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**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

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

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

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

## 8 **ORD Welcome and Brief Overview of the Human Health Research Program**

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

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

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

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

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

1 2 and 3. In terms of the prospective review, time has been reserved on the final day of the meeting to  
2 recap the highlights of future needs and plans, revisit the new science drivers, consider the realities of  
3 workforce planning and budget, and comment on the straw proposal for restructuring the Program into  
4 two integrated LTGs, one focusing on toxicity and the other on public health.

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

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

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

## 26 **LTG 1: Poster Session Overview**

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

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

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

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

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

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

### 38 **LTG 1: Poster Session**

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

### 43 **LTG 1: Subcommittee Discussion**

#### 44 *BOSC Human Health Subcommittee*

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

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

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

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

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

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

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

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

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

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

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

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

## 29 **Subcommittee Discussion**

### 30 *BOSC Human Health Subcommittee*

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

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

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

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

#### 4 **Public Comment Period**

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

#### 6 **LTG 2: Poster Session Overview**

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

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

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

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

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

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

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

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

### 13 **LTG 2: Poster Session**

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

### 18 **LTG 2: Subcommittee Discussion**

#### 19 *BOSC Human Health Subcommittee*

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

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

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

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

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

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

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

## 26 **LTGs 1 and 2: Partner Testimonials**

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

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

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

1 *21st Century: A Vision and Strategy.* HHRP has provided mechanistic data in risk assessment that  
2 demonstrate the use of “omic” technologies to efficiently identify toxicity pathways, and provides data on  
3 specific chemical classes that directly support ongoing risk assessment decisions. HHRP’s cumulative  
4 risk work is valuable because it provides data and models on specific chemical classes that directly  
5 support cumulative risk assessment decisions and lays the foundation for the pyrethroid cumulative risk  
6 assessment. HHRP’s exposure research will benefit OPP’s overall risk assessment program by providing  
7 procedures for using the SHEDS Model, child-specific exposure factor data, residential standard  
8 operating procedures, and improvement of the use and interpretation of biomarkers. HHRP researchers  
9 also plan to develop a systems biology approach in defining underlying biological mechanisms of  
10 chemical mixtures and increase understanding of the influence of dose and mixture composition on  
11 chemical interactions and the joint toxic action of mixtures. Dr. Dellarco stressed the importance of ORD  
12 and program office partnerships, stating that ORD has contributed greatly to regulatory acceptance and  
13 applications. It is critical to enter the regulatory framework via transferable methods such as staff  
14 training, stakeholder engagement, peer review, and science policy development.

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

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

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

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

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

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

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

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

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

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

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

## 22 **WEDNESDAY, JANUARY 14, 2009**

### 23 **Review of Yesterday's Activities and Overview of Today's Agenda**

24 *Dr. Klaunig, Subcommittee Chair*

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

### 26 **LTG 3: Poster Session Overview**

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

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

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

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

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

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

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

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

### 35 **LTG 3: Poster Session**

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

### 40 **LTG 3: Subcommittee Discussion**

#### 41 *BOSC Human Health Subcommittee*

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

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

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

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

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

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

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

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

**1 Subcommittee Discussion****2 BOSC Human Health Subcommittee**

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

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

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

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

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

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

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

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

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

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

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

#### 27 **LTG 4: Poster Session Overview**

28 *Dr. Andrew Geller, EPA/ORD/NHEERL*

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

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

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

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

### 25 **Partner Testimonial**

26 *Dr. Peter Preuss, EPA/ORD/NCEA*

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

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

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

## 9 **Inter-Relationships Between Human Health and Clean Air Research Programs**

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

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

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

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

## 39 **LTG 4: Poster Session**

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

**1 LTG 4: Subcommittee Discussion****2 BOSC Human Health Subcommittee**

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

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

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

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

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

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

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

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

#### 24 **LTGs 3 and 4: Partner Testimonials**

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

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

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

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

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

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

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

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

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

## 5 **THURSDAY, JANUARY 15, 2009**

### 6 **Review of Yesterday's Activities and Overview of Today's Agenda**

7 *Dr. Klaunig, Subcommittee Chair*

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

### 9 **Future Directions**

10 *Dr. Darney, EPA/ORD*

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

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

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

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

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

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

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

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

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

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

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

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

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

### 23 **Preliminary Subcommittee Discussion of Charge Questions/Rating of LTGs**

#### 24 *BOSC Human Health Subcommittee*

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

### 28 **General Report Out**

#### 29 *Dr. Klaunig, Subcommittee Chair*

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

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

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

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

- 1 2. *Increased expertise and integration of epidemiology and biostatistics throughout the LTGs.* As the  
2 Program moves forward with more public health approaches, internal epidemiology and biostatistics  
3 expertise will be very important.
- 4 3. *Reassessment of LTG groupings.* Reassessing the LTG structure may increase communication within  
5 and between the various LTGs and decrease silos.
- 6 4. *Development of a systematic process of prioritization and selection.* Establishing such a process for  
7 determining which agents will be prioritized will create needed transparency.
- 8 5. *Implementation of a communication plan.* The impact of Program research must be disseminated to  
9 the Agency, clients, and the general public; one potential method is to strengthen the training  
10 provided for end-users of Program products and models.
- 11 6. *Increased collaborations.* The Program should explore more opportunities to collaborate with other  
12 agencies and academia to strengthen the Program, save resources, and leverage external expertise.
- 13 7. *Increased susceptibility and epidemiology across the LTGs.* The susceptibility factors examined in  
14 children's health could be expanded to all lifestages and across the other LTGs.

15 Dr. Klaunig provided comments regarding the review itself. The Subcommittee members found it  
16 challenging to navigate the program evaluation materials, not only in terms of quantity but how the  
17 material was presented. The conference calls were helpful for providing background information. The  
18 poster session and the poster book were well done. Perhaps adding one poster at the beginning of each  
19 session that highlighted all work done to date under each LTG would enhance each poster session.  
20 Inclusion of posters presented at national scientific meetings during the previous 2 years, or an abstract  
21 book detailing such posters, also would be helpful to the reviewers. Additionally, the Subcommittee  
22 would have benefited from hearing about more specific partner interactions. One suggestion is to include  
23 Program partners and clients in the review so that they must justify how they use Program products.  
24 Another suggestion is to include partner testimonials in the poster sessions so that there can be more  
25 interaction between Subcommittee members and partners and clients.

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

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

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

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

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

- 34 ➤ LTG 1: Meets expectations.
- 35 ➤ LTG 2: Meets expectations.
- 36 ➤ LTG 3: Meets expectations.
- 37 ➤ LTG 4: Exceeds expectations.

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

### 39 **Action Items**

- 40 ✧ Subcommittee members will send their written assessments to Dr. Klaunig following e-mail  
41 discussions within the LTG workgroups.
- 42 ✧ Dr. Klaunig will draft the report from the Subcommittee members' assessments and send it via e-mail  
43 to Ms. Houk to distribute to the Subcommittee members.
- 44 ✧ 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 Environmental 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.



**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
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8:40 a.m.	BOSC Designated Federal Officer (DFO) Remarks	Ms. Virginia Houk, DFO, Office of Research and Development (ORD)
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8:50 a.m.	ORD Welcome & Brief Overview of the Human Health Research Program	Dr. Sally Darney, National Program Director (NPD), HH, ORD
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**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
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9:20 a.m.	LTG 1: Poster Session (Atrium)	
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11:40 a.m.	LTG 1: Subcommittee Discussion - Poster Session Discussion - Q & A	HH Subcommittee
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12:25 p.m.	Break to Get Lunch	
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12:40 p.m.	Working Lunch—Subcommittee Discussion	HH Subcommittee
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1:40 p.m.	Public Comment	
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**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
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**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**

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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**

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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	