

US EPA ARCHIVE DOCUMENT

**HUMAN HEALTH SUBCOMMITTEE**

**Conference Call Summary**  
**Monday, December 1, 2008**  
**11:00 a.m. – 2:15 p.m. Eastern Time**

**Welcome**

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

Dr. James Klaunig, Subcommittee Chair, welcomed the Board of Scientific Counselors (BOSC) Human Health Subcommittee members to the conference call. He asked Subcommittee members and other participants to identify themselves and reviewed the call agenda, which included the Designated Federal Officer's (DFO) remarks, a summary of the partner survey and bibliometric analysis, and four presentations on the Program's Long Term Goals (LTGs) by Environmental Protection Agency (EPA) staff members. He reminded participants that the Subcommittee's face-to-face meeting is scheduled for January 13-15, 2009, and told them that an e-mail with information about assignments to workgroups would be sent during the conference call and discussed at the end of the call. He noted that the workgroups should consist of two to four people, ideally with four people in each workgroup on each day, and that each workgroup would need a primary and secondary writer. A list of the Subcommittee members and other participants is attached to this summary, along with the agenda for the conference call.

**BOSC DFO Remarks**

*Ms. Virginia Houk, EPA, Office of Research and Development (ORD), DFO*

Ms. Virginia Houk thanked the Subcommittee members for participating in this public call and informed them that she has replaced Heather Drumm as the DFO for this BOSC Subcommittee.

She explained that the BOSC is a federal advisory committee, and the DFO is responsible for ensuring that the call complies with the requirements of the Federal Advisory Committee Act (FACA). All BOSC meetings and deliberations are open to the public per FACA, and the DFO must be present at all meetings to ensure that FACA requirements are met. These requirements include the opportunity for public comment and maintenance of records of Board deliberations, which are available to the public. A contractor from The Scientific Consulting Group is present to take notes and prepare the summary of the call. The minutes of this meeting will be made available on the BOSC Web Site (<http://www.epa.gov/osp/bosc>) after they are certified by the Subcommittee Chair. Notice of this meeting was published in the *Federal Register*, and an electronic public docket has been established. The Docket Number is EPA-HQ-2008-0649, and the docket can be found at <http://www.regulations.gov>.

EPA has worked to ensure that all appropriate ethics regulations are satisfied. Subcommittee members should inform Ms. Houk if they discover a potential for conflict of interest in any of the topics under discussion during this call.

This call was convened to provide an overview of the LTGs of the Human Health Research Program (HHRP) and to continue preparations for January's face-to-face-meeting. All Subcommittee members should have received background materials and presentations prior to the call. No member of the public requested time for comment prior to the call; however, there will be time for public comment at 12:30 p.m. If anyone on the call wishes to offer a public comment, they can do so at that time. Ms. Houk reminded the Subcommittee members and EPA staff that, for the record, they need to identify themselves before speaking.

### **Summary of Partner Survey and Bibliometric Analysis**

*Mr. Phil Juengst, EPA, ORD, Accountability Team Leader*

Mr. Juengst said that the partner survey was conducted to collect additional quantitative data on program management and performance to help inform the BOSC's review and assessment of the HHRP. The survey was conducted in September and October 2008 to gather systematic feedback about EPA partners' perceptions of the Program's effectiveness and the extent to which partners used the science and technical support to inform their decision-making from 2003 to 2008. Surveys will be conducted biennially to serve as a program management and performance assessment tool.

In 2005, ORD began trying to survey partners in a systematic way to obtain their feedback about ORD's performance. Pilot surveys began in 2005 for a few programs, not including HHRP, partly in response to requests from several BOSC subcommittees. Efforts have been made in the past few years to work across all programs to develop a more scientifically valid survey instrument. In 2008, ORD began implementing the survey process for each of its programs in advance of the BOSC reviews.

The HHRP survey was the largest conducted to date and the fourth survey completed in 2008. A total of 222 partners, including executives, mid-level managers, and staff scientists, were invited to participate in a Web-based survey. Eighty-five individuals (38%) completed the survey, of whom 27 percent represented EPA regions and 64 percent represented EPA program offices. Seven percent of the respondents were from outside EPA. One of the challenges in conducting the survey has been obtaining a robust response. For the HHRP, a large group of potential respondents was identified, including executives, managers, and staff members at a variety of levels; the response rate was a little lower than hoped for, but the results were useful.

Mr. Juengst said that, in general, the feedback from the survey was very positive, indicating that HHRP products and services are highly regarded and used by EPA program offices and regions. Sixty-eight percent of respondents rated the overall quality, timeliness, and responsiveness of the HHRP's research products and services as "good" or better. Across ORD, roughly 60 percent of partners have given similarly positive answers; the data point for the HHRP is higher, indicating that the HHRP is one of ORD's stronger programs. In addition, eighty-six percent of respondents were satisfied with the scientific support they receive for programmatic and

regulatory decisions. Consistent with feedback from other ORD program surveys conducted thus far, respondents were less satisfied with the HHRP's flexibility in accommodating partners' needs and communication of research project progress and products. However, 69 percent were somewhat, mostly, or completely satisfied with the HHRP's willingness to include partners in science planning. That's another area where the HHRP survey data are more positive than the survey data for other programs.

Overall, those were the few areas where the HHRP stands out and the few areas where the survey indicated improvements can be made.

Dr. Henry Falk, Vice Chair of the Subcommittee, asked if the non-respondents were from EPA or from outside the Agency. Mr. Juengst replied that almost all of the people invited to participate in the survey were from EPA; only a small number of non-EPA federal officials were included, and the number of non-federal individuals who could participate was limited to nine because a larger number would trigger Office of Management and Budget's (OMB) approval of the survey, which is a long process.

Dr. Joel Schwartz commented that 38 percent was a reasonably good response rate but that it would be valuable to have information on the characteristics of respondents versus non-respondents and to determine whether the two groups were significantly different in any way (senior versus less senior, those in one area versus another, etc.). He also suggested extending the survey to people on the Science Advisory Board's (SAB) Clean Air Scientific Advisory Committee (CASAC) because they would be reviewing the scientific basis of standards. Mr. Juengst said that he would pull together data on respondents versus non-respondents. In general, the response rates did not differ greatly among various categories of respondents.

Dr. Paul Blanc asked whether the survey was anonymous and how those conducting the survey could know who did or did not respond. Mr. Juengst said that the survey was anonymous but that each respondent received a unique identifier, thus making it possible to identify who had and had not responded. There was no access to the individual feedback that respondents provided because the data were aggregated by an external system. Dr. Blanc asked whether the people who fill out the surveys trust this system, and Mr. Juengst said that this had not been an issue. He noted that a disclosure statement was sent out with the surveys saying that all the data would be treated completely confidentially and anonymously. Dr. Blanc thought the response rate was low and he found it difficult to find meaning in a survey for which the respondents were almost exclusively EPA employees. He questioned whether junior scientists in regional offices would consider themselves "partners" and suggested that such respondents might be reluctant to make highly critical comments. Mr. Juengst said that the feedback received had been useful and had provided ORD with guidance on how to improve the Program. Dr. Sally Darney, the Acting National Program Director for Human Health, added that conducting these surveys has been a learning experience for ORD and she sees the surveys as more of a tool for the HHRP and other programs to obtain feedback rather than as a valid instrument for an anonymous satisfaction evaluation. Dr. Darney said that the HHRP has many clients and partners, including some from within ORD, who are likely to provide varied feedback on the Program's performance. The survey also could help to inform partners of the products and services that the HHRP provides.

Mr. Juengst stated that the bibliometric analysis, like the survey, was intended to provide the BOSC Subcommittee members with detailed information to enhance their ability to evaluate the impact of the HHRP. Overall, a little more than 25 percent of HHRP's publications are highly cited—a standard metric that ORD has agreed upon with the OMB. Across ORD, about 23 percent of the publications are highly cited. A little more than half of HHRP's publications are published in high-impact journals, the highest for any ORD research program. The process of benchmarking analysis of publication in high-impact journals has just begun; this is not a standard metric. Before the face-to-face review, decision citation analysis data, showing the percentage of products and publications that are cited in EPA regulations and decisions as captured in EPA electronic dockets and on EPA Web sites, will be made available to the Subcommittee.

Dr. Klaunig asked Mr. Juengst to discuss the table showing the findings for the LTGs that were included in the materials sent to the Subcommittee members. Mr. Juengst clarified that the table provides a breakdown of results by each of the LTG areas and explained that the percentages in the table indicate the proportion of respondents who rated each LTG as 4 or better on a 7-point scale. Dr. Darney clarified that the numbers listed indicate the number of people who gave responses of 4 or better, not the total number of respondents. Dr. Klaunig asked for more complete data. Dr. Darney replied that extensive data were available in graphic form and agreed to provide them in advance of the face-to-face meeting. Dr. Klaunig asked whether any narrative data were available. Dr. Darney indicated that respondents had the option of providing written comments and she would provide those to the Subcommittee. Dr. Donald Mattison asked where he could find the bibliographic data that Mr. Juengst and Dr. Darney had discussed. Dr. Darney said that the bibliography was on the CD that had been mailed to Subcommittee members and that the bibliometric analysis and a narrative overview of the program, including a one page summary of the bibliometric analysis, were sent to the Subcommittee and should be placed under Tab N and Tab G, respectively.

Dr. Schwartz said that it might be helpful to have the bibliometric analysis broken down by intramural versus extramural publications. Dr. Darney responded that the BOSC Executive Committee had decided not to require that programs breakdown the data in this way (a fact that she reconfirmed during the call). She suggested bringing up the issue at the Executive Committee level if members of the Subcommittee wanted the intramural and extramural data presented separately. Dr. Christopher Portier said that, like Dr. Schwartz, he would like to see the bibliometric data broken down by intramural, extramural, and combined. Ms. Houk stated that the Subcommittee could request the materials they would like to receive for the review. Dr. Klaunig indicated that the Subcommittee would like to see the bibliometric data broken down by intramural, extramural, and combined. Dr. Darney said that she and Ms. Houk would follow up on this issue.

Dr. Blanc mentioned that the highly cited papers in the bibliometric analysis were sorted by date rather than number of citations and questioned the rationale for doing it that way. He noted that one would not expect a large number of citations of very recently published papers and suggested that perhaps this was the reason for this arrangement.

### **Review Materials Update**

*Dr. Sally Darney, EPA, ORD, Acting National Program Director for Human Health*

Dr. Darney stated that a substantial number of materials had been added since the last call in October. She drew members' attention to the HHRP documentation package overview, which explained the purpose of each piece of the package. She also emphasized the importance of some of the materials that were provided to members only on CD. This is the first time that materials have been provided electronically; this method was chosen because it provides the opportunity to link to primary sources. Resources provided in electronic format include a summary of National Center for Environmental Research (NCER) grants under the HHRP from 2002 through 2008, with a link to the NCER Web Site; biosketches of HHRP scientists in ORD; a bibliography of all publications from 2004-2008, with PubMed Web Site links; and some key products, including EPA reports, that can be difficult to locate in other ways.

The list of materials available only on CD is in Tab E, and the overview of the HHRP is in Tab G. A chart on page 13 of the HHRP overview document shows linkages between each documentation piece and the four general program evaluation measures: relevance, quality, performance, and leadership. Hard copies of the Human Health Research Accomplishments Report have been mailed to Subcommittee members. The report was prepared in 2007 to capture plenary products and outcomes from this Program; its intended use is to communicate with program offices or other groups visited by HHRP scientists or to be distributed at meetings. An electronic version of the Report on the Environment's human health chapter, which is a primary product of the HHRP, also has been provided, as have NCER's report *The Decade of Children's Health* and other documents. Less information has been provided on future directions at the HHRP because this information will be provided in the posters at the face-to-face meeting. In addition, the advent of a new Administration will influence future directions at the HHRP.

Dr. Portier said that the linked Table of Contents does not work on his Mac computer. Dr. Darney replied that she would have MAC experts resolve this problem for him.

### **Overview of LTG 1: Use of Mechanistic Data in Risk Assessment**

*Dr. Julian Preston, EPA, ORD, National Health and Environmental Effects Research Laboratory (NHEERL), Acting Associate Director for Health*

Dr. Julian Preston said that he would give an overview of the philosophy and directions of LTG 1 research and noted that further details could be found in the abstracts that had been provided to the participants and in the posters to be displayed at the face-to-face meeting. The overall goal of ORD's research plan for LTG 1, as defined in the Human Health Research Plan (2006-2013), is to address the requirement for risk assessors and risk managers to use ORD's methods, models, or data to address uncertainty in risk assessment using mechanistic or mode of action information. The research in LTG 1 is guided by the following key research questions:

- ✧ What methods and models are needed to identify modes or mechanisms of action that can be used for risk assessment?
- ✧ How can knowledge of toxicity pathways inform the development of pharmacokinetic and pharmacodynamic models for risk assessment?

- ✧ How can knowledge of toxicity pathways or mode of action be used to reduce uncertainty in extrapolation in risk assessment, including extrapolation from high to low dose, extrapolation from laboratory animals to humans, extrapolation from *in vitro* data to *in vivo* exposures, and harmonization of cancer and non-cancer risk assessments?

Dr. Preston noted that extrapolation can be difficult because data often are collected at levels outside the range to which humans would be exposed, and that harmonization of cancer and non-cancer risk assessments is a major emphasis within the LTG 1 program.

The strategy for the LTG 1 research plan is to develop a comprehensive research implementation plan that consists of a set of research projects designed to investigate key events in the mode of action for adverse health outcomes. Although specific chemicals are studied, the main questions of interest are broader, with implications across a broad range of chemicals and chemical classes. The answers to these questions also may be of interest to other programs, such as the air and water programs, thus linking the Human Health Research Plan with other plans.

The following definitions are crucial to understanding the LTG 1 plan:

- ✧ *Mode of action*, defined in the context of cancer, is a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A similar definition applies in non-cancer contexts.
- ✧ A *key event* is an empirically observable (measurable) precursor step that is a necessary element of the mode of action or is a biologically based marker for such an element. Identifying key events is critical to the development of the LTG 1 program, and their identification helps to define modes of action.
- ✧ A *biomarker* is considered to be a surrogate marker of exposure or an early biological marker of effect. In contrast, a biological marker of effect that is itself a key event along the pathway from a normal cell to a transformed one is described as a *bioindicator*.

Dr. Schwartz raised the issue of selecting biomarkers and bioindicators for non-cancer endpoints. Dr. Blanc suggested that for neurotoxicity, acetylcholinesterase inhibition might be a biomarker, and that nerve conduction changes could serve as a bioindicator. More specifically, in the situation of elevated manganese exposure and Parkinsonism, elevated blood or urinary excretion of manganese might be a biomarker, whereas imaging showing increased manganese concentrations at sites within the central nervous system related to Parkinsonism could serve as a bioindicator. Dr. Preston agreed that these were good examples and commented that it is necessary to be very specific with non-cancer endpoints. Dr. Andrew Geller commented that Dr. Schwartz had pinpointed an important challenge for going forward—working with non-cancer endpoints.

Dr. Preston stated that a framework developed by EPA, the International Life Sciences Institute (ILSI), and the International Program on Chemical Safety (IPCS) has been proposed for use for

the conduct of both cancer and non-cancer risk assessments. It is based on an animal mode of action and Human Relevance Framework (HRF). The use of an animal mode of action is necessary because of the lack of pertinent epidemiologic data and the fact that most of the available mechanistic data come from animal models. In the risk assessment, key events are identified that support a specific mode of action in animals for a cancer or non-cancer endpoint. Using these, a mode of action is developed for a particular chemical in an animal model. The human relevance of this mode of action then is established using the HRF. Decisions on the necessity for a quantitative risk assessment are based on the HRF. If the mode of action is relevant to humans, more extensive quantitative risk assessment is required. If the mode of action is not feasible in humans, it is not necessary to carry out more extensive risk assessment.

The key input data for the risk assessment framework are:

- ✧ Key events for the mode of action (mechanistic data in mammalian and human cells, animal models, and humans);
- ✧ Mode of action development from key events and models (toxicity pathways);
- ✧ Toxicity data from animal models (targeted testing); and
- ✧ Human epidemiologic data (if possible).

All of these data inputs can be used in a quantitative risk assessment if one is required.

The development of bioindicators of adverse health outcomes as part of LTG 1 is a cornerstone to a mechanistic approach to the conduct of cumulative risk assessments (LTG 2), a better understanding of the basis for individual and population susceptibilities and sensitivities (LTG 3), and assessment of the outcomes of risk management decisions (LTG 4). Thus, LTG 1 is related to the other three LTGs in the HHRP.

The projects that constitute LTG 1 are grouped into five themes:

- ✧ Theme 1: Determine utility of emerging technologies in risk assessment. This theme emphasizes the development or adaptation of technologies, but their relevance and utility in risk assessment also must be established.
- ✧ Theme 2: Develop mode of action data for reproductive and developmental risk.
- ✧ Theme 3: Identify pharmacokinetic and pharmacodynamic issues underlying uncertainties for extrapolation.
- ✧ Theme 4: Identify the roles of oxidative stress in cancer and non-cancer risk assessments.
- ✧ Theme 5: Establish systems-based models for use in risk assessments.

Dr. Blanc noted that Theme 4 was strikingly different from the others because it focuses on a particular process, oxidative stress, and questioned why such a specific theme was chosen. Dr. Preston said that there was an overriding need to pull together much research where oxidative stress was a clear potential mode of action. Therefore, the HHRP thought it would be best to bring together and synthesize all of the research related to oxidative stress in a single theme. Dr. Geller indicated that as the HHRP moves toward identifying toxicity pathways and modes of action rather than focusing on specific compounds, it may be worthwhile to reconsider whether separating out oxidative stress is appropriate. Dr. Klaunig agreed that this was a good point.

Going into more detail on each of the themes, Dr. Preston noted that two posters relevant to the first theme would be presented at the face-to-face meeting, focusing on the application of toxicogenomics to risk assessments and on the more specific topic of the use of toxicogenomics in the discrimination of conazoles and related chemicals from phenobarbital. All three of the Theme 2 posters will focus on non-cancer endpoints (birth defects, pregnancy loss, and neuroendocrine function). One of the posters in Theme 3 will discuss how ORD research on mode of action contributes to the risk assessment for polybrominated diphenylether (PBDE) mixtures, and the second would focus on arsenical metabolism and dosimetry. Dr. Preston explained that the LTG 1 project on arsenic, which was originally designed to investigate cancer risk at low arsenic concentrations, had been re-evaluated in a series of meetings with the program offices and an outside advisory group, and has been modified to concentrate on the dosimetric aspects of arsenic toxicity and carcinogenicity. Thus, the project has changed its focus to physiologically based pharmacokinetic (PBPK) modeling for estimating effective doses to target tissues. For the fourth theme, one poster will focus on progress toward the use of oxidative stress as a broadly applicable key event in environmental toxicity, and the other will focus on future application of oxidative and other stress pathways to mode of action studies. Dr. Preston said that the HHRP was seeking guidance on how oxidative stress fits into a risk assessment framework. Four posters on developmental programs will be presented related to Theme 5, focusing on systems biology and toxicity testing, the development of virtual tissue models such as the virtual liver, the development and use of biologically based dose response (BBDR) models, and constructing a BBDR model to refine risk assessment approaches to respiratory effects from inhaled chlorine.

In conclusion, Dr. Preston stated that the HHRP is firmly of the view that the current LTG 1 research program, represented by the first 10 abstracts/posters, meets its goal of addressing the requirement for risk assessors and risk managers to use ORD's methods, models, or data to address uncertainty in risk assessment using mechanistic or mode of action information. In developing plans for the future, as exemplified in abstracts 11 through 14, the HHRP will be initiating an integrated toxicology-systems approach to respond to the challenges presented by EPA's Futures of Toxicity Testing Strategic Plan and the National Academy of Sciences Report on the Future of Toxicity Testing. These approaches take advantage of new whole genome assessments and their link to adverse outcomes in animal models and ultimately humans through the application of a mode of action and human relevance framework. Modes of action and key events are still the framework, at least for LTG 1, but the Program will be moving in new directions to take advantage of new technology.

### **Public Comment**

At 12:30 p.m., Ms. Houk called for public comment. No comments were offered.

### **Overview of LTG 2: Cumulative Risk**

*Dr. Linda Sheldon, EPA, ORD, National Exposure Research Laboratory (NERL), Associate Director for Human Health*

As background, Dr. Linda Sheldon noted that EPA is responsible for public health protection from environmental stressors. To do that, the Agency determines whether protective actions need to be taken, what those actions should be, and whether those actions have had an impact. To determine whether to take action, the Agency uses the risk assessment process. Risk, as defined in the early 1980s by the National Research Council (NRC), is the product of exposure and hazard. Historically, a very simplistic approach to risk assessment was used because the focus was on a single chemical acting through a single pathway, and most of the situations addressed involved high concentrations of high-toxicity substances. The problems were obvious (e.g., when EPA was founded, an Ohio River was on fire), and highly sophisticated risk assessment was not needed. Today's complex problems, however, often involve exposure to low levels of multiple chemicals and other stressors, the health effects of which may be poorly understood. Putting that information together is much more difficult. Among other questions, one must ask which of various regulatory options is most appropriate and whether any of the options might create new risks.

The Food Quality Protection Act (FQPA) and Safe Drinking Water Act (SDWA), passed in the late 1990s, required EPA to take the following factors into account in risk assessment:

- ✧ Aggregate exposures (exposures to a single substance from all sources, routes, and pathways).
- ✧ Cumulative risk (risk from aggregate exposures to all chemicals with a common mode of action).
- ✧ Special considerations for susceptible populations (e.g., infants and children, elderly people, groups with pre-existing disease).

Thus, there was regulatory pressure to begin to understand cumulative risk and aggregate exposure.

In addition, various groups—including the last BOSC program review, as well as the National Academy of Public Administrators, environmental justice groups, the EPA Risk Assessment Forum, and a 1997 memorandum from the EPA Administrator—have called for broadening the scope of cumulative risk to encompass risks associated with exposure to multiple stressors, including social, economic, and behavioral factors as well as chemicals.

To meet the needs described above, improved tools are needed. The current tools for risk assessment are blunt, and there is little linkage between measures of exposure and measures of health outcomes. Understanding cumulative risk will require moving beyond these tools. A systems approach is needed to describe and link processes to create more predictive models. The

NRC report *Toxicity Testing in the 21st Century* articulated the need for new tools and approaches for risk assessment and incorporated a systems approach. The research under LTG 2 is consistent with this vision, but EPA has enlarged the exposure component of the systems approach. The LTG 2 approach does not look at *in vitro* assays for assessing toxicity but it does look at the processes to determine how to link models. This is research that was designed 5 to 7 years ago; it has evolved during that period and will continue to evolve during the next 5 to 6 years.

A systems approach is feasible because understanding of biological systems and exposure processes is improving and because new tools—including better and more sensitive analytical methods, new “omic” tools, advanced computational methods, and better computing power—are available and are constantly being developed further. The development of increased computational power has been crucial. In the Air Program, for example, 5 or 6 years ago the Agency could not make practical use of its model for forecasting air quality because it took 4 or 5 days to model a single day of air pollution. Today, with advanced computational models, it is possible to predict air pollution levels throughout the United States for a full season. Models from exposure through to outcome require this kind of computational power.

The overall goal of LTG 2 research is to develop scientific knowledge and tools to understand and predict cumulative risks that reflect real-world situations in which people are exposed to multiple chemicals and other stressors. The three research tracks in LTG 2 are as follows:

- ✧ Track 1: This track focuses on the development of the science that is needed to perform the legislatively mandated cumulative risk assessments. The overall goal is to develop and enhance the scientific understanding, data, and modeling tools for cumulative risk assessments, focusing on chemicals with common modes of action. Fundamental research is being conducted to determine how chemicals interact biologically, to determine whether there is dose additivity, and to investigate modes of action, mechanisms of interaction, low dose effects, and links between toxicity and PBPK outputs. Exposure levels and co-occurrence of chemicals and linked exposure/PBPK models also are being studied, and doses at target tissues are being calculated to understand how multiple chemicals affect a target tissue over time. LTG 2 has been working very closely with program offices, particularly the Office of Pesticide Programs (OPP), to provide them with the tools that they can use to conduct cumulative risk assessments. An iterative approach is being used to develop and apply methods for specific risk assessments, including those pertaining to organophosphate pesticides (as reported in the last BOSC review), carbamate pesticides (this work has been completed), and pyrethroid pesticides (this work is in progress). For this track, there will be six posters at the face-to-face meeting: an overview poster and five posters on specific topics, including posters that will explain the work on cumulative risk assessments for carbamate and pyrethroid pesticides.
- ✧ Track 2: Evaluation of biomarkers and bioindicators to enhance cumulative risk assessments and to help understand the processes and linkages that lead to risk. The goal is to develop scientific knowledge and tools that will allow biomonitoring data to be used to improve future cumulative risk assessment. Efforts are being made to understand how to predict human exposures from exposure biomarkers by analyzing existing databases for

relationships, developing exposure/PBPK models, and developing methods for reverse dosimetry. Dr. Sheldon noted that the FQPA says that assessments must be based on high-quality, high-quantity data or models based on reliable data. On the exposure side, there is only a small quantity of data. On the other hand, extensive biomonitoring data are available from the Centers for Disease Control and Prevention (CDC), the National Health and Nutrition Examination Survey (NHANES), and other sources. The question is how best to use the data in risk assessment.

- ✧ Track 3: Evaluation of cumulative risk from chemical and non-chemical stressors, moving beyond regulatory mandates to evaluate risks in the real-world context of public health protection. The goal of this track is to develop methods to evaluate risk for exposures to both types of stressors for use in cumulative risk assessments, in epidemiological studies such as the National Children's Study, and in evaluating risk management options and outcomes. The approach involves a focus on community because fundamental issues occur within this domain. Evaluation of the state-of-the-science and development and application of tools also are priorities. Currently, the Program is studying exposures; ultimately, this will be linked to risk.

The overall goals of these three tracks—to understand the processes along the continuum and to develop models that mathematically describe and link processes—relate to other LTGs and Multi-Year Plans (MYPs) in several ways. Data developed in LTG 1 and LTG 3 are used to develop and evaluate models. The results of LTG 2 enhance the science and tools used in other LTGs and MYPs. The linked source-to-outcome models developed in LTG 2 feed into LTG 3 and are applied directly in LTG 4. Cumulative risk assessment methods are used directly by EPA's OPP in assessing risk from pesticides. The guidance for collecting and using biomarkers developed under LTG 2 will be used to improve future exposure and epidemiologic studies. Methods for assessing cumulative exposures in communities will be used in future studies, for community risk assessments, and by EPA regions and local communities to assess risk options.

Dr. Edo Pellizzari asked Dr. Sheldon to clarify the distinction between aggregate and cumulative exposure. Dr. Sheldon responded that aggregate exposure is exposure to a single chemical from all sources, routes, and pathways. Cumulative exposure is exposure from all chemicals that have a single mode of action.

Dr. George Daston commented that it would be helpful to see examples of how the systems approach is being applied. Dr. Sheldon replied that this is the direction in which the Program is trying to go, for example, in the pyrethroid risk assessment, but that the goal has not yet been achieved. Dr. Daston expressed concern that the data are 95 percent exposure and 5 percent other aspects of risk and said that he would like to see greater integration. Dr. Sheldon answered that the biological work in this LTG is to look at the impact of multiple chemicals; the integrative work is being done to a greater extent in LTG 1. Dr. Daston indicated that he was confused about the community approach to multiple stressors and how it would be helpful in risk management. He would like to see greater clarification of the community approach at the face-to-face meeting in January.

Dr. Schwartz said that, at the January meeting, he would like to see more information on multiple chemicals and population average risk, depending on whether there is a correlation among exposures to different chemicals. Similarly, differences in genetic susceptibility can affect risk. He would like to see information on the distribution of risk in these kinds of scenarios.

### **Overview of LTG-3: Susceptible and Vulnerable Populations**

*Dr. Devon Payne-Sturges, EPA, ORD, NCER, Assistant Center Director for Human Health*

Dr. Devon Payne-Sturges stated that ORD's research plan for LTG 3 involves addressing the requirements for risk assessors and risk managers to use ORD's methods, models, and data to characterize susceptible and vulnerable populations and provide adequate protection for them. This research is of great importance because risk may be far higher for vulnerable or susceptible individuals than for the average person. Thus, quantifying risks for vulnerable or susceptible populations could significantly affect policy, programmatic, and regulatory decisions by EPA and other regulatory agencies, including state and local government agencies. In some situations, the risk to the average person may be acceptable but the risk to a vulnerable or susceptible person may be unacceptable. Therefore, LTG 3 research is critically applicable to public policy.

Key research questions include whether there is differential life-stage responsiveness or exposure to environmental contaminants, including special effects of aging and in children; which methods and models are appropriate for longitudinal research with children; and how predisposing factors for diseases such as asthma and the indoor air environment affect susceptible populations. Current studies are focusing on life stages and asthma as conditions affecting human susceptibility.

LTG 3 uses the environmental public health paradigm, also known as the exposure-dose-effect paradigm, a conceptual model that links contaminant formation and release from its source to transport and transformation in the environment, then to human exposure, followed by entry into the body, early signs or effects indicative of altered structure or function, and finally adverse health effects. The greatest gaps in knowledge in this model involve susceptibility, which can influence exposure or modify the health effects of exposure to environmental contaminants.

Susceptibility is a subset of the broader concept of vulnerability. The term *vulnerability* encompasses both inherent sensitivity/susceptibility and external factors. Populations may be vulnerable based on:

- ✧ Susceptibility/sensitivity factors such as age, gender, genetic predisposition, or pre-existing health conditions;
- ✧ Differential exposure, for example, as caused by economic structural inequalities, lifestyle factors, cultural practices, dietary factors (such as subsistence fishing), activity patterns, and proximity of homes, playgrounds, farms, or gardens to a pollutant source;
- ✧ Differential preparedness because of immunizations against diseases, nutrition, social capital, or other factors; and/or

- ✧ Differential ability to recover because of differences in healthcare access, general health and nutritional status, psychosocial stressors or support, and other factors.

Vulnerability is a research focus of the HHRP. Aspects of vulnerability will be highlighted in the LTG 3 posters. The HHRP's research emphasizes inherent susceptibility/sensitivity factors and differential exposures, which EPA generally evaluates at an individual level, although others outside the Agency may evaluate it at the neighborhood or societal levels. Asthma is a specific focus of LTG 3 research, but other pre-existing conditions, such as cardiovascular disease, kidney disease, liver disease, and prematurity, also can affect susceptibility. Differential preparedness and differential ability to recover will be investigated in the future, and the HHRP is interested in the BOSC members' thoughts on this research. A multilevel approach to the study of vulnerability is likely to provide the clearest understanding and is an emerging area of environmental research.

Both intramural and extramural research are being conducted under LTG 3, and the strengths of the two programs complement one another. For example, epidemiologic studies and community-based participatory research are conducted extramurally, while much development of assays to measure chemicals in biospecimens and PBPK modeling is intramural. The two programs share some strengths; both intramural and extramural research include exposure assessment, the use of biomarkers of human exposure, toxicological studies in animal models, and environmental sampling.

Ten of the 13 LTG 3 posters to be presented at the face-to-face meeting will cover research on life stage (Track 1) and methods for longitudinal research (Track 2); the other three will describe research on asthma (Track 3). In addition to grouping into tracks, LTG 3 abstracts can be grouped into three themes: research to understand environmentally mediated disease and life-stage susceptibility to environmental contaminants, especially pertaining to children, aging, and asthma (Theme 1); exposure factors (Theme 2); and tools, methods, and ethical considerations in conducting research on vulnerable population groups (Theme 3).

In summary, LTG 3 research is multidisciplinary. It builds on the strengths of both the intramural and extramural programs, and it is highly productive. The number of published papers from LTG 3 is higher than from the other LTGs. LTG 3 provides findings that inform and uses the results of the other LTGs. It has impacts on the following activities:

- ✧ Exposure and risk assessment practice, especially the use of uncertainty factors to protect susceptible and vulnerable populations. For example, epidemiological studies of children have provided parallel information on health effects of specific environmental contaminants that have been noted in animals. This information strengthens animal-based risk assessment.
- ✧ Regulatory development at the federal level, such as pesticide safety factors and farmworker safety practices.

- ✧ State and local interventions, such as implementing integrated pest management in public housing, California's new legislation limiting siting of new schools in proximity to major roadways, and New York City's conversion of its bus fleet to clean diesel.
- ✧ Community-based participatory research and research translation. LTG 3 has demonstrated that community-based participatory research enhances data quality and quantity and the relevance of collected data and information dissemination, improves research definition and direction, enhances translation of research into policy, and increases the trust of community residents toward funding agencies and academic researchers.

LTG 3 research is forward thinking. Stable birth cohorts, mainly from the Children's Research Centers, will allow examination of the influence of social factors on exposure and toxic effects. Longitudinal studies, such as the National Children's Study, will enable LTG 3 researchers to test the developmental origins of adult disease hypothesis. The new Duke Southern Center on Environmentally Driven Disparities in Birth Outcomes will determine how environmental, social, and host factors jointly contribute to health disparities. Finally, research results from LTG 3 will contribute to the development of a community-specific risk assessment program under LTG 2.

#### **Overview of LTG 4: Developing Tools To Evaluate Risk Management Decisions**

*Dr. Andrew M. Geller, EPA, ORD, NHEERL, Assistant Laboratory Director for Human Health and Computational Toxicology*

Dr. Geller began his presentation by emphasizing that EPA is a regulatory agency with a public health mission. The Agency exists to protect human health and the environment, but at times the connection between the Agency's regulations and public health gains can be difficult to elucidate. LTG 4 is focused on just that—providing risk managers and risk assessors with methods and models to evaluate risk management decisions through the development, evaluation, and linkage of indicators of environmental health.

LTG 4 involves two research tracks, which address the following key questions:

- ✧ What are the trends in health status in the United States?
- ✧ What tools are available to determine the impact of regulatory decisions on exposures to environmental stressors that lead to adverse health outcomes? This track involves the development of tools through projects that involve collaboration between intramural staff in program and regional offices and Science To Achieve Results (STAR) grantees.

LTG 4 is about accountability and assessing the effectiveness of the Agency's risk management decisions. This requires "closing the loop" that includes assessment of risk, informing risk management options, and assessing the effectiveness of decisions. The drivers of this research include a 1997 NRC report that called for confirming that environmental policies are having the desired effect, the 2001 ORD Strategic Plan, the 2001 EPA Environmental Indicators Initiative, the 2003 EPA Strategic Plan, the 2003 ORD Human Health Research Strategy, and a 2004 Government Accountability Office (GAO) report stating that EPA should identify specific

milestones, resources, and other requirements for developing and using environmental indicators. Overall, in LTG 4, the Agency develops, evaluates, and links indicators that can be used to demonstrate the effectiveness of risk reduction and risk management decisions. LTG 4 has been given the task of evaluating how well the Agency assessed a risk and determining what adjustments might need to be made. The goal of this program is not to second-guess the Agency's program offices; it is to develop additional data to better understand whether EPA has achieved what it intended to achieve and to predict the public health impact of the Agency's actions.

Information about such factors as mode of action, cumulative risk, and susceptibility that is generated in the other three LTGs is used in this endeavor for two purposes: (1) to address uncertainty and characterize variability to improve risk assessment, and (2) to assess the public health impacts of risk management decisions. For example, in the case of asthma, under mode of action, scientists develop an understanding of the immune response and the allergic airway disease, which is the mode of action of induction of asthma. They must understand cumulative risk, which is the relative potency of dust mite allergens and particulate matter for eliciting and inducing asthma. They also must understand susceptibility—those life stage-specific processes or gene-environment interactions that contribute to asthma. As these data stream in, they contribute to the scientific basis for rulemaking. On the other side are tools to assess the effectiveness of risk mitigation strategies on the induction and maintenance of asthma.

One research track under LTG 4 examines trends in human exposure and health status, using data from a variety of sources. The Human Exposure and Health chapter in EPA's *Report on the Environment* presents biomonitoring and health outcome indicators to address three fundamental questions:

- ✧ What are the trends in human exposure to environmental contaminants?
- ✧ What are the trends in health status in the United States?
- ✧ What are the trends in human diseases and conditions for which environmental contaminants may be a risk factor, including across population subgroups and geographic regions?

The primary sources of data for biomonitoring indicators are the CDC and NHANES. For looking at trends in health status, HHRP depends on many sources, including the National Center for Health Statistics. Challenges in this track include developing an integrated set of health indicators for use at all spatial and time scales, developing indicators that would allow risk assessors and risk managers to distinguish acceptable from unacceptable conditions, and establishing links between indicators of exposure and changes in risk of a public health outcome. At the present time, systematic linking of indicators at different levels is lacking; developing those links is an important research challenge.

Another research track under LTG 4 involves tools for evaluating outcomes of risk management decisions. Assessing the impact of such decisions is an integral part of the risk assessment and risk management paradigm. This requires understanding linkages in the source-to-exposure-to-effects paradigm, so that valid indicators of health outcomes can be developed.

Assessing outcomes of risk management decisions involves six linked levels of measures: (1) laws, rules and guidance; (2) process measures; (3) reduced emissions or toxicity; (4) reduced ambient levels; (5) reduced exposure or body burden; and (6) improved human or ecological health. Most of the measures in use today are at levels 1 through 4; there is a lack of data at levels 5 and 6. For example, efforts to evaluate the impact of a rule to enhance the microbiological safety of drinking water might be evaluated through a Level 3 measure (measuring changes in the pathogen load at a water treatment plant) or a Level 4 measure (measuring the change in pathogen load in tap water at homes), but it would be more meaningful to use a Level 5 measure (measuring changes in biomarkers of exposure to pathogens) or a Level 6 measure (measuring changes in gastrointestinal events associated with pathogen exposure); this is not being done currently.

Another, more population-based approach to evaluating risk management decisions is to use existing databases to evaluate processes, exposures, and outcomes at the population level. The last BOSC review called for devoting increasing resources to this effort. Much of the research here is extramural, involving large-scale epidemiology.

The HHRP is framing its research to support the effort to assess the effectiveness of risk management by reducing uncertainties in risk assessment and developing and linking valid indicators of risk. Through the development of better indicators, it should be possible to provide better answers to the questions of whether mitigation of a potential risk is necessary, how best to mitigate the risk, and whether mitigation was successful.

In conclusion, the HHRP has moved forward on LTG 4 by drafting the Framework document (available to Subcommittee members on the CD) and by dedicating intramural and extramural resources to building the elements necessary to make the necessary linkages from source to outcome. There are great challenges in this area, including the gaps between federal regulatory decisions and their implementation at local levels, the multiple determinants of disease, and temporal lags between exposures and ultimate outcomes. Nevertheless, the program retains the potential to serve as a unifying theme for the HHRP and to provide EPA with invaluable tools for assessing the impacts of its actions.

Dr. Blanc commented that the work under LTGs 3 and 4 seems strongly disconnected from that under LTG 1 in that nothing under methods development would seem to impact the goals as delineated here. For example, because there does not seem to be any work on ecological epidemiologic methods or qualitative research methods, it is difficult to see how, from a methods point of view, these goals are being promoted. The impression is that EPA is dependent on research conducted by others, especially epidemiologic research, and is not systematically addressing research needs. Dr. Geller replied that the Agency actually is involved in some efforts in ecological epidemiology, including work with pesticides, where the acreage of different crops is used as a surrogate for pesticide exposure and put together with health data at the county level in research intended for hypothesis generation. As the Agency goes forward and recognizes its limitations in terms of the research it can do in field epidemiology, it is investing in greater access to health databases, putting together environmental quality indicators with public health indicators to see whether associations can be detected.

Dr. Klaunig asked whether the example just described and other examples would be part of the poster presentation, and Dr. Geller replied in the affirmative. Dr. Payne-Sturges said that there would be a set of posters under LTG 3 focusing specifically on methods development.

Dr. Pellizzari commented on the “closing the loop” concept, saying that if measurements at various levels were made and were indicative of no changes in exposures or public health indicators, there would be a need for diagnostic indicators to indicate why the management decisions failed to improve public health. Would it be possible to distinguish whether it was the management decision or the state-of-the-science that led to the lack of reduction of risk? He suggested that this issue would be worth discussing at the face-to-face meeting.

### **Preparation for Face-to-Face Meeting**

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

Dr. Klaunig was concerned that the time was running out on the call to discuss plans for the workgroups. Ms. Heather Drumm pointed out that, if necessary, the workgroups could be discussed offline; such administrative matters need not be discussed in a public forum. Several members indicated that they could only stay on the line for a few more minutes.

Dr. Klaunig said that he had placed members into workgroups, taking into account their stated preferences as much as possible, and that the workgroups were as follows:

- ✧ LTG 1: Drs. Hoel, Portier, Daston, and Schwartz
- ✧ LTG 2: Drs. Blanc, Mattison, Falk, and Pellizzari
- ✧ LTG 3: Drs. Blanc, Hoel, Mattison, and Daston
- ✧ LTG 4: Drs. Falk, Portier, Pellizzari, and Schwartz

Dr. Portier agreed to be the primary author on LTG 1. Dr. Blanc expressed a preference for being an author on LTG 3 rather than LTG 2. Dr. Falk said that he would prefer to be an author, either primary or secondary, on LTG 4 rather than LTG 2. No other preferences were expressed. Dr. Klaunig said that unless he heard otherwise from members by the end of the day, he would assign members to the remaining writing assignments.

Dr. Klaunig reminded the Subcommittee members that the only matters they are permitted to discuss outside of a public forum are administrative ones; issues relating to the content review may not be discussed. He thanked members for their participation and adjourned the teleconference.

### Action Items

- ✧ Mr. Juengst will provide the Subcommittee with information on the characteristics of respondents versus non-respondents to the HHRP partner survey. Before the face-to-face meeting, he also will provide the Subcommittee with decision citation analysis data.
- ✧ Dr. Darney will provide more detailed data about responses to the partner survey, in graphic form, to the Subcommittee members before the face-to-face meeting. She also will provide the written comments from the survey respondents.
- ✧ Dr. Darney and Ms. Houk will investigate whether the results of the bibliometric analysis can be broken down into extramural, intramural, and combined categories.
- ✧ Dr. Darney will arrange for MAC experts to resolve the problems with the use of the linked Table of Contents on the CD on Mac computers.
- ✧ Dr. Klaunig will contact Subcommittee members to give them their writing assignments for the face-to-face meeting.

## PARTICIPANTS LIST

### Subcommittee Members

**James E. Klaunig, Ph.D., Chair**

Indiana University  
School of Medicine

**Henry Falk, M.D., M.P.H., Vice Chair**

Director, Coordinating Center for Environmental  
Health and Injury Prevention  
Centers for Disease Control and Prevention

**Paul D. Blanc, M.D., M.S.P.H.**

Chief, Division of Occupational and  
Environmental Medicine  
Department of Medicine  
University of California, San Francisco

**George P. Daston, Ph.D.**

Miami Valley Laboratories  
The Proctor & Gamble Company

**David G. Hoel, Ph.D.** (not present)

Medical University of South Carolina

**Donald Mattison, M.D.**

Senior Advisor to the Directors of the National  
Institute of Child Health and Human  
Development, and the Center for Research for  
Mothers and Children  
National 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

**Richard Callan**

U.S. Environmental Protection Agency

**Sally P. Darney, Ph.D.**

U.S. Environmental Protection Agency  
Office of Research and Development  
Human Health National Program Director

**Vicki Dellarco**

U.S. Environmental Protection Agency

**David Diaz-Sanchez**

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

**Heather Drumm**

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

**Michael Firestone**

U.S. Environmental Protection Agency

**Roy Fortmann, Ph.D.**

U.S. Environmental Protection Agency

**Andrew M. Geller, Ph.D.**

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

**David Herr**

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

**Ross Highsmith**

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

**Sidney Hunter**

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

**Phillip Juengst**

U.S. Environmental Protection Agency  
Office of Research and Development  
Office of Resources Management  
Administration

**Jocelyn Keehner**

U.S. Environmental Protection Agency  
Office of Water

**Danelle Lobdell**

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

**Robert McPhail**

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

**Ginger Moser**

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

**Devon Payne-Sturges, Dr.P.H.**

U.S. Environmental Protection Agency

**Dan Petersen**

U.S. Environmental Protection Agency

**R. Julian Preston**

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

**James Quackenboss**

U.S. Environmental Protection Agency  
Human Exposure and Atmospheric  
Science Division

**William Sanders**

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

**Laurel Schultz**

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

**Deborah Segal**

U.S. Environmental Protection Agency

**Maryjane Selgrade**

U.S. Environmental Protection Agency

**Linda Sheldon, Ph.D.**

U.S. Environmental Protection Agency

**Jane Ellen Simmons, Ph.D.**

U.S. Environmental Protection Agency

**Marsha Ward, Ph.D.**

U.S. Environmental Protection Agency

**Valerie Zartarian**

U.S. Environmental Protection Agency

**Hal Zenick, Ph.D.**

U.S. Environmental Protection Agency  
National Health and Environmental Effects  
Research Laboratory

**Contractor Support**

**Kathleen Meister**

The Scientific Consulting Group, Inc.

**APPENDIX A: Teleconference Agenda**

**HUMAN HEALTH SUBCOMMITTEE TELECONFERENCE AGENDA**

**December 1, 2008**

**11:00 am – 2:00 pm Eastern Time**

11:00-11:15 am	Welcome - Overview of Agenda - Summary of Ongoing Activities	Dr. James Klaunig, Subcommittee Chair
11:15 -11:20 am	BOSC DFO Remarks	Ms. Virginia Houk, Office of Research and Development (ORD)
11:20-11:35 am	Summary of Partner Survey and Bibliometric Analysis	Mr. Phil Juengst, Accountability Team Leader, ORD
11:35-11:40 am	Review Materials Update	Dr. Sally Darney, Acting National Program Director for Human Health, ORD
11:40-12:05 pm	LTG 1 - <i>Overview (20 min)</i> - <i>Q &amp; A (5 min)</i>	Dr. Julian Preston, Acting Associate Director for Health, NHEERL, ORD
12:05-12:30 pm	LTG 2 Overview - <i>Overview (20 min)</i> - <i>Q &amp; A (5 min)</i>	Dr. Linda Sheldon, Acting Associate Director for Health, NERL, ORD
12:30-12:35 pm	Public Comment	
12:35-12:50 pm	Break	
12:50-1:15 pm	LTG 3 Overview - <i>Overview (20 min)</i> - <i>Q &amp; A (5 min)</i>	Dr. Devon Payne-Sturges, Assistant Center Director for Human Health, NCER, ORD
1:15-1:40 pm	LTG 4 Overview - <i>Overview (20 min)</i> - <i>Q &amp; A (5 min)</i>	Dr. Andrew Geller, Assistant Laboratory Director for Human Health, NHEERL, ORD

1:40-2:00 pm Preparation for Face-to-Face Meeting  
- Workgroups

2:00 pm Adjourn

Dr. James Klaunig,  
Subcommittee Chair