# Overview of Human Health Research Program (HHRP): Documentation of Progress and Strategic Directions for the Future

Prepared for the 2009 HHRP BOSC subcommittee

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## Executive Summary:

The Human Health Research Program (HHRP, www.epa.gov/hhrp ), one of ORD's larger programs, is crossing-cutting by design and provides research results that EPA uses to solve environmental health problems across environmental media. As articulated in the HHRP Multi-Year Plan (MYP, 2006), the overall goal of this program is to characterize and reduce uncertainties in extrapolations inherent in the risk assessment process by elucidating the fundamental determinants of exposure and dose, and the basic biological changes that result from exposure to environmental contaminants. The over-arching premise of the program is that by defining and understanding the linkages in the exposure-to-effect continuum, this program will enable EPA decision makers to predict risk and reduce harmful exposures with increasing accuracy and precision. The program addresses four long term goals (LTGs) using an interdisciplinary approach wherein scientists with expertise in many disciplines (toxicology, systems biology, chemistry, exposure science, engineering, public health, bioinformatics) work together across ORD Laboratories and Centers and as grantees funded through ORD's Science to Achieve Results (STAR) program, to understand real world risks in our communities and develop improved means by which EPA can evaluate the effectiveness of its risk management decisions.

This documentation package supports ORD's second full review of the HHRP by the Board of Scientific Counselors (BOSC). The review consists of two public conference calls (October 10, 2008 and December 1, 2008) and a 3-day face-to-face meeting (January 13-15, 2009). The BOSC's charge is to "…conduct a retrospective and prospective review of ORD's Human Health Research Program, and evaluate the program's relevance, quality, performance, and scientific leadership." The materials in the documentation package, including those in electronic format (see Table of Contents), are designed to provide information pertinent to this charge, including the following:

- Goals and evolution of this program and its context within ORD and EPA.
- Research progress and accomplishments toward meeting its goals since the last full BOSC review in February 2005 through 2008, which defines the current evaluation period.

- Impact of the Program for EPA and its partners as evident since the HHRP was instituted in 1998, focusing on the current evaluation period.
- Changes made in response to recommendations from the mid-cycle BOSC in January 2007, and new drivers that have emerged more recently.
- Emerging drivers and issues that will influence future directions for this program in anticipation of revising the program plan in 2009.

The scientific accomplishments of the program and their impact for EPA are presented in detail during the second conference call and face-to-face meeting. The BOSC is asked to provide a rating for each LTG; therefore this documentation is presented by LTG. Senior scientists selected to coordinate the presentation of the documentation for each LTG provide overview presentations accompanied by abstracts and corresponding posters for each project. These LTG overview presentations highlight the regulatory bases and drivers for the research program, illustrate how each goal is related to and informs the others, and show how the program has impacted or is expected to impact EPA's decision making ability.

The poster sessions provide the HHRP BOSC subcommittee members the opportunity to interact with the ORD scientists who conduct the research. Posters form the "meat" of the review and are constructed to convey the scientific questions, aims, approach, results and impact of program projects. Unlike poster presentations at scientific meetings that report the results of individual studies, the BOSC posters present programmatic goals and outputs on a broad scale, telling a story that includes how intramural and extramural research addresses the fundamental questions laid out in the MYP. The face-to-face meeting also includes oral testimonials by some of the program's partners who describe the impact and usefulness of HHRP research products for their organizations.

Because the HHRP addresses broad questions that cut across programs, its research products are used by diverse partners within and outside EPA. Most of the partners listed below are represented on HHRP's Research Coordinating Team and provide regular input to insure that the HHRP remains responsive to their highest priority needs.

- EPA Program Offices, especially the Office of Air and Radiation (OAR), the Office of Water (OW), and the Office of Prevention, Pesticides and Toxic Substances (OPPTS), and EPA's Office of Children's Health Protection.
- EPA Regions (along with state and local government and health organizations) through collaborations such as RARE and CARE projects.
- ORD's Research Programs, especially those with health components such as Clean Air, Drinking Water, Safe Products/Safe Pesticides, and Endocrine Disruptors.
- ORD Centers:
    - The National Center for Environmental Assessment (NCEA), with HHRP providing data and models related to the goals of the Human Health Risk Assessment MYP;
    - The National Center for Computational Toxicology (NCCT), with HHRP collaborating on projects related to the CompTox implementation plan.
- Federal partners, particularly at NIH: CDC, NICHD, NIEHS.

This documentation package also provides information derived from a variety of program assessment/evaluation approaches, some of which are relatively new to the BOSC review process. For example, it includes the results of a survey that ORD conducted to solicit feedback from the HHRP partners listed above regarding the relevancy and usefulness of HHRP data, methods, models and advice for their regulatory and risk assessment needs. A thorough bibliometric analysis of the HHRP publications since 1998, and an analysis of EPA decision documents for citations of HHRP products, are also provided to help the BOSC evaluate the quality and relevance of HHRP outputs. In addition, a summary of ORD's internal tracking of annual performance goals with associated performance measures is included as an indicator of the program's timeliness and accountability. These and other measurement approaches are responsive to recommendations in the 2008 National Research Council (NRC) report *Evaluating Research Efficiency in the U.S. Environmental Protection Agency.*

As mentioned above, the BOSC is charged with conducting a review that is prospective as well as retrospective. Hence this documentation package includes information about new drivers that will influence the strategic directions of this program in the future. Clearly NRC's report *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy* published in 2007 shortly after the mid-cycle BOSC, is a major driver for this program and for ORD in general. Other imminent NRC reports expected to significantly influence this program include: *Health Risks of Phthalates* (expected in 2008 and directly relevant to cumulative risk assessment), *Improving Risk Analysis Approaches used by the US EPA* (anticipated in 2008), *Public Health Decision-Making under Uncertainty* (anticipated in 2009), and *A New Biology for the 21st Century: Ensuring that the United States Leads the Coming Biology Revolution* (anticipated in 2010). The fields of environmental health science and risk assessment are on the cusp of a revolution in which information gathered in the past, often on individual contaminants and under specific situations, will be integrated and evaluated using a systems approach that takes advantage of advanced computer power and modeling strategies. This documentation package will illustrate how ORD is positioning itself to lead this revolution.

## Evolution of ORD's Human Health Research Program

The current HHRP MYP (2006), provided with this documentation package, represents an extension and revision of the first formal HHRP MYP (2003); however, its roots go back much farther in time. ORD has long recognized the need for research to strengthen and improve EPA's risk assessment methods and approaches and reduce the inherent uncertainties. In the 1990s EPA's National Health and Environmental Effects Research Laboratory (NHEERL) formalized a program called "Research to improve health risk assessment" with this specific goal in mind. Subsequently, a team of ORD scientists, under the executive direction of Dr. Hal Zenick (Laboratory Director, NHEERL) developed the Human Health Research Strategy document (2003) that identified and prioritized the research needed to "improve the scientific foundation for health risk assessments." This document (provided electronically) laid out two overall strategic directions that continue to guide the program. From its formal inception as a major ORD research program, HHRP has been viewed as a cross-cutting program involving multidisciplinary research with results and products that are of general use to multiple EPA program offices and regions. Congress has provided relatively stable funding for this program over the last ten years, indicative of its support for a program of broad scope and that includes a significant extramural component.

The first full BOSC review of HHRP took place in February of 2005, evaluating programmatic relevance, quality, performance and scientific leadership over the preceding four to five years. Thus, the initiation date for the HHRP and the body of research defined by its bibliography was somewhat arbitrarily set at 1998, although human health research has been ongoing in ORD since the 1980s. During the previous performance period HHRP included research conducted by the National Center for Environmental Research (NCEA). Since that time NCEA, under the direction of Dr. Peter Preuss, has developed its own MYP (www.epa.gov/hhra and is now considered an HHRP partner (user of HHRP research findings). HHRP research is currently designed and prioritized to provide data, methods and models to NCEA (along with its longer standing program office partners).

Shortly after the last BOSC review, ORD inaugurated the National Center for Computational Toxicology (NCCT, www.epa.gov/comptox) under the direction of Dr. Robert Kavlock. Some of the scientists working in HHRP and having expertise in modeling structure-activity and dose-response relationships migrated to this new center, which is now viewed as an HHRP partner. During this transition, HHRP scientists have continued to collaborate with NCCT to provide data (particularly on molecular and genomic toxicity pathways and dose response) for incorporation into NCCT models. With an increased focus on toxicity pathways, application of systems biology approaches, and the development of virtual models in both programs, this partnership between HHRP and NCCT is expected to grow ever stronger in the future.

The current MYP (2006) reflects these changes. The four LTGs are similar to those in the 2003 plan but reflect the increasing emphasis on the need to integrate data, methods, and models relevant to individual compounds in order to address cumulative risk from related chemicals (with respect to both exposure models and effects predictions) and to extend those findings to assess community risks from a large variety of chemical and non-

chemical stressors. The LTGs were also reformulated to focus on outcomes, i.e. *use* of the research products by partners, and to address susceptibility issues based on life stage with emphasis on children's health and impacts on aging populations. In addition, the 2006 plan placed increased emphasis and resources on identifying indicators by which EPA could evaluate the effectiveness of its risk management decisions. This shift is evident in research conducted by ORD's intramural program and in the definition of research needs articulated in NCER's Requests for Applications (RFAs). Detailed descriptions of these changes and all responses to the 2005 BOSC review are provided in the materials for the 2007 mid-cycle review which are included with this documentation package.

The MYP lays out a critical path for each LTG, including the identification of Annual Performance Goals (APGs) as stepping stones along the path, and Annual Performance Measures (APMs) as milestones to achieving the APGs. ORD has since revised its approach for MYPs, recognizing that MYPs must be "living documents" based on the inherent nature of scientific research. Thus, the APMs identified in 2006 have changed over time as the research results come in and adjustments are made. ORD has decided that future MYPs will provide APMs as an appendix that is updated on an annual basis considering research findings, emerging research issues, budgetary constraints and changing Agency priorities. ORD tracks the completion of APGs, along with the APMs contributing to those APGs. A summary report is provided as a measure of program performance (see section on program management and evaluation).

Achieving the ambitious goals set forth in the 2006 MYP requires both intramural and extramural efforts and their integration. Over the last ten years, NCER's Science to Achieve Results (STAR) program has developed RFAs that are directly responsive to HHRP goals, and has funded an array of outstanding grantees, either as individual grants or as program projects. A spreadsheet is provided with this documentation package that summarizes these RFAs and provides electronic links to program and project descriptions on NCER's website. As will be detailed under LTG 3 presentations, the Centers for Children's Environmental Health Research program, co-funded with NIEHS, has a stellar record for implementing epidemiological research on the impact of environmental factors on children's health. The major accomplishments of the first decade of this program were recently synthesized in an NCER document "A Decade of Children's Environmental Health Research" (a key product included in this documentation package). This Center program will transition into its second decade with the release of a new RFA in November 2008. The list of past, ongoing, and planned NCER RFAs funded by HHRP illustrates the responsiveness of NCER to the LTGs and objectives of the HHRP (see text box).

***NCER RFAs funded by HHRP with primary LTG identifier****

- Centers for Children's Environmental Health & Disease Prevention Research, 1998, 2001, '03, '05, '08 (LTG 3, supports all LTGs)
- Children's Vulnerability to Toxic Substances in the Environment, 2001 (LTG 2&3)
- Complex Mixtures, 2000 (LTG 2)
- Biomarkers for the Assessment of Exposure & Toxicity in Children, 2002 (LTG 3)
- Lifestyle & Cultural Practices of Tribal Populations & Risks from Toxic Substances in the Environment, 2002, 2007 (LTG 2)
- Application of Biomarkers to Environmental Health & Risk Assessment, 2004 (LTG 2)
- Early Indicators of Environmentally Induced Disease, 2004 (LTG 3)
- Interpretation of Biomarkers using Physiologically Based Pharmacokinetic Modeling, 2007 (LTG 2)
- Development of Novel Environmental Health Outcome Indicators, 2007 (LTG 4)
- Planned: Community-based Cumulative Risk Assessment (LTG 2)
- Planned: Novel Approaches for Assessing Exposure for School-Aged Children in Longitudinal Studies (LTG 2 & 3)

*Black text indicates past RFA, red indicates current, and blue indicates planned.

The HHRP planning process insures that the extramural program solicits research that the intramural program is either not well equipped to conduct, or that can best be conducted in a cooperative manner. For example, a new RFA underdevelopment will solicit epidemiological research to explore non-chemical stressors and economic and sociological factors that impact vulnerability to environmental contaminants, and thereby capitalize upon the broader expertise available in the academic community.

## Changes in the Human Health Research Program in response to the mid-cycle review (2007) and newly emerging drivers

HHRP underwent a mid-cycle BOSC review in January 2007. Based upon the program's accomplishments (late 2004 through late 2006) and responsiveness to the recommendations from the 2005 BOSC review, the BOSC rated HHRP "meets expectations" in its report of July 23, 2007. That report included a list of new and continuing recommendations to which ORD, in turn, responded in a report to the BOSC Executive Committee in January 2008. The three documents associated with the mid-cycle BOSC are provided for reference with this 2009 documentation package, and summarized below.

Many of the 2007 BOSC recommendations related to new directions and initiatives described at the 2007 mid-cycle review. For example, the first recommendation encouraged HHRP to increase involvement of its partners in research planning and to pursue the initiatives described for LTG 4 on evaluating the effectiveness of risk management decisions and on community based risk assessment (LTG 2). Overviews and posters under LTGs 2 and 4 of the current review provide details of HHRP-specific progress on these initiatives.

Seven of the 19 recommendations related to clarifying and/or increasing efforts under LTG 4**.** In response, HHRP committed to: "….continue to work toward greater partner involvement in planning and evaluating research products and develop emerging research areas such as community risk assessment and evaluation of public health impacts of risk management decisions;…to work with its scientists and partners to define the scope of LTG 4 to reflect the growing emphasis on evaluating and demonstrating the impact of its research on improving environmental health;" and "...on approaches to capture information on public health impacts of risk management decisions;" and to "…broaden its mission statement to reflect the greater diversity of information and participation necessary to achieve the objectives of LTG 4."

Progress towards this end is detailed in the LTG 4 overview and six associated posters. Briefly, HHRP contributed to the Health Chapter of the 2008 *Report on the Environment* in which the need for better environmental health indicators and research on evaluating public health impacts is emphasized. This chapter now serves as a major driver for future HHRP planning. HHRP scientists also developed a document entitled *A Framework for Assessing the Public Health Impacts of Risk Management Decisions* (2007) and held a workshop in January 2008 on this topic. This workshop featured updates on two pilot projects currently underway in collaboration with scientists in Region 1, and grants funded under a 2007 NCER RFA on this topic (*Development of Novel Environmental Health*

*Outcome Indicators*). Another RFA on this topic is under consideration for release in 2009 reflecting the increased emphasis on LTG 4. Consideration is being given to funding some of these projects as cooperative agreements whereby intramural scientists can collaborate with STAR grantees.

HHRP appreciates that the regions encounter real world exposures wherein ORD's advice and assistance is particularly relevant. HHRP scientists are currently collaborating on several projects in ORD's Regionally Applied Research Effort or RARE program. HHRP is also initiating meetings with ORD's Office of Science Policy (OSP) to foster collaborations between HHRP's intramural scientists and EPA's regional scientists related to regional needs. Furthermore, HHRP is developing a workshop in collaboration with Region 5 on cumulative risk assessment (planned for late 2009) that is obviously relevant to LTG 2. In summary, HHRP has expanded its focus and efforts in LTGs 2 and 4 and is seeking opportunities for leveraging these efforts with other organizations. Recommendation 14 was to obtain additional resources for demonstration projects in LTG 4. In 2008, funding added to the ongoing projects was made possible by a congressional add-back to the Human Health, and future plans will depend upon the findings of the two pilot projects. However, funding for new projects is uncertain. Therefore HHRP is adding emphasis on partnering with ongoing studies or using existing data to address this goal. Especially for observational and epidemiological studies, the STAR program can serves as a platform for such collaborative research. Future emphasis on the potential impacts of global warming or biofuels on human health may provide additional opportunities for new projects under LTG 4.

The NRC released its report on *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy* (2007) about six months after the HHRP mid-cycle review. In response to that report and as will be detailed under LTG 1, EPA has entered into a memorandum of understanding with the National Human Genome Research Institute and the National Toxicology Program to collaborate in efforts to transform toxicity testing. The approach is to develop and validate high through put assays and elucidate molecular pathways of toxicity to improve the efficiency and effectiveness to testing, and to conduct targeted in vivo research to anchor the predictive power of the high through put systems. HHRP will participate in this effort in cooperation with NCCT. This new effort, including the movement towards incorporating a systems biology approach, is detailed further in the last three posters under LTG 1.

The mid-cycle BOSC also suggested that the HHRP mission statement should be reformulated beyond addressing uncertainty in risk assessment to better convey the objectives articulated in LTG 4. LTG 4 is envisioned to design tools at the relatively local level to address regional and national problems, extrapolating from the laboratory to the real world and from the individual to the population level. These concepts will be carried over into planning activities for revising the HHRP in 2009, taking under consideration additional input from the current BOSC subcommittee.

## Program Evaluation Measures

Most of the other recommendations from the 2007 mid-cycle BOSC related to the need for better articulation of the process through which the program involves partners in planning, better ways to evaluate research products for relevance and quality, clear performance-based measures, and better articulation of investment criteria, i.e. how HHRP determines the relative effort in each LTG, and between the intramural and extramural programs.

***Involvement of partners in program planning and evaluation:***

Ongoing since the last review, HHRP continues to communicate its program accomplishments and solicit input from its partners through several channels. One of these is via regular (monthly) conference calls with the HHRP Research Coordination Team (RCT). The HHRP includes representatives from partners in ORD labs and centers, Program Offices and Regions

**HHRP Research Coordinating Committee, 2008 membership**

Sally Darney, ORD, NPD (Acting)
Carlos Nunez, Assistant Laboratory Director for Health, NRMRL
Ross Highsmith, Assistant Laboratory Director for Health, NERL
Andrew Geller, Assistant Laboratory Director for Health, NHEERL
Devon Payne-Sturges, Assistant Center Director for Health, NCER
Stan Barone, Assistant Center Director for Health, NCEA
Jerry Blancato, Deputy Director, NCCT
Ray Putnam (Region 1)
Marian Olsen (Region 2)
Ravi Rao (Region 4)
David Macarus (Region 5)
Lesley Vazquez-Coriano, Santhini Ramasamy, Crystal Rogers-Jenkins, Kesha Forest, Sandhya Parshionikar, OW
Michael Firestone, Office of Children's Health Protection and Environmental Education (OCHPEE)
Scott Jenkins, OAR
Jeff Evans, Anna Lowit, OPPTS.

HHRP is a cross-cutting program and as such, it has multiple and diverse partners, each with its own particular research needs. Because the problems addressed by HHRP are long term in nature, and not specific to a particular program office, immediate benefits of the research program may be less apparent to certain partners. Therefore, where possible, efforts are being made to target specific program elements to specific partners.. For example, one of the projects in LTG 2 is an interdisciplinary effort underway in collaboration with OPPTS to conduct research in support of OPPTS' upcoming cumulative risk assessment for pyrethroid pesticides. While long term in nature, and designed to provide methods and models for cumulative risk assessment that can be used by any program office, this project is

staged to provide specific information for a series of meetings scheduled by OPPTS's Science Advisory Panel on Pyrethroids. The study team includes a member of OPPTS's pyrethroids team (who is also a member of the HHRP RCT). This insures that HHRP products will be responsive to the program office's needs and delivered in timely fashion.

As mentioned above, HHRP also considers seeking solutions to EPA's regional offices' "real world" problems to be of high priority. The NPD and ALDs are expanding efforts to visit with partners in EPA regions (e.g., NPD spent a day with R3 recently), and to participate in program office meetings in partnership with the NPDs for the targeted research programs. For example the HHRP will participate in upcoming senior management meetings with OAR (December 2008), and OW and OPPTS (early 2009), along with the program-specific NPDs. Also, HHRP Assistant Laboratory Directors gave presentations on program office relevant aspects of HHRP when representatives from OPPTS, OW and NCEA visited the laboratories this past year. Furthermore, HHRP contributed research highlights to the Office of Children's Health Protection for incorporation into its 2007 and 2008 Annual Children's Health Highlights reports.

***Performance-based measures of program relevancy, quality and performance***

As mentioned in the response to the mid-cycle BOSC ORD developed a partner survey in 2008 and sent it to more than 200 partners in EPA program offices, regions, ORD Centers (NCEA and NCCT), and others. Examples of key research products (including those provided in this documentation package) were listed by LTG (with electronic links to these products) and partners were asked to score the relative usefulness and quality of these products. A summary report of the survey findings is provided and shows that HHRP partners consider its key products both useful and relevant to their needs, although the extent to which this is true varies somewhat by LTG. Feedback from the BOSC on the usefulness of this evaluation tool is welcome.

Peer reviewed journal articles are an established currency of research *quality* and program *productivity*. In fact, only peer reviewed data can be used in risk assessments. In addition, periodic reviews of the literature provide valuable summations of the state of the science and help to identify data gaps and rationale for research planning and prioritization. Likewise, reviews or syntheses of the results of multiple HHRP products at the end of a project, as when an Annual Performance Goal is met, also serve as indicators of program performance and effectiveness. The latter can sometimes be more useful to EPA partners and decision makers than the individual, incremental research papers. An updated bibliography of papers and chapters published under the HHRP program is included with this documentation package. It is provided in electronic format with links to the abstracts in *PubMed* where the full articles are often available.

To evaluate the *quality* of these publications, ORD conducted a thorough Bibliometric analysis of all HHRP publications (peer reviewed journal articles) published from 1998 through the first half of 2008 inclusive. A similar analysis was conducted for the mid-cycle BOSC. This analysis reports the frequency and timeliness with which HHRP papers are cited in the scientific community and the quality of the journals in which they are

published. The full report is included with this documentation package. The following summary indicates that HHRP publications continue to be of high quality and many are highly cited.

**Summary of 2008 Bibliometric Analysis**

More than one-fourth of the 2,520 Human Health journal publications are highly cited papers. 644 (25.6%) of the 2,520 Human Health journal publications qualify as highly cited when using the *ESI* criteria for the top 10% of highly cited publications. This is 2.6 times the number expected. 88 (3.5%) of the Human Health journal papers qualify as highly cited when using the *ESI* criteria for the top 1%, which is 3.5 times the number expected. 10 (0.4%) of the Human Health publications qualify as very highly cited when using the criteria the ESI criteria for the top 0.1% of highly cited publications, which is 4 times higher than the number expected. 2 (0.1%) of the Human Health publications qualify as extremely highly cited when using the criteria for the top 0.01% threshold for the most highly cited papers. This number is 10 times the number of papers expected to meet this highest threshold.

The Human Health journal publications are more highly cited than the average paper. Using the *ESI* average citation rates for papers published by field as the benchmark, in 16 of the 21 fields in which the 2,520 Human Health journal papers were published, the ratio of actual to expected cites is greater than 1, indicating that the Human Health journal publications are more highly cited than the average papers in those fields. For all 21 fields combined, the ratio of total number of cites to the total number of expected cites (47,067 to 27,118.1) is 1.7, indicating that the Human Health journal papers are more highly cited than the average paper.

More than one-half of the Human Health journal papers are published in high impact journals as determined by Impact Factor. 1,287 of the 2,520 journal papers were published in the top 10% of journals ranked by *JCR* Impact Factor, representing 51.1% of the Human Health journal publications. This number is 5.1 times higher than expected.

More than one-third of the Human Health journal papers are published in high impact journals as determined by Immediacy Index. 1,027 of the 2,520 papers appear in the top 10% of journals ranked by *JCR* Immediacy Index, representing 40.8% of EPA's Human Health journal publications. This number is 4.1 times higher than expected.

There were 15 hot papers among the 2,520 Human Health publications. Using the hot paper thresholds established by *ESI* as a benchmark, 15 (0.6%) hot papers were identified in the analysis. This is six times higher than the number expected. Hot papers are papers that are highly cited shortly after they are published.

The authors of the Human Health journal publications cite themselves much less than the average author. 1,732 of the 47,067 total cites are author self-cites. This 3.7% author self-citation rate is well below the accepted range of 10-30% author self-citation rate.

78 (1.1%) of the 6,882 authors of the Human Health journal publications are included in *ISIHighlyCited.com*, which is a database of the world's most influential researchers who have made key contributions to science and technology during the period from 1981 to 1999.

The 81 nonjournal publications were cited 220 times in journals and the authors cited themselves 16 times (7.3% self-citation rate), which is less than the literature-reported 10-30% range for author self-citation.

As shown in the next table, the results of this recent analysis compare favorably with those of the previous analysis conducted in 2006, as might be expected because the analysis is inclusive of the papers evaluated at that time (1998- most of 2006).

**Comparison of the 2006 Human Health Research Program Bibliometric Analysis Results and the 2008 Human Health Research Program Bibliometric Analysis Results**

| **Bibliometric Analysis** | **Human Health 2006** | **Human Health 2008** |
|---|---|---|
| No. of Papers Analyzed | 1,835 | 2,520 |
| No. of Papers Cited At Least Once in a Journal | 1,561 (85%) | 2,249 (89%) |
| Highly Cited Publications (Top 10% Threshold) | 462 (25.2%) | 644 (25.6%) |
| Highly Cited Publications (Top 1% Threshold) | 64 (3.5%) | 88 (3.5%) |
| Highly Cited Publications (Top 0.1% Threshold) | 6 (0.3%) | 10 (0.4%) |
| Highly Cited Publications (Top 0.01% Threshold) | 0 (0%) | 2 (0.1%) |
| No. of Times Cited | 22,937 | 47,067 |
| Expected No. of Times Cited | 13,742 | 27,118 |
| Ratio of Actual Cited to Expected Cites | 1.7 | 1.7 |
| Papers in High Impact Journals by Impact Factor | 932 (50.8%) | 1,287 (51.1%) |
| Papers in High Impact Journals by Immediacy Index | 938 (51.1%) | 1,027 (40.8%) |
| No. of Author Self Cites (%) | 992 (4.3%) | 1,732 (3.7%) |
| No. of Hot Papers (%) | 15 (0.8%) | 15 (0.6%) |

The following chart summarizes the number of papers published since 2004 arrayed by LTG. Note that the number for 2008 captures only about half the year. Also research products for LTG 4 are not anticipated yet because the projects are still underway. Also note that the number of papers is highest for LTG 3, reflecting the outputs of the Children's Environmental Health Centers, many of which also address problems in the other LTGs. LTG 3 accounts largely for discrepancies in the total number of papers each year. These numerical outputs are consistent with the allocation of FTE and resources by LTG as well (see below).

**Number of HHRP papers published per year (2004-08)**

| | 2004 | 2005 | 2006 | 2007 | 2008 |
|---|---|---|---|---|---|
| **Long-Term Goal 1:** Use of Mechanistic Information in Risk Assessment | 87 | 90 | 92 | 51 | 24 |
| **Long-Term Goal 2:** Aggregate/Cumulative Risk | 49 | 52 | 24 | 30 | 20 |
| **Long-Term Goal 3:** Susceptible Populations | 141 | 234 | 258 | 145 | 85 |
| **Long-Term Goal 4:** Evaluate Public Health Outcomes | 3 | 2 | 10 | 5 | 3 |
| Totals for Each Year | 280 | 378 | 384 | 231 | 132 |

A Bibliometric analysis does not necessarily indicate the *relevancy* of the papers to EPA's needs and their use in the conduct of risk assessments, setting regulations or justifying risk mitigation. Therefore, ORD is also "mining" EPA dockets and other toxicology and risk assessment documents for citations of HHRP papers. The results of this analysis will be included in the final documentation package.

Another indication of scientific quality and excellence is the credentials of the scientific staff who contribute to this HHRP. Over 120 principal investigators contributed to the research profiled in the posters. Their biosketches are provided in electronic format for reference and as documentation of their expertise, productivity and leadership. A list of these scientists with their position titles is also included to illustrate the diversity of expertise and capabilities in ORD laboratories and centers upon which HHRP projects can draw. This expertise is necessary for multi-disciplinary research that addresses the full range of processes from exposure to effect.

The BOSC is also charged with evaluating the scientific leadership of this program. A summary report of leadership activities conducted by HHRP scientists is provided in order to highlight their contributions to the scientific community, and advice and assistance provided to the agency. Mentorship of pre- and post-doctoral students is also considered a measure of program effectiveness because one of ORD's goals is to train the next generation of environmental scientists, including future scientific leaders for EPA. A list of trainees

conducting research funded by HHRP that includes their current place of employment shows the effectiveness of HHRP mentors in this regard.

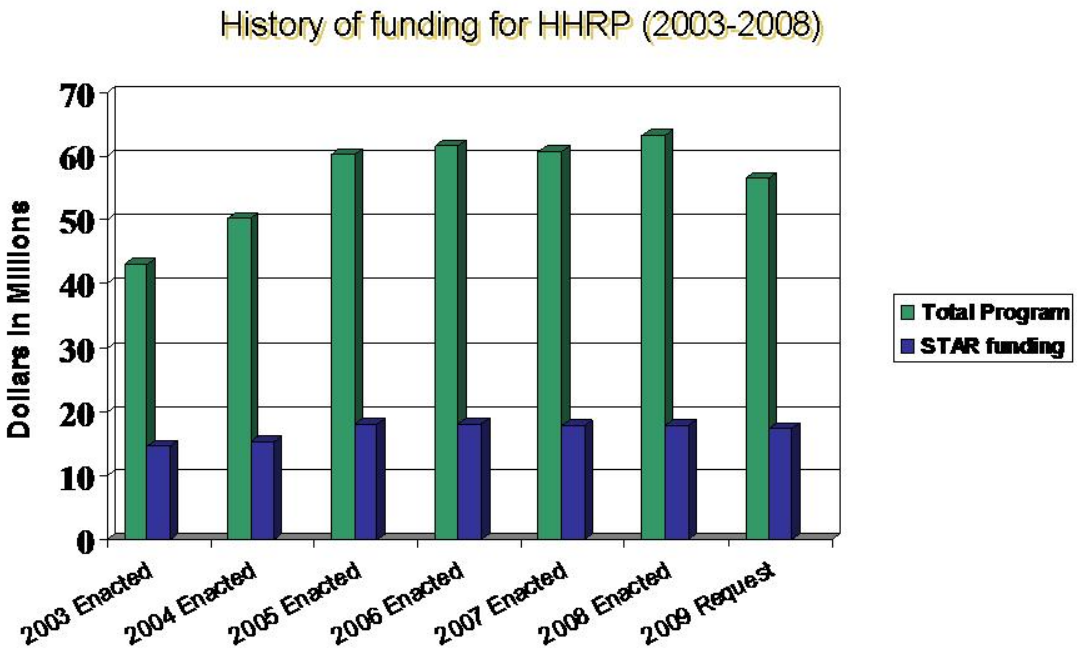
Programmatic leadership at the national and international levels is important and the mid-cycle BOSC asked for more information on the extent to which HHRP research was coordinated with other research organizations these levels. This question relates to both leadership and efficiency measures since it is obviously desirable for EPA to partner effectively in accomplishing its research mission, avoiding overlap with the efforts of other agencies, while strategically addressing the problems of most importance to EPA. A report is provided with examples of where this is being done at the HHRP and ORD level by interactions with organizations such as the Office of Economic Cooperation and Development (OECD) and leadership in planning international meetings with such organizations. Many scientists who contribute to HHRP research also contribute to targeted programs such as ORD's Drinking Water, Safe Pesticides/Safe Products, Endocrine Disruptors and Clean Air programs. Thus their participation on work groups and higher level harmonization and decision-making activities on the national and international scale reflects positively upon ORD.

In summary, a variety of program evaluation measures are provided with this documentation package. Nearly all of them are indicative of program *performance*. On the other hand, some of them are also specific indicators of program *relevancy, quality* and/or *leadership* as conveyed in the following chart.

| Documentation | Relevance | Quality | Performance | Leadership |
|---|---|---|---|---|
| MYP | x | | | x |
| HHRP overview | x | x | x | x |
| APM/APG fact sheet | | | x | |
| NCER RFA summary | x | | x | x |
| LTG overviews | x | | x | x |
| Abstracts and Posters | x | x | x | x |
| Bibliometric Analysis | | x | x | |
| Bibliography | | x | x | |
| Biosketches | | | x | x |
| Decision document analysis | x | | x | |
| Partner Survey Report | x | | x | |
| Advice & Assistance to EPA | x | | x | x |
| Leadership in Scientific Community | | | | x |
| Trainee Summary | | | | x |
| Key Products | x | x | x | x |

**Investment Criteria:**

Congress allocates human and capital resources to the HHRP under the program area Health and Ecological Research. As presented at the first conference call (October 10, 2008), and shown in the following graph, the allocations for HHRP have been relatively stable since 2005 and include ~%16 million/year for NCER (grants program). However, salaries have increased as have costs of laboratory equipment and supplies. Once these fixed costs are considered the amount of funds available for contract and cooperative agreements is greatly diminished. Also, funds available in the 2009 President's Budget (under the current continuing resolution) are lower than the 2008 enacted budget. As a consequence, the conduct of some projects, particularly observational and epidemiological studies that depend on contracts and cooperative agreements, will be impacted.

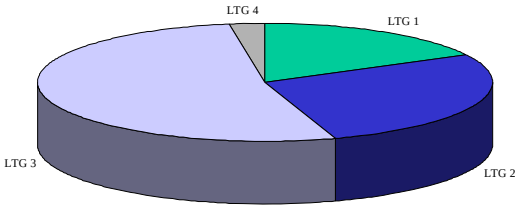



Funding levels reflect total program including payroll, travel, working capital fund, and operating expenses. STAR: Science to Achieve Results extramural grants

The following pie charts convey the allocation of HHRP resources by LTG. These charts show a relative increase in allocation to LTG 4, consistent with the increased emphasis on this goal, with a corresponding decrease to LTG 3, although LTG 3 remains the most heavily invested LTG. The higher investment in LTG 3 is in part a reflection of EPA's continued commitment to protecting children's health through research conducted by the EPA-NIEHS co-sponsored Children's Environmental Health Research Centers program.

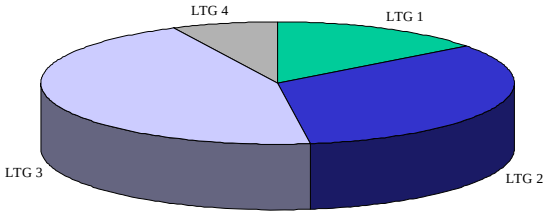
**FY 2007 Enacted**

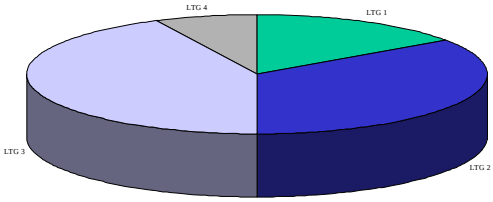
**$60.9 M**




**FY 2008 Enacted**

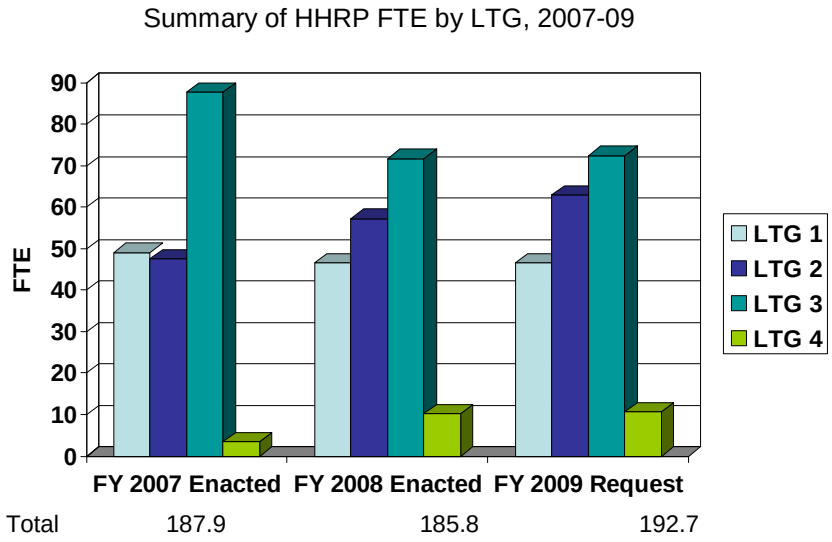
**$63.2 M**




**FY 2009 President's Budget** **$56.3 M**

These charts are consistent with the allocation of FTEs by LTG shown below. The number of FTEs allocated to LTG 4 has increased modestly with the institution of the pilot projects, although the total investment is low. Funding of the STAR RFA Development of Novel Environmental Health Outcome Indicators has increased research effort in this goal without increasing the number of federal FTE associated with it. That is, the federal FTE allocations do not reflect the number of grantees engaged in the research. The level of effort in LTG 1 is relatively stable. This number does not, however, reflect an increasing number of FTE in NCCT who are engaged in collaborative research with HHRP scientists. The decrease in FTE for LTG 3 reflects a modest decrease in the intramural program balanced by a modest increase in LTG 2 efforts reflecting an increased emphasis on community exposure assessment.




***Performance Goals***:

As described earlier, the HHRP MYP (2006) diagrams the intermediary steps towards achieving its LTGs, articulating and tracking these as Annual Performance Goals (APGs). Ideally the APGs are planned to culminate in a plenary synthesis document (or "key product"). ORD tracks these APGs and the APMs within them to provide a measure of program *performance*. As summarized below, the HHRP has completed all APGs scheduled since the last full BOSC review.

**Human Health Research Program, Annual Performance Goals, 2005-2008**

*APGs represent a program's major milestones toward accomplishing its long-term goals. The following charts outline the program's success in meeting its planned APGs on time.*

**FY 2005**

| APG Title | Status | Associated Key Products |
|---|---|---|
| Provide risk assessors and managers with methods and tools for measuring exposure and effects in children, characterizing risk to children, and reducing risks to children in schools from harmful environmental agents to support EPA risk assessment and risk management. | Met | |

**FY 2006**

| | | |
|---|---|---|
| Develop measurement-based models and modules that represent the source-exposure-dose-effect relationships for aggregate exposures. | Met | |

| | | |
|---|---|---|
| Develop partnerships for data collection and new indicators and metrics for exposure and health effects. | Met | |

**FY 2007**

| | | |
|---|---|---|
| Evaluate the variation in vulnerability to environmental agents as a result of health status as reflected by nutritional status and pre-existing disease. | Met | |
| Develop Health Chapter for Report on the Environment. | Met | EPA's Report on the Environment, 2008 |
| Provide Assessment and Analytical tools for Region and Program Offices in using biomarkers for assessing and addressing cumulative risks. | Met | Biomonitoring Workshop Report, 2007; Community Based Risk Assessment Needs Workshop Report, 2007 |

**FY 2008**

| | | |
|---|---|---|
| Identify PK/PD issues underlying uncertainties for extrapolation | Met | |
| Identify MOAs for Risk Assessment | Met | |
| Provide refined models, methods and guidelines for assessing aggregate exposures and effects | Met | Important Exposure Factors for Children, 2007 |
| Develop methods for longitudinal research. | Met | EPA contributions to NCS Research Plan, 2008 |
| Identify pharmacokinetic / pharmacodynamic issues underlying uncertainties for extrapolation. | Met | |
| Determine utility of emerging technologies in harmonizing risk assessment. | Met | |
| By 2008, provide risk assessors and managers with methods and tools for assessing differences in exposures and responses to harmful environmental agents between the elderly and younger adults. | Met | A Decade of Children's Environmental Health Research, 2007 |
| Provide improved tools, systems, methods, models into framework by which EPA and others can measure or model changes in public health from risk management options. | Met | Framework for Assessing the Public Health Impacts of Risk Management Decisions, 2007 |
| Provide Refined models, methods, and guidelines for assessing aggregate exposures and effects. | Met | Community Based Risk Assessment Needs workshop, 2007 |
| By 2008, analyze and demonstrate the role of genetic factors in causing cancer and non-cancer endpoints. | Met | |

ORD's Office of Management and Accountability tracks performance based on the timely completion of all Annual Performance Measures (APMs) that contribute to the APGs, and sets future targets for program progress on the other measures of program performance. The following report indicates that HHRP has achieved its performance objectives during the current rating period (2005- 2008).

**Summary of HHRP Long-Term Outcome Measures: BOSC ratings**

| Measure | 2007 Baseline | 2009 Target |
|---|---|---|
| Rating of the appropriateness, quality, and use of ORD methods and models for risk assessors and risk managers to evaluate the effectiveness of public health outcomes. | Meets Expectations (Mid-Cycle program rating*) | Exceeds Expectations |
| Rating of the appropriateness, quality, and use of ORD methods, model, and data for risk assessors and risk managers to characterize aggregate and cumulative risk in order to manage risk of humans exposed to multiple environmental stressors. | Meets Expectations (Mid-Cycle program rating*) | Exceeds Expectations |
| Rating of the appropriateness, quality, and use of ORD methods, models, and data for risk assessors and risk managers to use mechanistic (mode of action) information to reduce uncertainty in risk assessment. | Meets Expectations (Mid-Cycle program rating*) | Exceeds Expectations |
| Rating of the appropriateness, quality, and use of ORD methods, models, and data for risk assessors and risk managers to characterize and provide adequate protection for susceptible subpopulations. | Meets Expectations (Mid-Cycle program rating*) | Exceeds Expectations |

*Mid-Cycle program ratings are not formal data points.

**Decision Document Analysis Measures**

Through analyses of partner documents, the program assesses the extent to which partners use ORD science in decision-making. This process was first applied for the 2005 BOSC providing a baseline for the program. An improved process is underway, considering the updated HHRP bibliography and will be provided to the BOSC subcommittee before the Face-to-Fact meeting.

| Measure | 2005 Baseline | 2009 Target | 2013 Target |
|---|---|---|---|
| Percentage of peer-reviewed EPA risk assessments in which ORD's characterization of aggregate/cumulative risk is cited as supporting a decision to move away from or to apply default risk assessment assumptions. | 5% | 5.5% | 6% |
| Percentage of peer-reviewed EPA risk assessments in which ORD's mechanistic information is cited as supporting a decision to move away from or to apply default risk assessment assumptions. | 15% | 16.5% | 18% |
| Percentage of peer-reviewed EPA risk assessments in which ORD's methods, models or data for assessing risk to susceptible subpopulations is cited as supporting a decision to move away from or to apply default risk assessment assumptions. | 3% | 3.5% | 4% |

**Bibliometric Analysis Measures**

As mentioned above, the bibliometric analyses conducted every two years reports, among other measures, the extent to which the scientific community cites HHRP publications. This indicator is being tracked over time. The percentage based on the 2008 analysis shows a slight increase in this measure.

| Measure | 2005 Baseline | 2006 Actual | 2008 Actual | 2010 Target |
|---|---|---|---|---|
| Percentage of Human Health program publications rated as highly cited papers in research journals. | 24% | 25% | 25.6% | 26.5% |

**Annual Output Measures**

At the end of each fiscal year, the program reports on its success in completing its planned annual outputs (APMs). This chart shows the HHRP has consistently met its APM commitments.

Percentage of planned outputs delivered in support of mechanistic data long term goal.

| 2000 Baseline | 2001 Actual | 2002 Actual | 2003 Actual | 2004 Actual | 2005 Actual | 2006 Actual | 2007 Actual | 2008 Actual |
|---|---|---|---|---|---|---|---|---|
| 100% | 100% | 100% | 100% | 100% | 93% | 92% | 100% | 100% |

Percentage of planned outputs delivered in support of the cumulative risk long term goal.

| 2000 Baseline | 2001 Actual | 2002 Actual | 2003 Actual | 2004 Actual | 2005 Actual | 2006 Actual | 2007 Actual | 2008 Actual |
|---|---|---|---|---|---|---|---|---|
| 80% | 83% | 80% | 87% | 88% | 86% | 100% | 100% | 100% |

Percentage of planned outputs delivered in support of the susceptible populations long term goal.

| 2000 Baseline | 2001 Actual | 2002 Actual | 2003 Actual | 2004 Actual | 2005 Actual | 2006 Actual | 2007 Actual | 2008 Actual |
|---|---|---|---|---|---|---|---|---|
| 100% | 100% | 100% | 93% | 98% | 100% | 100% | 100% | 100% |

Percentage of planned outputs delivered in support of the public health outcomes long term goal.

| 2000 Baseline | 2001 Actual | 2002 Actual | 2003 Actual | 2004 Actual | 2005 Actual | 2006 Actual | 2007 Actual | 2008 Actual |
|---|---|---|---|---|---|---|---|---|
| 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |

**Annual Efficiency Measure**

To monitor and improve its efficiency in grants processing, the program reports annually on grants processing time. In 2008 NCER met its goal of processing grants in less time than in preceding years. Note: The program may replace or alter this measure as ORD considers recent National Academy of Sciences (NAS) recommendations on research efficiency measurement.

Average time (in days) to process research grant proposals from RFA closure to submittal to EPA's Grants Administration Division.

| 2003 Actual | 2004 Actual | 2005 Actual | 2006 Actual | 2007 Actual | 2008 Actual |
|---|---|---|---|---|---|
| 405 | 350 | 340 | 277 | 254 | 250 |

## Strategic Directions for the Future:

By definition, research is unpredictable and dynamic. So, too, are the challenges facing EPA because the environment and the contaminants entering it are constantly in flux. Thus EPA frequently calls upon the NRC to research and report upon environmental and risk assessment issues of paramount importance. The resulting NRC reports help ORD determine its priorities and strategic research directions.

A number of NRC reports relevant to HHRP goals are anticipated in the near future (0 to 18 months from the time of the HHRP BOSC review), as detailed on the NRC website.

1. An NRC committee has reviewed the human health risks and the potential for conducting a cumulative risk assessment for phthalate esters. The review included critical scientific data and the report, expect in December 2008 will address questions related to human relevance of experimental data, modes of action, exposure information, dose-response assessment, and

the potential for cumulative effects. It is expected to include discussion of the strengths and weaknesses of cumulative assessment approaches that will be informative and directly relevant to efforts in HHRP LTG 2.

2. NRC was also asked in 2006 to develop recommendations for Improving Risk Analysis Approaches used by the US EPA, based upon a thorough review of current concepts and practices. The report will be comprehensive and address analyses applied to contaminants in all environmental media (water, air, food, soil) and all routes of exposure (ingestion, inhalation, and dermal absorption). The report is expected to have broad implications for human health risk assessment and to comment upon many topics under study in HHRP including quantitative characterization of uncertainty and the use of sound science to derive uncertainty factors, approaches for assessing cumulative risk, variability in susceptible and sensitive populations, and dose-response relationships. .

3. Another committee began work in 2007 on the topic Public Health Decision-Making Under Uncertainty. This committee will prepare a report for EPA on decision-making about environmental threats to human health under various types of uncertainty.

4. A longer-term and broad-based effort initiated in 2008 will focus on " A New Biology for the 21st Century: Ensuring that the United States Leads the Coming Biology Revolution." This committee will address all-encompassing questions of central importance for EPA and other Federal Agencies:
"How can a fundamental understanding of living systems reduce uncertainty about the future of life on earth, improve human health and welfare, and lead to the wise stewardship of our planet? Can the consequences of environmental, stochastic or genetic changes be understood in terms of the related properties of robustness and fragility inherent in all biological systems?
" How can federal agencies more effectively leverage their investments in biological research and education to address complex problems across scales of analysis from basic to applied? In what areas would near term investment be most likely to lead to substantial long-term benefit and a strong, competitive advantage for the United States? Are there high-risk, high pay-off areas that deserve serious consideration for seed funding?
" What federal initiatives could be considered to ensure that the US is positioned to take maximum advantage of a vast increase in biological data and understanding, and position itself to be the leader in technologies derived from it? Is the biology research portfolio appropriately balanced among biology subdisciplines and new areas that cross traditional biology subdisciplines? Are new funding mechanisms needed to encourage and support cross-cutting, interdisciplinary or applied biology research?

ORD, in concert with its partners, is discussing new ways to mobilize its talents to address broad problems of national significance in response to environmental challenges faced by a world impacted by the activities and resource utilization of our ever-growing human population. Furthermore we face fundamental changes in global climate with many impacts on human health and ecosystems predicted. These issues, coupled with revolutions in genomics and toxicology testing forecast by the NRC in its 2007 report mentioned earlier, will be major drivers as ORD shapes its future research programs, including HHRP. Several changes in approach have already been discussed, including an increased emphasis on using

a systems-based approach in toxicology, incorporation of advanced modeling approaches in exposure assessment, and development of improved indicators of public health for use in evaluating the effectiveness of EPA's risk management decisions. We face these challenges as research budgets are diminished, motivating increased efforts to collaborate with other agencies and partners in order to leverage limited resources and take advantage of combined expertise. As ORD revises its fundamental research program in human health, the priorities of the new US administration will also be brought into play. The recommendations of this BOSC subcommittee are more important now than ever before.

## **Acknowledgements**:

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Linda Sheldon, Associate Laboratory Director for Health, NERL and Ross Highsmith, Assistant Laboratory Director for Health, NERL, LTG 2
Devon Payne-Sturges, Assistant Laboratory Director for Health, NCER, LTG 3
Andrew Geller, Assistant Laboratory Director for Health, NHEERL, LTG 4

A list of poster titles with presenting authors is included in the documentation package. These scientists from ORD Labs and Centers are acknowledged for working with ORD principal investigators and selected grantees to develop an integrated set of posters for each LTG and insure their completeness. Over 100 ORD scientists contributed to the abstracts and posters (see list of contributors). Many more bench scientists generated the data behind the posters, and many support staff contributed to the generation of the documentation materials.

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