee

Dr. Portier noted that each of the poster sessions had a great deal of participation outside of HHRP staff, which shows a vibrant research community. The products derived from the Program are very important to EPA, but the Program still is nascent. He suggested that HHRP be moved to the Office of the Science Advisor. He noted that the *Report on the Environment* breaks things down into individual pieces, but other countries examine burden of disease and morbidity and mortality, which the *Report on the Environment* does not addresses. This should be included to make the report more comparable globally. Additionally, the Agency should work more closely with the CDC, which has better health surveillance data, so that EPA can better examine the environmental impact on public health. The *Report on the Environment* also should have close ties to community-based risk assessment; it is necessary to go beyond the national and state levels to the county level to determine local trends and what may be driving them. There was nice use of advanced modeling to make predictions about the degree of impact, so this could be used to design how to measure the impact and partner with local communities or universities to test the predictions. It will be difficult to apply this at a national level, and the Program must provide thought about how to move forward.

Dr. Schwartz commented that overall he liked the research he saw under LTG 4; it is a beginning effort and making good progress. The researchers are very enthusiastic, and the *Report on the Environment* is a very important product. Although some of the work is not generalizable, it still is important. It is easier to monitor and estimate changes in exposure that result from a change in policy than it is to determine the changes in health outcomes. He noted that it is sometimes difficult to determine cause and effect and asked how the HHRP plans to avoid following foolish lines of inquiry suggested by less sophisticated entities. Dr. Gellar noted that changes in particulate levels and changes in health sometimes are linked and sometimes are not. There is a difference between surveillance/tracking and making linkages. Criteria for the standard of evidence that will be required must be developed. Instead of relying on just making the links from a change in monitoring levels to a change in health outcomes, making reasonable links along the chain also will be part of the criteria.

Dr. Pellizzari stated that the LTG 4 research is superb, and he was impressed with the progress that has been made in a short period of time. Good products have been produced under this relatively new LTG. LTG 4 researchers should plan and coordinate with and extract the knowledge and science from the other LTGs to ensure that work is not duplicative; researchers should ensure that institutional memory is retained regarding measurements of exposure and health to determine whether there has been true improvement or an improvement in the method only.

Dr. Blanc commented that, regarding the work that is examining impacts of specific research findings on public policy, it is important to recognize that methods related to documenting linkages exist; they are sophisticated and may be outside the expertise of internal scientists and their external partners. To pursue this it may be beneficial to obtain targeted consultation with policy research experts with an interest in how science data inform public policy decisions. Researchers also may want to consider how to disseminate state-of-the-art methods (e.g., geographic information systems and linkages).

Dr. Schwartz suggested that HHRP obtain data from the CDC and the Centers for Medicare and Medicaid Services (CMS) for health tracking. The Agency for Healthcare Research and Quality also is interested in health trends; the Program should leverage with this agency.

Dr. Portier commented that the grants program on the development of novel environmental health outcome indicators is a good program, and there is an opportunity to partner with other granting agencies, specifically the NIH and the National Science Foundation (NSF). The NSF has a role in developing tools that might be of use to the Program, and the NIH has a large number of epidemiological studies that could contribute to Program research. HHRP could aggressively contact the NIH and determine how it can

contribute to the environmental aspect of the studies. He had hoped to see more about the concept of how modern technology can be useful in terms of types of questions that have not been thought of previously. He described a collaboration between the NIH and another part of the Department of Health and Human Services that highlighted how creative thinking provided an unexpected source of data (i.e., trends in over-the-counter cold and flu medication purchases from large chain drugstores that indicated a flu outbreak). He asked whether HHRP is using such creative thinking and considering what tools are missing or what research projects can be developed. Dr. Geller responded that the Program is communicating with the CDC about syndromic health data and has moved forward on ecological epidemiology identifying different kinds of surrogates and reasonable comparison sets. One novel approach suggested at one of the workshops was to track Viagra® sales and determine a linkage to arsenic levels as data indicate that arsenic causes impotence. Dr. Portier added that large drugstore chains can track sales by ZIP code, and Dr. Hoel noted that the Department of Defense has a system in place for medical reporting as part of its homeland security charge. Dr. Schwartz also provided more examples of medications being used as surrogate indicators.

Dr. Blanc asked for clarification regarding workshops. How are they organized? Who organizes them? Are some more applicable to certain LTGs than others? Dr. Geller explained that workshops occur on different levels. Some are internal, at which Program scientists meet with program and regional offices to discuss science and applications. He described some of the workshops HHRP sponsored; two informed LTG 2, and one was an international conference on biomonitoring. Dr. Blanc noted that the workshops appeared to be organized on an as-needed basis by internal and external suggestions. Dr. Gellar confirmed this and added that the Program is working with the regions on a workshop dealing with cumulative risk, which should highlight to ORD what tools are needed by the regions to perform community-based risk assessment.

LTGs 3 and 4: Partner Testimonials

Mr. Michael Firestone, EPA/Office of Children's Health Protection and Environmental Education (OCHPEE); Dr. Peter Scheidt, NIH/National Institute of Child Health and Human Development; and Mr. Michael Kenyon, EPA/Region 1

Mr. Michael Firestone explained that OCHPEE was established as a cross-cutting program in 1997 as a result of Executive Order 13045, which states that federal agencies must identify and assess environmental health and safety risks that may disproportionately affect children and address these risks. OCHPEE is comprised of nine professional employees plus support staff, and its mission is to make the health protection of children and the aging a fundamental goal of public health and environmental protection in the United States and globally. Environmentally related illness in U.S. children is estimated to cost $54.9 billion annually or 3 percent of total U.S. health care costs; lead poisoning accounts for 80 percent of this figure. LTG 3 research helps improve policies and risk assessment practices, but more importantly it provides information to OCHPEE that is disseminated to the public to improve children's health. OCHPEE and ORD have collaborated on a number of items, including developing RFAs and guidance regarding children's health, producing the *Child-Specific Exposure Factors Handbook*, and determining the future of toxicity testing and chemical risk assessment. OCHPEE has a number of critical research issues that affect children's environmental health, including endocrine disruptors, inhalation risk assessment methods, gene-environment interactions, neurodevelopmental disease triggers, biomarkers of exposure and effect, risk prevention, and many others. Critical research issues for environmental health in the aging include the development of methods to assess health that move beyond a 70-year lifespan, cumulative risk assessment methods that consider pre-existing health issues and drug interactions, biomarkers of exposure and effect, epidemiological studies that evaluate age and lifestage sensitivity, evaluation of the Barker Hypothesis, prevention, and the impact of climate change on health. ORD research is invaluable in providing data and methods critical to improving the assessment and management of children's environmental health risks, although research on aging is just beginning. The declining budget is a concern given the high economic cost associated with children's and seniors'

environmental health issues. Current needs include risk assessment methods and tools, surveillance to relate exposure to health outcomes, risk reduction, and additional research regarding children and the aging.

Dr. Peter Scheidt explained that the NCS, launched in 2000, is the largest long-term study of children's health and development ever to be conducted in the United States. Within the study, "environment" is defined broadly to include chemical, physical, behavioral, social, and cultural factors. Dr. Scheidt provided an overview of the current status of the NCS, including funding levels, number of centers and study sites, protocols, and data collection. EPA has had extensive involvement with the NCS since its planning stages and is a full member of the interagency coordinating committee that provides oversight and planning of the study. Additionally, EPA's Science To Achieve Results (STAR) grants program initiative supports research applicable to the NCS. EPA has had a valuable impact on the NCS in providing leadership, research, and scientific expertise; EPA provides unique expertise for monitoring and assessing of chemical exposures and determining their significance. There are many opportunities for continued partnership participation. For example, the STAR program could provide methods and models for exposure assessment, lessons learned for future stages of the NCS protocol, approaches for assessing nonchemical stressors, and community engagement and outreach strategies. Additionally, EPA scientists can continue to work with the NCS, providing leadership and support.

Mr. Michael Kenyon provided an overview of the role of EPA regions, which serve as primary partners with state and tribal environmental programs and work directly with municipalities and community organizations on health issues. The regions directly implement water and air permit programs in some states and most tribes, conduct hundreds of inspections, bring enforcement actions in coordination with the Department of Justice and the EPA Office of Enforcement and Compliance Assurance, implement and/or oversee Superfund cleanups, respond to and make decisions about spills and emergencies, and work with states and tribes on water and air quality monitoring. Science needs in regions often are applied and immediate in nature. ORD's human health research drives much of the regions' core work; for example, Superfund clean-up decisions are driven by risk assessments made using ORD tools (e.g., IRIS). Additionally, there are opportunities for regions to provide input on ORD research plans, such as recent HHRP NPD visits to Regions 1, 5, and 9 to obtain regional input and regional participation on Research Coordination Teams (RCTs). ORD operates several programs to support specific regional needs, such as the Regional Applied Research Effort and the Regional Environmental Monitoring Assessment Program, and other ORD research projects align with regional needs and become productive collaborations. Three HHRP projects that Region 1 found particularly useful were: (1) "Salivary Antibody as a Novel Indicator of Incident Waterborne Infections" in Lawrence, Massachusetts; (2) "A Feasibility Study on Assessing Public Health Impacts of Cumulative Air Pollution Reduction Activities" in New Haven, Connecticut; and (3) the development of exposure concentrations for regional cultural tribal risk assessment for the Penobscot Indian Nation in Maine. In conclusion, ORD produces tools and data critical to regional work to implement air, water, and waste programs, and there are many opportunities for ORD–regional collaborations to use real-life problems to address immediate community and long-term research needs.

Dr. Schwartz asked how the results of the drinking water studies would affect long-term plans. Mr. Kenyon responded that the results of the studies are useful when assessing similar issues in other communities. Dr. Schwartz asked whether beneficial results from one community would be communicated to other communities. Mr. Kenyon could not speak to the specific plans of the regional drinking water program, but there was interest in this type of dissemination.

Dr. Portier commented that HHRP's partner survey indicated that the majority of regional personnel are not interested in PBPK modeling and asked whether there was a disconnect in that the HHRP is planning a good deal of PBPK modeling work. Mr. Kenyon explained that regional employees generally are far removed from basic health research, and modeling generally is used to set standards, which regional personnel are not engaged in; this probably explains the regional response to this question. If the question

had been phrased differently, there probably would have been a different outcome. Dr. Blanc commented that partner surveys must be designed so that they can be informative; the survey should be redesigned and re-administered.

Dr. Klaunig thanked EPA staff and partners for their information and recessed the meeting at 5:29 p.m.

THURSDAY, JANUARY 15, 2009

Review of Yesterday's Activities and Overview of Today's Agenda

Dr. Klaunig, Subcommittee Chair

Dr. Klaunig reconvened the meeting at 8:08 a.m. and reviewed the day's agenda.

Future Directions

Dr. Darney, EPA/ORD

Dr. Darney explained that many factors, including BOSC input, were considered during future planning. She reviewed the BOSC review process, including summarizing information presented via the two conference calls, the program evaluation materials, and the face-to-face meeting. She displayed a chart that illustrated how each of the program evaluation materials informs the four review criteria and summarized the general themes on which the Subcommittee had commented during the face-to-face meeting.

The methods by which partner communication occurs is via RCTs; regular meetings of program office and laboratory directors; the partner survey; targeted workshops; the ORD Regional Summit; visits to laboratories, program offices, and regions; seminars, briefings, and reports to science advisory panels; reports distributed to the appropriate partners; reviews; and primary products such as papers, reports, and abstracts. The bibliometric analysis that was completed was a learning exercise and is one of many measures of program quality and performance. It measures the quality of papers and their use by the general scientific community, but it does not measure relevance to EPA. It is not an indicator of the quality of intramural versus extramural programs, nor does it measure the success of any given project; however, the decision document analysis, which was conducted via the computerized data mining of EPA documents that reference HHRP papers, is indicative of the impact of past products. This was a preliminary effort, and the future plan is to search and track impact in a more strategic manner.

Dr. Darney noted that there are 11 NCER RFAs within HHRP and, in response to a previous question, noted that the response rate of the partner survey was 38 percent. Future directions include partnering with the National Center for Computational Toxicology (NCCT) and other EPA research programs; using omics and bioinformatics expertise to move toward a systems approach and methods for predictive toxicology; virtual tissue modeling and BBDR in collaboration with NCCT, NHEERL, and NCEA; and meshing exposure databases with databases for toxicology and genomic (pathway) data. One vision is focused on developing a comprehensive plan for how EPA evaluates contaminants and making this plan a new MYP or incorporating it as one-half of HHRP. There are two types of cumulative risk assessment: (1) targeted models and (2) safe communities. In terms of targeted modeling, HHRP is working with a program office, using tools and PBPK information to develop models. In the case of safe communities, the focus is on public health, including the evaluation of risk management decisions; more complex cumulative risk that includes all factors (i.e., a community risk assessment); and placing the Children's Environmental Health Research Program under this umbrella. Dr. Darney provided an overview of past and current HHRP funding levels and explained that the trend has been relatively flat, with a decrease in funding expected for the current fiscal year. BOSC input will help the Program with workforce planning. HHRP will focus on research issues in which it can have the greatest impact with its unique capabilities and available resources.

Dr. Geller explained that HHRP takes peer review very seriously and reviewed the goals and outcomes of several of the projects presented during the poster sessions. These projects will allow HHRP to apply sophisticated, 21st-century data to risk assessments and use toxicogenomic data to establish a generalized approach. Several of the projects have moved forward faster than anticipated, including those regarding computational fluid dynamics, molecular modeling, and reactive gases. HHRP is building a collaboration with North Carolina State University that will allow the leveraging of resources. Once the model is completed, it will be possible to move forward to address more complex problems, such as particulate matter. Work with cumulative community risk also is moving forward, and research is examining how changing various factors changes health outcomes, which will help make predictions.

Dr. Geller and Ms. Houk discussed how the Subcommittee members could be utilized to help the Program address the scientific issues brought up during the review; all communication should go through the DFO until the final report is completed.

Dr. Daston commented that using toxicogenomics as the sole method to demonstrate mode of action is insufficient. It is a hypothesis-generating mechanism and can accelerate the process of narrowing the field of possible modes of action, but it is not the ultimate proof. HHRP is full of talented people performing valuable research, and this research needs to be put in a cohesive package. It is necessary to determine a method to evaluate and group research on core competence that will consider different time lines, time horizons, levels of contribution, and types of programs, some of which may be indirect; this will be a challenge for HHRP as it moves forward. There are many different ways in which the Program can be organized, whether it is keeping the same LTGs and matrixing the projects between the LTGs or creating a new set of LTGs. The Program should utilize the Subcommittee's comments when determining the organization of HHRP. Another important aspect is communication; it must be creative and include robust thinking about how to communicate HHRP research and results in ways other than journal articles, technical reports, and other documents. Face-to-face training and salesmanship should be increased. Good research is the foundation of HHRP and necessary to the Agency; therefore, the Program must organize, prioritize, and communicate in a manner that illustrates its value.

Dr. Schwartz agreed that the HHRP is involved in good science, although it is not obvious scientifically that the selection of chemicals has been optimal. HHRP should review input regarding toxin selection in a broader view to determine whether important toxins are missing; in this manner, HHRP may be too responsive to program office needs. In terms of categorizing, some projects apply to multiple categories and should be "double counted" when necessary. Seeing a full picture of the distribution of skills within the Program would be helpful, and greater internal epidemiological expertise is needed to improve the products and optimize the work of the biomarker and exposure researchers.

Dr. Portier commented that Program research, especially that on cumulative risk assessment, is solid but not timely; what is being done now could have been done 10 years ago. The Program is doing exactly what needs to be done, but it needs to do it faster. The two potential LTG groupings that Dr. Darney mentioned are logical and reasonable, and Dr. Portier reminded Program leadership that the future of toxicity testing must include animals.

Dr. Klaunig commented that if modes of action of compounds are similar to pharmaceutical modes of action, pharmaceutical human data can be leveraged for better decision-making.

Dr. Mattison commented that the previous full BOSC review identified available resources as a challenge. The concern during that review was whether the Program could build a new, emerging set of research activities, given the mix of professional competencies and interests. It appears that the Program has accomplished this, but given the new set of competencies the new concern is how the Program will maintain the growth, which will require mentoring and other leadership efforts. Dr. Darney explained that the current emphasis is on growing new leaders. Dr. Mattison suggested that HHRP examine the

possibility of streamlining the LTGs to determine whether some can be merged or activities matrixed to enhance productivity.

Dr. Blanc stated that program evaluation factors such as the bibliometric and decision analyses and the impact assessment of the extra- and intramural research could be addressed if the Program developed internal capabilities and expertise to perform needed research in timely manner and if HHRP interfaced with grantees so that they understand what information the Agency needs and how to gather it. The research tools would be the same, and the Program may get "more bang for the buck." HHRP also should examine what information is needed so that there is maximum flexibility in changing and reorganizing the LTGs should the Program wish to do so. Dr. Klaunig agreed that this is an area that needs to be addressed, but the BOSC should not dictate how the Program goes about this process.

Dr. Pellizzari commented on the decision-making process and asked whether selection and prioritization of agents included a gap analysis. Also, EPA should observe what other agencies are planning that will help populate the Agency's data needs. For example, NIEHS exposure biology research has many different components, some of which may be useful to HHRP. Dr. Darney answered that this issue spoke to the value of information analysis, and the Program has examined how to approach this in the best manner. Another issue is leveraging. EPA is designed to respond to emerging issues and crises, whereas NIEHS is not. In terms of examining disease-based planning, entire NIH institutes deal with this topic, and there is an enormous amount of information. The question is whether the process of ferreting out all of the available information is worth the time and effort, considering the benefits. Dr. Pellizzari commented that dwindling resources dictate increased leveraging, and there needs to be a concerted effort and cross-talk between agencies. Dr. Klaunig added that this can be done in an informal manner, such as a monthly lunch with counterparts at other agencies at which needs are discussed.

Preliminary Subcommittee Discussion of Charge Questions/Rating of LTGs
BOSC Human Health Subcommittee

The Subcommittee members assigned to the various LTG workgroups used the first segment of the working session to discuss their portions of the evaluation report. The Subcommittee members then reached consensus on their ratings for each of the LTGs and devised their strategy for the report out.

General Report Out
Dr. Klaunig, Subcommittee Chair

Ms. Houk and Dr. Klaunig thanked the Subcommittee members for their time and effort in performing this review. In debriefing EPA staff, Dr. Klaunig summarized the Subcommittee's preliminary responses to the charge questions. He reminded the staff that the report out is preliminary and could be modified as the members begin to draft the written report. The overall rating will be assigned when the full Subcommittee is present and will be included in the report.

Overall, the Program is responsive to emerging issues. The poster sessions and overviews were excellent, and the Subcommittee appreciated the attendance and enthusiasm displayed during the poster sessions. Questions were answered readily, and the Subcommittee appreciates the efforts of Program staff to prepare and present the information and materials for the review. There appears to be a good scientific impact, but the bibliometric analysis is difficult to interpret and understand, especially with the commingling of intra- and extramural publications; this analysis should be modified and improved or discontinued. The leadership was excellent to outstanding from the senior to the laboratory levels.

The Subcommittee members identified seven needs that the Program should address:

1. *Development of a better partner survey*. The partner survey should be improved so that it is informative or should be abandoned.

2. *Increased expertise and integration of epidemiology and biostatistics throughout the LTGs*. As the Program moves forward with more public health approaches, internal epidemiology and biostatistics expertise will be very important.

3. *Reassessment of LTG groupings*. Reassessing the LTG structure may increase communication within and between the various LTGs and decrease silos.

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

5. *Implementation of a communication plan.* The impact of Program research must be disseminated to the Agency, clients, and the general public; one potential method is to strengthen the training provided for end-users of Program products and models.

6. *Increased collaborations*. The Program should explore more opportunities to collaborate with other agencies and academia to strengthen the Program, save resources, and leverage external expertise.

7. *Increased susceptibility and epidemiology across the LTGs*. The susceptibility factors examined in children's health could be expanded to all lifestages and across the other LTGs.

Dr. Klaunig provided comments regarding the review itself. The Subcommittee members found it challenging to navigate the program evaluation materials, not only in terms of quantity but how the material was presented. The conference calls were helpful for providing background information. The poster session and the poster book were well done. Perhaps adding one poster at the beginning of each session that highlighted all work done to date under each LTG would 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. Additionally, the Subcommittee would have benefited from hearing about more specific partner interactions. One suggestion is to include Program partners and clients in the review so that they must justify how they use Program products. Another suggestion is to include partner testimonials in the poster sessions so that there can be more interaction between Subcommittee members and partners and clients.

Dr. Schwartz summarized the findings under LTG 4. The research has made good progress, and integration and management structure are good. The set of databases that the Program uses to assess health trends is too limited, and the Subcommittee suggests leveraging with agencies such as CMS and NIH to obtain more data. The Subcommittee also suggests examining the burden of disease; the pieces are available, and it would be useful to bring them together. Overall, the reviewers were impressed with the quality of the community-based studies.

Dr. Hoel summarized the findings for LTG 1. He noted that the Subcommittee members found the leadership and staff to be outstanding. The objective of this LTG is essential to EPA if the Agency is to improve risk assessment methodologies. The computational toxicology and reproductive effects research are impressive, and the pathway approach is solid. The Subcommittee suggests that the areas of epigenetics, genetic polymorphism, and susceptibility be incorporated into the research to a greater extent. Additionally, the Program should consider integrating epidemiology to a greater extent in the dose-response work. Modes of action and BBDR should be integrated to address low-dose effects and biological problems. The Program is responsive to stakeholders, but it was not obvious whether the stakeholders were making the best use of HHRP results and products. A true integration of quantitative risk assessment may influence the program offices to better integrate the mode of action work. The Subcommittee members also thought that the Program needs to establish the validation of its models, make better use of NHANES and other data, and evaluate the uncertainty of the models. The Program also should consider disseminating the science to program offices in a proactive manner.

Dr. Pellizzari summarized the findings regarding LTG 2. The Subcommittee members thought that LTG 2 research is addressing the questions that support the overall research goals surrounding cumulative risk assessment and susceptible populations as set forth in the MYP. The Program demonstrated the ability to move from single chemicals with multiple pathways to multiple chemicals with similar modes of action. There are clear attempts to enhance the risk assessment methods, and Program objectives are appropriate. The translation of the approaches to ongoing educational activities is not obvious, however. Planning is guided by the MYP, but it is not comprehensive because there is a lack of cross-LTG planning. The Subcommittee members thought that LTGs 2 and 3 would be synergistic if interaction and communication between them is increased. The Program must be aware of using outdated methods or recreating tools already available; researchers with epidemiological expertise should be consulted to reduce instances of this. The work done with OPP is a good example of the cooperation across multiple laboratories that have resulted in positive regulatory outcomes. A broader array of models will increase the quality of the research. Although the Program is responsive to and meeting the needs of program offices, increased engagement with the regions should be a future goal. Additionally, training and outreach will be of increasing importance as more complex models and products are developed. The tools and Web sites currently being developed are beneficial to local decision-making.

Dr. Blanc summarized the LTG 3 findings. The research on susceptible populations and subpopulations is highly relevant; however, there are structural difficulties in choosing lifestages at opposite ends of the spectrum as the basis of the research. Some of the work being conducted under LTG 3 is relevant to LTG 2. Although the focus on childhood susceptibility appears to be appropriate, it stemmed from the consensus across external advisory bodies; the Program should consider an internal relevancy review of this topic. The asthma research, as conceptualized, may be problematic; HHRP should consider examining asthma as a health condition that is a prototype for how health conditions can be defined across lifestages. The epidemiology is strongest in this LTG, and strong intra- and extramural components are well integrated. There is good communication and coordination within this LTG. Although the childhood and asthma components are highly productive, the aging research component was less so. Neurodegenerative diseases and their relationship to susceptibility would be relevant to aging if the childhood exposures could prove to be predictive. The scientific leadership is excellent, as demonstrated by its role in the NCS; the external support program also is excellent. Within the narrow area of susceptibility, however, it is not clear how the susceptibility work translates to risk assessment. When considering only the childhood susceptibility work, LTG 3 research exceeds expectations; however, the research should have a broader focus.

The Subcommittee assigned the following ratings to each of the LTGs:

- LTG 1: Meets expectations.
- LTG 2: Meets expectations.
- LTG 3: Meets expectations.
- LTG 4: Exceeds expectations.

Dr. Klaunig thanked everyone for their participation and adjourned the meeting at 11:34 a.m.

Action Items

- ✧ Subcommittee members will send their written assessments to Dr. Klaunig following e-mail discussions within the LTG workgroups.

- ✧ Dr. Klaunig will draft the report from the Subcommittee members' assessments and send it via e-mail to Ms. Houk to distribute to the Subcommittee members.

- ✧ Ms. Houk will arrange a follow-up conference call for mid-February 2009.

PARTICIPANTS LIST

Subcommittee Members

James E. Klaunig, Ph.D., Chair
Robert B. Forney Professor
Department of Toxicology
School of Medicine
Indiana University

Paul D. Blanc, M.D., M.S.P.H.
Chief
Division of Occupational and Environmental Medicine
Department of Medicine
University of California at San Francisco

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

David G. Hoel, Ph.D.
Distinguished University Professor
Department of Biostatistics, Bioinformatics, and Epidemiology
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
The Eunice Kennedy Shriver National Institute of Child Health and Human Development
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

Designated Federal Officer

Virginia Houk
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

EPA Participants

James Allen, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Melissa Anley-Mills
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Stanley Barone, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Timothy Barzyk, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Lisa Baxter
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Deborah Best
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Doris Betancourt, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Linda Birnbaum, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Jerry Blancato, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Meta Bonner, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Maggie Breville
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Ann Brown
U.S. Environmental Protection Agency
Office of Research and Development
Immediate Office of the Assistant Administrator

Jane Caldwell, Ph.D.
U.S. Environmental Protection Agency
Office of Air and Radiation
Office of Air Quality Planning and Standards

Richard Callan, M.P.H.
ASPH/EPA Fellow
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Kathryn Conlon
ASPH/EPA Fellow
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Rory Conolly, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Ralph Cooper, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Chris Corton, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Dan Costa, Sc.D.
U.S. Environmental Protection Agency
Office of Research and Development
Clean Air Research Program

Kevin Crofton, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Rebecca Daniels, M.S.P.H.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Sally Perreault Darney, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
Human Health Research Program

Timothy Dean
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Vicki Dellarco
U.S. Environmental Protection Agency
Office of Pesticide Programs
Office of Prevention, Pesticides, and Toxic Substances

Mike DeVito, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

David Diaz-Sanchez, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Janet Diliberto
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

David Dix, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Janice Dye, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Stephen Edwards, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Andrey Egorov, Sc.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Hisham El-Masri, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Suzanne Fenton, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Nigel Fields, M.S.P.H.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Michael Firestone
U.S. Environmental Protection Agency
Office of Children's Health Protection and Environmental Education

Roy Fortmann, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Shay Fout, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Jack Fowle, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Melanie Fraites, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Elaine Francis, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
Pesticides and Toxics Research Program

Jane Gallagher, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Valerie Garcia, M.S.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Andrew M. Geller, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Jerome Goldman, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Christopher Gordon
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Kate Guyton, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Nicole Hagan
Environmental Management Fellow
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Davyda Hammond, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

David Herr, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Susan Hester, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Robert Hetes, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Ross Highsmith
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Erin Hines, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Heidi Hubbard
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Michael Hughes, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Sid Hunter
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Vlad Isakov, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Annie Jarabek, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Scott Jenkins, Ph.D.
U.S. Environmental Protection Agency
Office of Air and Radiation
Office of Air Quality Planning and Standards

Robert Kavlock, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Elaina Kenyon, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Michael Kenyon
U.S. Environmental Protection Agency
Region 1
New England Regional Laboratory (EAA)

Nagu Keshava, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Kirk Kitchin, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Thomas Knudsen, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Presada Kodavanti, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Adriana LaGier, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Susan Laws, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Audrey Levine, Ph.D., P.E.
U.S. Environmental Protection Agency
Office of Research and Development
Drinking Water Research Program

Xiaoyu Liu
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Danelle Lobdell, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

David Marr
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Mark Mason
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Thomas McCurdy, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Robert McPhail
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Enviromental Effects Research Laboratory

Lisa Melnyk, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Qingyu Meng, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Marsha Morgan, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Ginger Moser, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Shaibal Mukerjee, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Lynea Murphy, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Patricia Murphy, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Michael Narotsky, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Lucas Neas, Sc.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Stephen Nesnow, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Carlos Nunez
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Ed Ohanian, Ph.D.
U.S. Environmental Protection Agency
Office of Water

Jennifer Orme-Zavaleta, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Russell Owen, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Hâluk Özkaynak, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Dale Pahl
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Devon Payne-Sturges, Dr.P.H.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Dan Petersen, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

R. Julian Preston, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Peter Preuss, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

James Quackenboss, M.S.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Larry Reiter, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

John Rogers, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Jeffrey Ross, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Joyce Royland, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

William Russo, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Chris Saint, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

Dina Schreinemachers, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Laurel Schultz
U.S. Environmental Protection Agency
Office of Air and Radiation
Office of Air Quality Planning and Standards

Deborah Segal
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research

MaryJane Selgrade, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

R. Woodrow Setzer, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Tim Shafer, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Imran Shah, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Computational Toxicology

Linda Sheldon, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Jane Ellen Simmons, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Steve Simmons, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Emily Smith
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Peter Smith
U.S. Environmental Protection Agency
Office of Pesticide Programs
Office of Prevention, Pesticides, and Toxic Substances

Bob Sonawane, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment

Tammy Stoker, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Daniel Stout, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

David Szabo
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Kevin Teichman, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development

Sheau-Feng Thai, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

David Thomas, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Kent Thomas
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Rogelio Tornero-Velez, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Nicolle Tulve, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Elin Ulrich, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

John Vandenberg, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Stephen Vesper, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Sury Vulimiri
U.S. Environmental Protection Agency

Tim Wade, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Timothy Watkins, M.S.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Douglas Wolf, D.V.M., Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Jianping Xue, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Valerie Zartarian, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

Hal Zenick, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Robert Zucker, Ph.D.
U.S. Environmental Protection Agency
Office of Research and Development
National Health and Environmental Effects Research Laboratory

Other Participants

David Eastmond, Ph.D.
University of California at Riverside
Environmental Toxicology Graduate Program

Elaine Faustman, Ph.D.
University of Washington
Department of Environmental and Occupational Health Sciences

Frank Gilliland, M.D., Ph.D.
University of Southern California
Keck School of Medicine

Christian Hughes
Contractor

Annette Kirshner, Ph.D.
National Institutes of Health
National Institute of Environmental Health Sciences

Marie Lynn Miranda
Duke University

David Peden, M.D.
University of North Carolina
Center for Environmental Medicine, Asthma & Lung Biology

Peter Scheidt, M.D.
National Institutes of Health
The Eunice Kennedy Shriver National Institute of Child Health and Human Development

Contractor Support

Kristen LeBaron, M.S.
The Scientific Consulting Group, Inc.

Maria Smith
The Scientific Consulting Group, Inc.

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HUMAN HEALTH SUBCOMMITTEE

MEETING AGENDA
January 13-15, 2009

U.S. Environmental Protection Agency
Office of Research and Development
109 TW Alexander Drive
Building C, Rooms C111A, B, C
Research Triangle Park, North Carolina

Tuesday, January 13, 2009

8:00 a.m.	Registration	
Welcome and Overview		
8:30 a.m.	Welcome and Opening Remarks	Dr. James Klaunig, Human Health (HH) Subcommittee Chair
8:40 a.m.	BOSC Designated Federal Officer (DFO) Remarks	Ms. Virginia Houk, DFO, Office of Research and Development (ORD)
8:50 a.m.	ORD Welcome & Brief Overview of the Human Health Research Program	Dr. Sally Darney, National Program Director (NPD), HH, ORD
Human Health Research Program Long Term Goal 1: Use of Mechanistic Data in Risk Assessment		
9:05 a.m.	LTG 1: Poster Session Overview	Dr. Julian Preston, Associate Director for Health, NHEERL, ORD
9:20 a.m.	LTG 1: Poster Session (Atrium)	
11:40 a.m.	LTG 1: Subcommittee Discussion - Poster Session Discussion - Q & A	HH Subcommittee
12:25 p.m.	Break to Get Lunch	
12:40 p.m.	Working Lunch—Subcommittee Discussion	HH Subcommittee
1:40 p.m.	Public Comment	

Human Health Research Program Long Term Goal 2: Cumulative Risk

1:55 p.m.	LTG 2: Poster Session Overview	Dr. Linda Sheldon, Associate Director for HH, NERL, ORD
2:10 p.m.	LTG 2: Poster Session (Atrium)	
4:00 p.m.	LTG2: Subcommittee Discussion - Poster Session Discussion - Q & A	HH Subcommittee
4:55 p.m.	LTGs 1 & 2: Partner Testimonials	Dr. Vicki Dellarco, OPPTS Dr. Ed Ohanian, OW
5:30 p.m.	Recess LTG 1 & 2 Workgroups Breakout End of public session for the day	

Wednesday, January 14, 2009

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

Human Health Research Program Long Term Goal 3: Susceptible Populations

8:45 a.m.	LTG 3: Poster Session Overview	Dr. Devon Payne-Sturges, Assistant Center Director for HH, NCER, ORD
9:00 a.m.	LTG 3: Poster Session (Atrium)	
11:15 a.m.	LTG 3: Subcommittee Discussion - Poster Session Discussion - Q & A	HH Subcommittee
12:00 p.m.	Break to Get Lunch	
12:30 p.m.	Working Lunch—Subcommittee Discussion of Overall Program	HH Subcommittee

Human Health Research Program Long Term Goal 4: Evaluation of Risk Management Decisions

1:30 p.m.	LTG 4: Poster Session Overview	Dr. Andrew Geller, Assistant Laboratory Director, NHEERL, ORD
1:45 p.m.	Partner Testimonial	Dr. Peter Preuss, NCEA, ORD
2:00 p.m.	Inter-relationships between HH and Clean Air Research Programs	Dr. Dan Costa, NPD, Air, ORD
2:15 p.m.	LTG 4: Poster Session (Atrium)	
3:45 p.m.	LTG 4: Subcommittee Discussion - Poster Session Discussion - Q & A	HH Subcommittee
4:30 p.m.	LTGs 3 & 4: Partner Testimonials	Mr. Michael Firestone, OCHPEE Dr. Peter Scheidt, NIH/NICHD Mr. Mike Kenyon, Region 1
5:15 p.m.	Recess LTG 3 & 4 Workgroups Breakout End of public session for the day	

Thursday, January 15, 2009

8:00 a.m.	Review of Yesterday's Activities Overview of Today's Agenda	Dr. James Klaunig, HH Subcommittee Chair
8:15 a.m.	Future Directions	Dr. Sally Darney
9:15 a.m.	Break	
9:45 a.m.	Preliminary Subcommittee Discussion of Charge Questions/Rating of LTGs	HH Subcommittee
10:30 a.m.	General Report Out LTG 4 LTG 1 LTG 2 LTG 3	Dr. James Klaunig Dr. Schwartz Dr. Hoel Dr. Pellizzari Dr. Blanc
11:30 a.m.	ADJOURN	