United States
Environmental Protection Agency

Human Health Research Program
Multi-Year Plan
(FY 2006-2013)

Office of Research and Development
US Environmental Protection Agency

2 June 06

Administrative Note

The Office of Research and Development=s (ORD) Multi-Year Plans (MYPs) describe what research ORD proposes to accomplish over the next 5-10 years in a variety of areas. The MYPs serve three principal purposes: to describe where the research programs are going, to present the significant outputs of the research, and to communicate the research plans within ORD and with stakeholders and clients. Multi-year planning permits ORD to consider the strategic directions of the Agency and how research can evolve to best contribute to the Agency=s mission of protecting health and the environment.

MYPs are intended to be Aliving documents@. ORD will update MYPs on a regular basis to reflect the current state of the science, resource availability, and Agency priorities. This MYP was reviewed by ORD's Science Council in April, 2006, and approved in June, 2006. At the time of the review of the Human Health Research Program on February 28-March 2, 2005, the Board of Scientific Counselors requested that the Human Health Research Program update the MYP. ORD plans to provide the BOSC with the updated MYP for the mid-cycle review of the program in 2007.

Human Health Research Multi-Year Plan
Writing Team

ORD Members:
Stan Barone Jr. (NCEA)
Larry Cupitt (NERL)
Alva Daniels (NRMRL)
Kathleen Deener (NCER)
Nigel Fields (NCER)
Jim Jetter (NRMRL)
Andrew Geller (NHEERL)
Zhishi Guo (NRMRL)
Ross Highsmith (NERL)
Julian Preston (NHEERL)
Bruce Rodan (NCEA)
Chris Saint (NCER)
Linda Sheldon (NERL)
Hugh Tilson (ORD)
Hal Zenick (NHEERL)

Program and Regional Office Members:
Valerie Blank (OW)
Jeff Evans (OPPTS)
Lee Hofmann (OWSER)
Michael Firestone (OCHP)
Scott Jenkins (OAR)
Amal Mahfouz (OW)
Dennis Pagano (OAR)
Nicole Paquette (OEI)
Randy Pefetti (OPPTS)
Ravi Rao (R4)
Rita Schoeny (OW)
Hiba Shukairy (OGWDW)

Research Track Writing Teams:
See Attachment E

Science Council Reviewers:
Elaine Francis, National Program Director (SP2 and EDCs)
John Vandenberg, Associate Director for Health (NCEA)

Table of Contents

X Attachments

XI. Appendices

Figures

I. Executive Summary

The mission of the Environmental Protection Agency (the Agency) is to protect public health and safeguard the natural environment risk assessment. Risk management is an integral part of this mission. The Human Health Research Program (HHRP) Multi-Year Plan (MYP) describes the strategic approach for research to improve human health risk assessment-risk management (RA-RM) processes at the Agency. This MYP, developed by the Agency's Office of Research and Development (ORD), outlines a mission-oriented research effort to provide broadly applicable, more fundamental scientific information and tools that will improve the many problem-driven RA-RM decisions throughout the Agency's Program and Regional Offices. The main objective of the HHRP is to reduce uncertainties in the extrapolations necessary in the risk assessment process by providing a greater understanding of the fundamental determinants of exposure and dose and the basic biological changes that follow exposure to environmental toxicants.

The research proposed in this MYP is based on the needs of the Agency's Program and Regional Offices articulated during the spring and summer of 2005, recommendations of the Human Health Subcommittee of the Board of Scientific Directors (BOSC) during their review of the HHRP on February 28-March 2, 2005, and results from a review of the HHRP by the Office of Management and Budget during FY05. Research described in this HHRP MYP is consistent with themes described in ORD's *Human Health Research Strategy* and the Agency's *2003 Strategic Plan*, and builds on work articulated in the 2003 *Human Health Research Multi-Year Plan.*

This MYP discusses the research themes identified by Program and Regional Offices and identifies specific performance goals and measures needed to achieve those goals over a 5-10 year period. The results of this research will be incorporated into risk assessment methods, models and guidance, and ultimately risk assessments conducted under the ORD's Human Health Risk Assessment MYP and in the Agency's Program and Regional Offices.

ORD is unique among Federal agencies in its capacity to conduct research on all aspects of human health environmental health risk assessment. Over the next 5-10 years, ORD will focus on developing a multidisciplinary, integrated research program that addresses uncertainties in the

linkages between exposure, dose and effect. Products from this program will support moving away from default assumptions in the risk assessment process, as well as providing methods, models and data for risk assessors internal and external to the Agency. To accomplish its research objectives, ORD will utilize intramural scientific capability in conjunction with extramural grants, cooperative agreements, and interagency agreements. This MYP identifies and supports linkages to other ORD research MYPs that have a human health component. ORD will continue to identify and foster collaboration with other Federal and state agencies, as well as academic and private organizations having research programs complementary to ORD's research efforts.

The HHRP will focus on research to develop mechanistic data to reduce uncertainties in risk assessment, particularly as it relates to exposure-dose response extrapolation; principles for characterizing cumulative risk, especially extrapolation from single chemicals to multiple chemicals, stressors, and pathways; and research to protect susceptible subpopulations such as children and the elderly, i.e., intraspecies extrapolation. ORD human health research will also conduct research to develop tools and approaches to evaluate the effectiveness of risk management decisions.

ORD's research on the use of mechanistic data to reduce uncertainties in exposure-dose extrapolation will focus on 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 (i.e., key biologic events) 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 exposure/dose response extrapolation in risk assessment, including
    - Extrapolation from high to low dose?
    - Extrapolation from laboratory animals to humans?
    - Extrapolation of *in vitro* to *in vivo* data?
    - Harmonization of cancer and non-cancer risk assessments?

ORD's research on cumulative risk related to multiple chemical/pathway extrapolation in risk assessment will focus on the following Key Research Questions:

- How can biomarkers be used in cumulative risk assessment?
    - What tools are needed to identify biomarkers for cumulative risk assessment?
    - How can those biomarkers be applied for cumulative risk assessment?

- What source-to-dose models are needed for cumulative risk?
    - What methods and models are available for assessing cumulative risk?
- How can tools be used to conduct cumulative risk assessments on chemical mixtures?
- How can cumulative risk at the community level be evaluated?
    - What tools are necessary for community-based risk assessments?
    - How can those tools be applied for community-based risk assessments?

ORD's research on protecting susceptible subpopulations such as children and the elderly will focus on the following Key Research Questions:

- Is there differential life-stage responsiveness or exposure to environmental agents?
    - What are the long-term effects of developmental exposure to chemicals?
    - How does aging affect responsiveness to environmental chemicals?
    - How can we model exposure and effects to protect susceptible subpopulations, especially children?
- Which methods and models are appropriate for longitudinal research with children?
- What are predisposing factors for diseases such as asthma and how does the indoor air environment affect susceptible populations?

ORD's research on developing approaches to evaluate risk management decisions will focus on the following Key Research Questions:

- What are the trends in health status in the US?
- What tools are available to determine the impact of regulatory decisions on exposures to environmental stressors that lead to adverse health outcomes?

This MYP revises and updates the 2003 version of the HH MYP. ORD will update performance measures in the MYP on an annual basis to reflect current state of the science, resource availability, and Agency priorities. This MYP has been reviewed internally by ORD staff and Agency Regional and Program Offices, as well as ORD's Science Council. This revised MYP will be presented to ORD's Board of Scientific Counselors (BOSC) in response to their request for an updated MYP at review of the HHRP in 2005.

II. Introduction

The Office of Research and Development (ORD) initiated a multi-year planning process in Fiscal Year (FY) 2001 to plan the direction of its research in selected topics over the next 5-10 years. Multi-Year Plans (MYPs) are assessed annually to help ORD focus its current and future research on the highest priority issues and promote an integrated approach to achieving the

Agency=s long-term research goals. MYPs provide a framework that integrates research across ORD=s Laboratories and Centers in support of the Agency=s mission to protect human health and safeguard the natural environment. Each MYP is composed of 1) a narrative description of the plan and how the research is being developed to achieve one or more Long-Term Goals (LTGs); 2) "wiring" diagrams outlining the sequence and relationships of APGs needed to achieve each LTG; and 3) tables documenting Annual Performance Measures (APM) (milestones) that comprise each APG. The Human Health MYP (HH MYP) arrays ORD's research plans for the period FY06-FY13 and revises and updates the MYP prepared in 2003 (US EPA, 2003d). The HH MYP provides a focused research framework and direction that reflects available ORD scientific capabilities and capacity. The research described in this MYP assumes annual intramural and extramural resources of approximately 194 FTEs and $61.8 million, including payroll, travel and operating expenses.

The HH MYP sets forth ORD=s strategy for planning and conducting research in response to a number of Agency legislative mandates for research on human health, including the Food Quality Protection Act (FQPA)(1996), Clear Air Act (CAA) (1990), Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)(1996), Safe Drinking Water Act (SDWA) (1996), Children=s Health Act (2000), recommendations from the scientific community [Science Advisory Board (SAB), 1988; National Research Council (NRC), 1993, 1994, 1997], ORD strategic plans (US EPA, 1996, 1997, 2001a), Agency Strategic Plans (US EPA, 2000b, 2003a) and Program and Regional Offices (US EPA, 1990). The HH MYP also addresses research priorities related to human health research as articulated in ORD=s *Human Health Research Strategy* (US EPA, 2003b), the *Strategy for Research on Environmental Risks to Children* (US EPA, 2000a) and the *Asthma Research Strategy* (US EPA, 2002a). Major themes in the Human Health Research Program (HHRP) are related to research gaps identified in the *Research Plan for Endocrine Disruptors* (US EPA, 1998) and *Framework for a Computational Toxicology Program* (US EPA, 2003c). Human Health is also one of 10 high priorities identified in *ORD=s Strategic Research Plan* (US EPA, 2001a). The *2003-2008 EPA Strategic Plan* (US EPA, 2003a) articulates the need for measure-derived databases, methods, and models to assess the consequences of exposure of humans to the consequences of environmental agents.

The HH MYP responds to the recommendation of the NRC (1997) report *Building a Foundation for Sound Environmental Decisions* that the Agency maintain a balanced program of "core and problem-driven research". The NRC indicated that problem-driven research is targeted at understanding and solving particular, identified environmental problems. "Core research", on the other hand, aims to provide broader, more generic information that will help improve understanding of many problems now and in the future. According to the NRC, "core research" has three components: 1) the acquisition of a more systematic understanding of the physical, chemical, or biological processes that underline how humans can be affected by environmental agents; 2) the development of broadly applicable research tools for analyzing and using information in science-based decision making; and 3) the design and maintenance of programs that evaluate, analyze, synthesize and disseminate data and results. NRC makes it clear that "core" research projects should be selected based on their relevance to the Agency's mission, whether such research is already being sponsored by other agencies, and the quality of the work as determined by a peer-review process. The NRC noted that cross-cutting interdisciplinary studies would be particularly valuable. The HHRP meets the NRC criteria of a "core" program by conducting research to produce a fundamental understanding of the key biological, chemical and physical processes that underlie environmental systems, thus forging basic scientific capabilities and methods that can be applied to a wide variety of environmental problems. Projects in the HHRP are based on the ORD's annual planning process, which involves input and prioritization of research by the Agency's Program and Regional Office stakeholders and risk assessors/managers. Research from the HHRP addresses cross-cutting research needs pertinent to several problem-driven areas. Finally, its methods, models, and data are externally peer-reviewed and the program undergoes periodic external review by a board of scientific counselors (see Section VII- Relationship to the Research and Development (R&D) Investment Criteria for additional details.

III. Background

The main objective of the HHRP is to reduce uncertainties in the extrapolations necessary for the risk assessment process by providing a greater understanding of the

fundamental determinants of exposure and dose and the basic biological changes that follow exposure to environmental toxicants. This research supports risk assessment activities conducted under the ORD Human Health Risk Assessment (HHRA) MYP and in Agency Program and Regional Offices. Risk assessment has been defined as the process by which the Agency determines whether exposure to an environmental stressor may have adverse consequences for humans. Risk assessment is essential in deciding whether or not to take regulatory action, deciding what actions should be implemented and, after they are in place, determining whether those actions have been effective. Risk assessment integrates scientific data on exposure and associated adverse outcomes and provides scientific guidance to decision-makers, who must set air and water quality standards, waste site clean up levels, and set acceptable pesticide residue levels in food. As a result, this process has become an integral component of environmental decision-making under the statutes implemented by the Agency.

The NRC (1983) divided the risk assessment process into four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization (see text box). There are many uncertainties associated with the risk assessment process including

Four Components of Risk Assessment

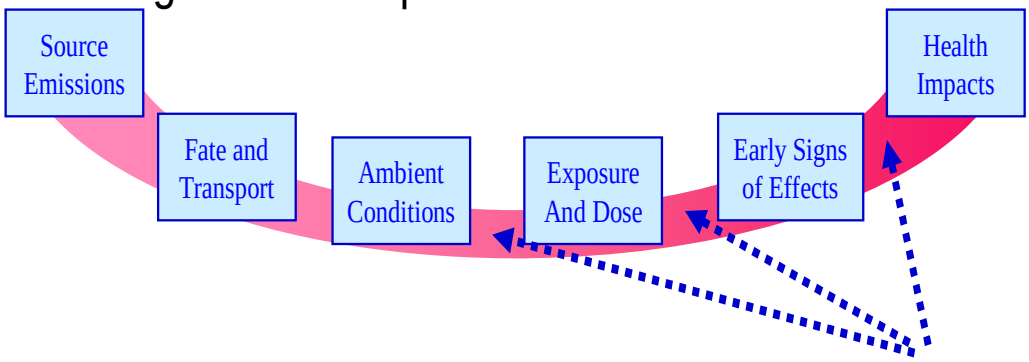
Hazard Identification: Determines whether exposure to an agent can cause an increased incidence of an adverse health effect

Dose-Response Assessment: Characterizes the relationship between exposure or dose and the incidence and severity of the adverse health effect hypothetical exposures of humans to the agent in question

Exposure Assessment: Characterizes anticipated level of exposure to relevant human populations

Risk Characterization: Combines assessment of exposure and response under various exposure conditions to estimate the probability of specific harm to an exposure individual or population

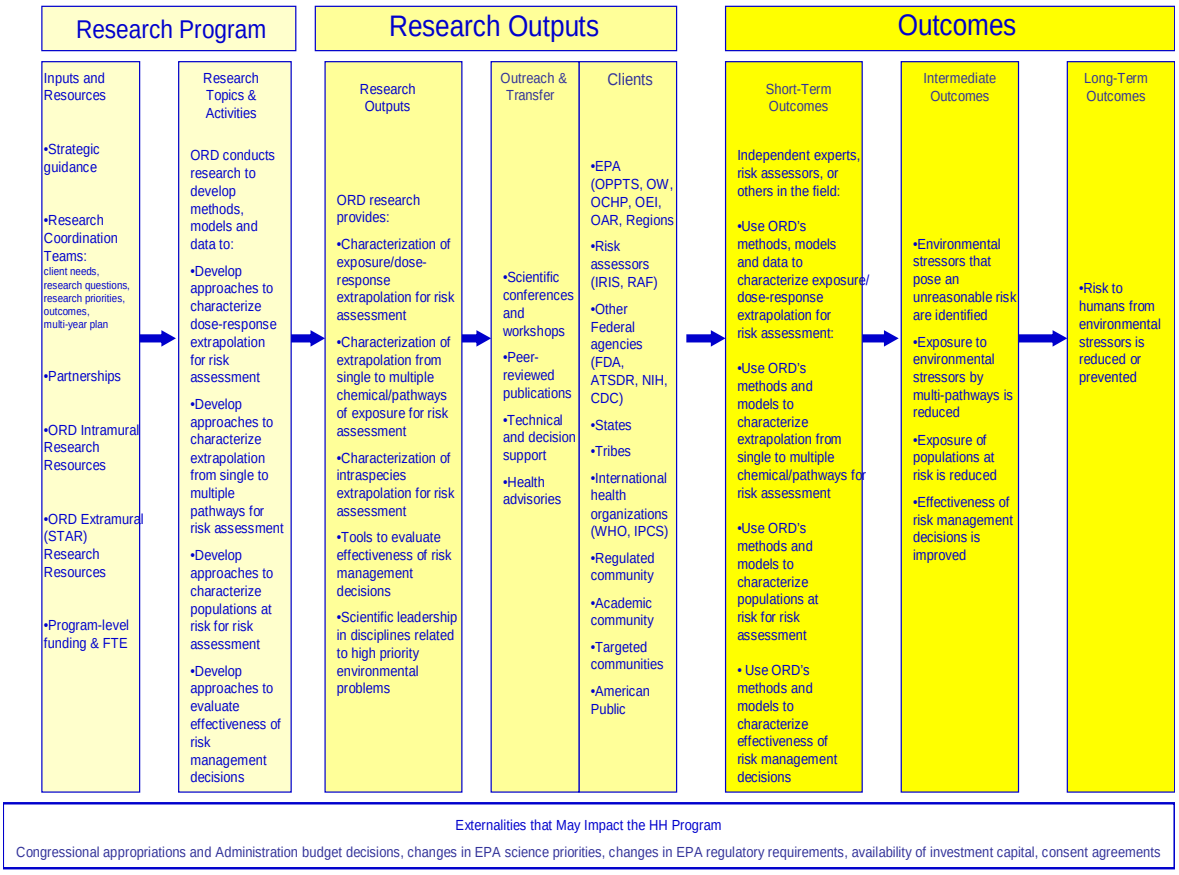
Figure 1 Human Health Research Program Addresses Linkages in the Exposure-Dose-Effect Continuum



- Human health research develops the methods, models, & data to reduce uncertainty in the 'critical links' across the exposure-to-effect paradigm
- Human health risk assessment is essential:
  - In deciding whether or not to take regulatory action
  - In deciding what actions are most effective
  - In evaluating the ultimate effectiveness of our actions

unknown levels of environmental concentrations of contaminants; human exposures to these contaminants; and relationships between human exposure, tissue, dose, and response. Many uncertainties in the risk assessment process are associated with understanding linkages in the exposure-dose-effect continuum (Figure 1). The HHRP is a multi-disciplinary research program that develops the methods, models, and data to reduce uncertainty in these "critical links." These uncertainties frequently result in the use of default assumptions, simplified approaches, and uncertainty factors (UFs) in risk assessments. As a result of these assumptions and simplifications, some of Agency's risk assessments may under- or overestimate the risk associated with a particular level of exposure, which could result in failure to protect adequately against environmental risks or in unnecessary expenditures of funds to achieve overly stringent

Figure 2 Human Health Research Program Design



standards. Much of the uncertainty in risk assessment is related to the need to extrapolate from existing data (NRC, 1994; Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997; US EPA, 2002b). Major sources of uncertainty include extrapolations (see arrows in Figure 1), i.e., extrapolation from ambient concentrations to assumed exposures; from exposure-to-dose-response (e.g., interspecies, high to low dose, acute to chronic, *in vitro* to *in vivo*); from single chemical and pathway to multiple chemicals, non-chemical stressors, and multiple pathways; intra-population extrapolation (i.e., susceptible subpopulations), and extrapolation of the effectiveness of risk management decisions over time. Research to reduce uncertainty in risk assessment benefits the public by supporting risk management decisions that achieve the optimal balance between costs and public health protection.

Figure 2 provides a conceptual framework for the HHRP, which links the resources to the

outputs and programmatic outcomes to protect human health and strengthen regulatory decision-making. The clients for the HHRP are risk assessors at the Agency's Program and Regional Offices, ORD's National Center for Environmental Assessment (NCEA), the states, other federal agencies, international health organizations, the regulated community, and the academic community. These stakeholders use the outputs of the HHRP to characterize and extrapolate risk from exposure/dose-response relationships measures in humans, laboratory animals, or *in vitro* models; single to multiple chemical/pathway extrapolation; and responses in laboratory animals relative to humans. Progress will be measured by the extent to which HHRP's methods, models or data are actually used in peer-reviewed risk assessments. The HHRP also develops approaches and tools so that effectiveness of risk management decisions can be evaluated, i.e., extrapolation of risk management decisions over time. Impact of this research will be determined by evaluation of risk management decisions using HHRP's approaches, databases and indicators. The use of HHRP's outputs by its clients will facilitate identification of environmental stressors that pose an unreasonable risk to human populations, reduce exposure of humans to multiple environmental stressors through multiple pathways, reduce exposure of populations at risk to environmental stressors, and improve effectiveness of risk management decisions.

ORD's multidisciplinary capacity to conduct research that focuses on all aspects of human environmental health risk assessment represents a unique strength among federal agencies. ORD sustains a research program with the capability to investigate the sources and environmental concentrations of contaminants, human exposures to contaminants, exposure-dose-response relationships, epidemiology, risk assessment and risk management. The HHRP consists of intramural research complemented by an extramural research program. This is in contrast to human health research in other federal agencies, which generally focuses on single aspects of the exposure-dose-effect continuum. Examples of major, complementary research programs with other research agencies may be found in Attachment A.

IV. Progress to Date/Changes from Previous Version

Major accomplishments of the HHRP during the 2000-2005 time-period are listed below. Since research from NCEA was covered in the 2003 HH MYP, products from that Center are

included in the lists that follow. Products have been organized according to the LTGs contained in the 2003 HH MYP.

Long-Term Goal 1 Use of Mechanistic Data in Risk Assessment

- HHRP mechanistic methods, models or data were utilized to inform default assumptions in 14 peer-reviewed human health risk assessments since 2000 (OMB PART Review, 2005)
- Benchmark Dose Software was developed and made publicly available with an on-line training program to evaluate dose-response relationships for chemicals http://www.epa.gov/ncea/bmds_training/software/overp.htm
- Research contributed to the de-listing of ethylene glycol monobutyl ether and retention of methanol as hazardous pollutants (OMB PART Review, 2005)
- Research contributed to revised guidelines for carcinogen risk assessment http://cfpub.gov/cnea/raf/recorddisplay.cfm?deid=55907
- Research contributed to document evaluating the Reference Dose (RfD)/Reference Concentration (RfC) process in risk assessment process http://cfpub.epa.gov/ncea/raf/RAFRPRTS.CFM?detype=document&excCol=archive
- Research contributed to drafting of framework for computational research at ORD http://www/epa.gov/comptox/comptox_framework.html

Long-Term Goal 2 Cumulative Risk

- Models and data were used to support the cumulative risk assessment of organophosphate and carbamate pesticides http://epa.gov/pesticides/cumulative/common_mech_groups.htm
- Developed probabilistic exposure model for risk assessment of chromated copper arsenate (CCA) (http://www.epa.gov/oppad001/reregistration/cca/)
- Developed a physiologically based pharmacokinetic (PBPK) model to simulate absorption, storage, metabolism, and elimination of chemicals in humans http://www.epa.gov/heasdweb/erdem/erdem.htm
- Stochastic human exposure and dose simulation model to predict multimedia, multi-pathway aggregate exposures for user-specified populations http://www.epa.gov/nerl/research/2003/g1-5.html
- Databases were provided for full and open public access for risk assessors, including the Technology Transfer Network (http://www.epa.gov/ttn/atw/), the Air Pollutants Exposure Model (http://www.epa.gov/ttn/fera/human_apex.html), The Consolidated Human Activity Database (CHAD) (http://www.epa.gov/chadnet1/), and the Human Exposure Database System (HEDS) (http://www.epa/nerl/research /2003/g8-1.html)
- National Health Exposure Assessment Survey (NHEXAS) http://www.epa.gov/nerl/research/nhexas/nhexas.htm
- Analytical methods were provided to support environmental assessments such as the American Healthy Homes Survey http://www.epa.gov/ord/scienceforum/2005/pdfs/ordposter/tulve_tulve_partnering.pdf
- Research contributed to updates of the Exposure Factors Handbook

http://www.epa.gov/ncea/exposfac.htm

- Research contributed to drafting framework for conducting cumulative risk assessment http://www.epa.gov/ncea/raf/pdfs/frmwrk_for_cra/Draft_Framework_April23_2002.pdf

Long-Term Goal 3 Susceptible Subpopulations

- Research contributed to characterizing exposures to toxic agents related to the World Trade Center Disaster http://www.epa.gov/wtc/
- Research contributed to developing Integrated Pest Management Program for intervention by local health departments and housing authorities http://www.epa.gov/pesticides/ipm/
- Research contributed to the development of the National Agenda for the Environment and the Aging (http://www.epa.gov/aging/agenda/index.htm)
- Research contributed to the development of protocols for the National Children's Study (NCS) (http://nationalchildrensstudy.gov/)
- Research contributed to drafting of the child-specific exposure factors handbook http://oaspub.epa.gov/eimscomm.getfile?p_download_id=36528
- Research contributed to the supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogens http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=439798
- Research contributed to writing of the framework for assessing risks of environmental exposures to children http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283
- Research contributed to developing guidance for selecting appropriate age groups for assessing childhood exposures
- Research contributed to characterizing aggregate exposures of young children to common contaminants in their everyday surroundings in the Children's Total Exposure to Persistent Pesticides Study (http://www.epa.gov/nerl/research/1999/html/g8-10.html)

Long-Term Goal 4 Evaluation of Public Health Outcomes

- Exposure research was done to determine pesticide levels in children in border regions between the US and Mexico http://www.nmsu.edu/~frontera/old_1996/nov96/1196heal.htm
- HHRP scientists contributed significantly to the Health Chapter in the Agency's Report on the Environment (RoE) http://www.epa.gov/indicators/

There are several significant changes in the 2006 version of the HH MYP relative to 2003. These changes are based on input from the Regional and Program Offices (see Attachment B for summary of research needs determined in the summer of 2005), recommendations from the Board of Scientific Counselors review (BOSC, 2005), feedback from an assessment by the Office of Management and Budget (OMB) (see Section VII-Relationship to the R&D Investment Criteria), guidance from the Executive Council during the FY07 contingency planning process,

and changes in resources. In addition, ORD-NCEA, which contributed research products to the previous version of the HH MYP, has re-assessed its mission and no longer undertakes primary research. The primary mission of NCEA is to receive data and primary methods from external and internal sources, including the HHRP, in order to undertake risk assessment activities for the Agency. NCEA is now considered to be significant clients of the research outputs from the HHRP. Outputs from NCEA and the Agency's Risk Assessment Forum are described in the RA MYP. A listing of significant changes in the current version of the HH MYP is as follows:

- LTGs 1-3 have been redefined to focus on outcomes of the research, i.e., methods, models and data that will be used by risk assessors and managers
- There is a decreased emphasis on aggregate risk due to decreases in resources in this area
- Research on Cumulative Risk (LTG 3) has been expanded to include research on community-based cumulative risk assessment
- Long Term Goal 4 "Evaluation of Public Health Outcomes" has been changed to "Assessment of Risk Management Decisions" to be more descriptive of the work being proposed
- Research from the HHRP contributes to outputs generated by NCEA
- The current plan contains a number of new APGs and APMs that were not included in the 2003 plan
- Some APGs have been eliminated and replaced with goals that more clearly articulate a critical path for the research and available resources
- Older adults have been added as a potentially susceptible subpopulation in LTG3

V. Planned Research Program

This HHRP MYP is an extension and more integrative update of the MYP presented to the Executive Council in 2003 (US EPA, 2003d). As mentioned above, several existing APGs have been eliminated or restated to more accurately reflect a critical pathway leading to meeting the LTGs. The proposed research is based on a step-wise approach to identify, select and prioritize future research to address fundamental, cross-cutting needs of Agency risk assessors in ORD and the Regional and Program Offices (see Attachment B for summary of research needs). The narrative that follows introduces the scientific basis and programmatic relevance for the themes selected for future research through the HHRP.

A. Key Research Questions

1. Use of Mechanistic Data in Risk Assessment

The pathway between exposure to an environmental agent and health effect (see Figure 1) cannot be fully characterized for every possible exposure scenario. In addition, much data on response to environmental agents must be gathered from laboratory animals under entirely different sets of exposure conditions than humans may experience. One of the most critical problems in decreasing uncertainties in the linkages in the exposure-dose-effect continuum is

Why Study Mechanism of Mode of Action?

- Biological effects of chemicals can originate via a variety of independent pathways-which ones should be used for risk assessment?
- Some MOAs cause effects in both laboratory animals and humans, while others are species-specific-which ones can be extrapolated from animals to humans?
- Some MOAs are present only at high doses- which ones can be extrapolated to low doses?
- Some MOAs are present *in vitro*, but not in *vivo*- which ones from *in vitro* studies can be used in risk assessment?
- Some MOAs are relevant to specific populations such as children- which ones can be used to protect susceptible subpopulations?
- Some MOAs are critical for predicting effects of chemicals in mixtures-which ones can be used for cumulative risk assessments?
- MOA information may be used to establish biological plausibility of observed effects
- MOA information may be used to harmonize cancer and non-cancer risk assessments
- MOA information may be used to reduce reliance on default assumptions in risk assessment

how to make accurate extrapolations in the risk assessment process (NRC, 1994; Presidential/ Congressional Commission on Risk Assessment and Risk Management, 1997). There is a level of uncertainty associated with efforts to extrapolate observed effects from one set of circumstances (e.g., cancer incidence in rats subjected to high, chronic exposures in controlled laboratory experiments) to an entirely different set of circumstances (e.g., individual excess cancer risks in humans experiencing intermittent, low-level exposures). Extrapolation from laboratory animal data to estimate human risks involves a variety of assumptions about interspecies differences between laboratory animals and humans which are associated with

application of default assumptions in the risk assessment process. Extrapolation from high to low dose from either laboratory animal or human data requires assumptions about the potential high to low dose difference in the shape of the dose-response curve.

A more thorough understanding of key events associated with exposure and the ultimate manifestation of an adverse health effect (i.e., the toxicity pathway or mode or mechanism of action; MOA) involves linking adverse outcomes of toxicological significance to initiating events, ideally through a cascade of biochemical and physiological changes that occur as a result of the initial interaction of environmental agents with biological target sites. Knowledge of the MOA allows for the overall process of extrapolation to be broken up into its biological elements. Experimental data can be developed as independent elements and the consequences to the overall

extrapolation determined. For example, the newly adopted cancer guidelines (US EPA, 2005) use MOA data to determine the relevance to humans of laboratory animal exposure-response data by establishing biological plausibility. Such an approach has also been proposed for non-carcinogenic endpoints as well (Seed et al., 2005). As knowledge of the underlying biological processes improves, understanding of linkages in the exposure-dose-effect continuum increases. This knowledge defines uncertainty in the extrapolation process and provides testable hypotheses for extrapolation currently accounted for by default assumptions and UFs in the risk assessment process (NRC, 1994). MOA information is being used with greater frequency in the risk assessment process (US EPA, 2005). The text box on the preceding page summarizes a number of questions or issues that may be addressed by MOA information in the risk assessment process.

One way to reduce uncertainty in extrapolation is to develop models that can estimate relevant toxic doses within the body after actual and realistically simulated exposures [pharmacokinetic (PK) models]. PK models are mathematical expressions that describe the kinetics of the uptake and distribution of environmental agents in laboratory animals and humans. The key physiological variables used in these models can be used to understand biological processes governing transport kinetics, which can decrease the uncertainty associated with extrapolation from high to low dose or route to route. Information derived from

comparable laboratory animal and human systems can be used to address uncertainties associated with interspecies extrapolation. A key scientific question is how PK information can be used in risk assessment to inform understanding of how tissue dose concentrations are associated with early biological changes leading to toxicity. Pharmacodynamic (PD) models describing key physiological and biological processes leading to adverse health outcomes need to be interfaced with PK models to fully understand the dose-response relationship and develop predictive toxicity models. Integrated PK/PD models are crucial first steps toward the development of computational or systems biology models that could be used to prioritize chemicals for screening and testing based on MOA information. Integrated PK/PD models can also be used to describe the dose-response for endpoints at various levels of organization. This information facilitates the integration of various endpoints rather than rely on a single, most sensitive outcome to arrive at a point of departure for risk assessment.

One initial step in utilizing a mechanistic approach to address uncertainties in exposure/route extrapolation is to develop and utilize emerging technologies to identify key steps in the toxicity pathway. Such an approach is described in the document *A Framework for a Computational Toxicology Research Program* (US EPA, 2003c). A key issue for risk assessment is an understanding of how well information derived from studies conducted *in vitro* or toxicogenomic or toxicoproteomic methods can be extrapolated to adverse effects *in vivo.* Identifying key precursors of toxicity is also necessary for the development of computational approaches to be used to prioritize screening and testing of chemicals. The Presidential/ Congressional Commission on Risk Assessment and Risk Management (1997) indicated that mechanistic knowledge will decrease the uncertainty in the margin of exposure and margin of protection approaches that have been adopted by the Agency for cancer and non-cancer risk assessments. The NRC (1994) has also indicated that the use of mechanistic approaches will lead to a more harmonized approach for cancer and non-cancer risk assessments. For carcinogens, the Agency has taken the default approach that, in the absence of biological information to the contrary, a linear low-dose approach to risk estimation is to be used, despite recognition that the actual risk could be between the estimated risk and zero. For non-cancer risks, the Agency uses UFs to establish a dose below which adverse effects are not expected to

occur. These estimates are generally considered to be conservative and are often made with little if any knowledge of whether biological effects occur at such low doses. Research to investigate those factors that affect the shape of the dose-response curve at low doses will improve both hazard identification and dose-response assessment in the risk assessment process. Mechanistic data may also be useful in deciding whether or not to use UFs or the magnitude of particular UFs for extrapolating from high to low dose, from animals to humans, or from route-to-route. Research is needed to determine how mechanistic data can be used to reduce uncertainties in applying various default assumptions in the risk assessment process. Principles for the use of mechanistic information in risk assessment can be derived by systematic dose-response studies on classes of compounds having different MOAs. Based on discussions with Program and Regional Offices (see Attachment A), the following Key Research Questions have been identified:

- 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 PK and PD 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?
    - Harmonization of cancer and non-cancer risk assessments?

2. Cumulative Risk

The development of risk assessment methodology during the 1970s and 1980s closely followed the Agency's strategy for pollution control which target single, high volume or high toxicity chemicals. As a result, risk assessment methodology has been focused on evaluating the risk of a single chemical and single exposure pathway scenario. However, most humans are exposed to mixtures of chemicals from multiple sources via multiple pathways and routes. These exposures to multiple chemicals through various media could cause unexpected cumulative effects. The combined risk from such exposures may be greater or less than what would typically be predicted from data on individual chemicals from single routes of exposure.

Cumulative risk assessment (CRA) is broadly defined as "the combined risks from

aggregate exposures to multiple agents or stressors." Agency risk assessors in ORD and program and regional offices have a great need for both exposure assessment information and risk assessment methods to evaluate human health risks from exposure to chemical mixtures. For example, the Office of Water (OW) is concerned with contaminant mixtures in drinking water in response to requirements of the SDWA Amendments of 1996, including mixtures of disinfection by-products and chemicals on the Contaminant Candidate List. The Office of Air Quality Planning and Standards (OAQPS) uses a mixture risk assessment approach for multiple route exposures in conducting air toxics assessment of air pollutants. The Office of Air and Radiation (OAR) has issued a proposed rule to evaluate the national emission standards for hazardous air pollutants (HAPs). The Office of Pesticide Programs (OPP) has conducted multiple-route assessment of organophosphates and carbamates in response to the FQPA and is working on a CRA for pyrethroid pesticides. The National Homeland Security Research Center is considering the potential toxicological interactions with co-exposure to respiratory toxicants, dust and smoke. The Office of Solid Waste and Emergency Response (OSWER) also evaluates contaminant mixtures at Superfund sites under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, 1980). The Agency's cross-agency Risk Assessment Forum has published guidance on the health risk assessment of chemical mixtures (US EPA, 2000c). As part of the implementation of FQPA, the Agency also developed guidance for conducting CRAs of chemicals that appear to act by a common mechanism of toxicity (US EPA, 2001b).

In developing approaches to evaluate cumulative risk, it is important to determine the source of the exposures and how much of a chemical actually gets to a target biological site. For example, it is important to determine whether emissions come from indoor or outdoor sources and which chemicals are actually released under real-world use or applications. Assessment of cumulative risk will require information about how multiple agents distribute, react with each other, and react with environmental media based on the properties of the agents and the media. It is also clear that people's exposures to chemicals having similar MOAs or to the same chemical through multiple avenues of exposure may differ for various chemical classes, i.e., patterns of cumulative exposure to organophosphate pesticides that inhibit acetylcholinesterase may differ

from patterns of exposures to air pollutants that act by inducing oxidative stress (OS). Cumulative risk to similar classes of chemicals such as pesticides may also differ for specific groups within the human population, i.e., exposure patterns of children to organophosphate pesticides may differ from older populations. Research is needed to develop source to exposure models to determine how exposures translate into internal doses at target sites for different classes of chemicals and different segments of the human population. Establishing databases of exposures to various chemicals and chemical classes for important subgroups in the human population is an important step in assessing cumulative risk.

Frequently, it is not possible to measure directly all of the forms of chemicals in the environment that may contribute to cumulative risk. In such cases, it is important to identify potential surrogates (i.e., biomarkers) that could be used to estimate exposure and dose. Depending on the level of biological information that is known, such biomarkers could also be characterized as biomarkers of effect or even susceptibility. Information concerning MOA or the basis for biological susceptibility will be crucial. Sensitive biomarkers can provide the basis for assessing the cumulative exposure from specific classes of environmental pollutants or from complex mixtures to estimate risk and to determine the efficacy of various remediation efforts.

It is the Agency's practice to use response-addition or dose-addition as the recommended default methods when the component chemicals in a mixture show dissimilar toxicity or similar toxicity, respectively. These are the methods most commonly used in site-specific assessments because they are relatively easy to apply and use single chemical toxicity and exposure information. Response- and dose-addition are, however, fundamentally different methods, and their use depends on what is known concerning the mode or mechanism of action. In order to conduct CRA of chemicals, the Agency needs to identify the methods, models and data necessary to determine the applicability of dose- and response-additivity default assumptions and the possibility of significant synergism. Furthermore, the Agency defines interactions as observed effects greater than (synergism) or less than (antagonism) those expected under a specified form of additivity. Agency policy indicates that mixtures risk assessment should reflect known toxicological interactions. In practice, sufficient data are seldom available to model interactions. Data on binary combinations of chemicals are most prevalent, so for mixtures of

more than two chemicals, the true nature of joint toxic action may be speculative at best. For exposures at low doses with low component risks, the likelihood of a significant interaction is usually considered to be low. Interaction arguments based on saturation of metabolic pathways or competition for cellular sites usually imply an increasing interaction effect with dose, so that the importance for most low environmental exposures is probably small. Fundamental research is needed to elucidate principles of chemical interaction for broad classes of chemicals.

It is now increasingly clear that CRA can include both chemical and non-chemical stressors, multiple-route exposures, and population factors that differentially affect exposure or toxicity. Community-based CRA has become an important research area, reflecting the interest of Agency Regional risk assessors, Program Offices, Office of Environmental Justice, and Office of Children's Health Protection (OCHP). In 2002, ORD jointly sponsored a workshop with the Agency's Regions to discuss current case studies, methods and research needs regarding community-based CRA. It was clear from this meeting that Regional scientists are often confronted with assessing risks from multi-media, multi-stressor exposures to a population in a specified geographic area. Successful completion of such assessments will require development of new data, methods, and guidance.

Based on discussions with Program and Regional Offices (see Attachment A), Key Research Questions in this area are as follows:

- How can biomarkers be used in cumulative risk assessment?
    - What tools are needed to identify biomarkers for cumulative risk assessment?
    - How can those biomarkers be applied for cumulative risk assessment?
- What source-to-dose models are needed for cumulative risk?
    - What methods and models are available for assessing cumulative risk?
- How can tools be used to conduct cumulative risk assessments on chemical mixtures?
- How can cumulative risk at the community level be evaluated?
    - What tools are necessary for community-based risk assessments?
    - How can those tools be applied for community-based risk assessments?

3. Susceptible Subpopulations

Human variability in exposure and response to environmental agents is a key uncertainty in health risk assessment (NRC, 1993, 1994). In that regard, legislation has called on the Agency to consider potentially susceptible populations in the risk assessment process. The

SDWA Amendments of 1996, for example, mandate that the Agency consider risks to groups within the general population that are identified as being at greater risk of adverse health effects, including children and the elderly. Similarly, the FQPA contains special provisions for the consideration of pesticide risks to children. The 1997 Federal Executive Order 13045 "Protection of Children from Environmental Health Risks and Safety Risks" (http://www.epa.gov/fedrgstr/eo/eo13045.htm) commits the Agency to consider the special vulnerability of children in risk assessment. In October 2002, Agency Administrator launched an Aging Initiative (http://www.epa.gov/aging/) to address issues related to the increased growth in the population of older Americans. Health risk increases with age and it is crucial that the Agency understand the possibility that responses to chemicals exposure to environmental agents may further increase the risk of adverse health effects with age.

When conducting risk assessments, the Agency examines populations and life-stages that may be especially sensitive to the stressor(s) being assessed. This does not imply, however, that these examined populations and life-stages are always at greatest risk. It is recognized that limited data are currently available for the *a priori* identification of susceptible populations and life-stages for many chemicals and risk assessments. Typically, when data are limited, default practices are used. For example for non-cancer effects, an intraspecies UF is used to account for variations in susceptibility within the human population. This UF typically has a value of 10-fold, but can be increased or reduced when sufficient data are available. The same UF may be applied to the output of a non-linear dose-response model for some non-mutagenic carcinogens. A database UF may also be applied for deficiencies in the available data or when existing data suggest that additional data may yield a lower reference value. This UF is most often used when developmental or two-generation reproduction studies or other critical effects (e.g., developmental neurotoxicity or immunotoxicity) are not available, but it may be applied in other life-stages. For cancer effects, an evaluation is made as to whether low-dose linear extrapolation is sufficient to protect susceptible populations. Research is needed to reduce reliance on UFs to protect potentially sensitive subpopulations in the risk assessment process.

Differential responsiveness to chemical exposure as a function of life-stage is most likely related to key PK and/or PD differences in biological processes or exposure patterns specific to

life-stage. Fundamental research is needed to develop an understanding of how absorption, metabolism, distribution and elimination vary as a function of life-stage. In addition, research is needed to determine special vulnerabilities to chemical exposures during specific periods of development, as well as changing potential for compensation and repair as a function of age. Research is also needed to determine how exposure to chemicals during development may influence onset of health problems later in life. This information may be critical to evaluating the long-term health consequences of effects such as decreases in body or brain weight during development and the relationship of these changes to adverse health effects during maturation. Research is also needed on life-stage related exposures so that appropriate source and exposure mitigation strategies can be considered to reduce risks of humans during all phases of the life-stage.

In addition to fundamental research on differential responsiveness and exposures as a function of life-stage, there is a clearly articulated public concern about the health of children. For example, it is accepted by many in the public health sector that the incidence of diseases such as autism appears to be increasing in the United States and other Western countries. In response to such concerns, the Children's Health Act laid the groundwork for a major national study of the impact of the environment on child health. The act authorized the National Institute of Child Health and Human Development (NICHD) "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development." It directed NICHD to establish a consortium of representatives from appropriate federal agencies, including the Agency to "1) plan, develop, and implement a prospective cohort study from birth to adulthood, to evaluate the effect of both chronic and intermittent exposures on child health and human development; and 2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes." The goal of the NCS (http://nationalchildrensstudy.gov) was to develop information that will ultimately lead to improvement in the health, development, and well being of children. The primary aim of the NCS was to investigate the separate and combined effects of environmental exposures (chemical, biological, physical, psychosocial), as well as gene-environment interactions on pregnancy

outcomes, child health and development, and precursors of adult disease. At the writing of this MYP, funding for a larger national study on children does not seem likely. However, there remains a need to develop methods, models and data that can be used in longitudinal assessments of children in order to identify biological and exposure factors that may be associated with environmentally related disease in children.

Research is also needed to develop methods, models and approaches for risk reduction in children. For example, a significant part of children's inhalation exposure occurs indoors because, on average, children spend over 80% of their time indoors. Consumer products such as building materials, paints, and cleaners are major sources of indoor air pollution. The Agency's Source Ranking Database complied formulation data for about 12,000 potential indoor pollution sources, which contain 1,377 chemical ingredients including a number of HAPs. Agency Regional Offices have identified indoor air pollution in schools as a key environmental quality issue. The Agency's Buy Clean Initiative and Tools for Schools program are aimed to protect school children from indoor exposure through risk management approach. In the past several years, ORD has supported these programs by generating data and analysis for evaluating potentially high risk products used in schools such as hard surface cleaners and dry eraser markers. Research to develop integrated risk management solutions to indoor air quality problems in schools is needed.

One disease that appears to be increasing, especially in children, is asthma. In 2001, 20.3 million Americans had asthma, and 12 million had an asthma attack in the previous year. In 1980, 3.6% of children had asthma. By 1995, the prevalence had increased to 7.5%, or approximately 5 million children. Statistics on those over 65 years of age are not available, but it plausible that the incidence of asthma may be increasing in that population as well. Because of its epidemic proportions, the US government has identified asthma as a top priority for research. Healthy People 2010, a guiding document for the Department of Health and Human Services (DHHS, 2001), identified asthma as a "serious and growing health problem" in need of action. Clearly, there is a need to understand the mechanistic underpinnings of the induction and exacerbation of asthma by pollutants and allergens, the cumulative effects of exposure to multiple stressors such as dust mites and molds, the factors responsible for susceptibility of

asthmatics to pollutants, and the effective risk management interventions or strategies to reduce the burden of asthma to the population.

Based on discussions with the Program and Regional Offices (see Attachment A), ORD will focus on the following Key Research Questions:

- Is there differential life-stage responsiveness or exposure to environmental agents
  - What are the long-term effects of developmental exposure to chemicals?
  - How does aging affect responsiveness to environmental chemicals?
  - How can we model exposure and effects to protect susceptible subpopulations?
- Which methods and models are appropriate for longitudinal research with children?
- What are predisposing factors for asthma as a function of life-stage and how do they interact with indoor air environments?

4. Assessment of Risk Management Decisions

The issue of ensuring that pollution control programs produce measurable benefits in human health is fundamental for the assessment of the Agency's mission to protect human health and the environment. It is important to assess the effectiveness of the Agency's tools, approaches, and indicators to demonstrate outcome-oriented measures of success of its risk management decisions. Under the Environmental Indicators Initiative (http://www.epa.gov/indicators/), the Agency has started a process to better assess the "state of the environment" that may result from its policies and actions to improve environmental quality. A centerpiece of this effort has been the publication of an initial Draft RoE (US EPA, 2003e) that will be supplemented by periodic updates; the next edition is due in 2006. In the Health Chapter of the RoE, a number of data gaps are identified that relate to the need for improved indicators of the actual public health impact associated with Agency decisions and actions. Research is needed to develop and validate such environmental public health indicators (EPHIs). These indicators, while complementing traditional process indicators such as decreases in emissions, discharges and pollutant levels in environmental media, are intended to reflect more closely the actual impacts on public health that result from environmental decision-making and contribute to clarifying the benefits and costs associated with further incremental environmental improvements. The research program in this area builds upon the current research programs in Human Health that improve the risk assessment process and improve the linkages discussed above.

Based on input from Program and Regional Offices (see Attachment A), Key Research Questions for this area are as follows:

- What are the trends in health status in the US?
- What tools are available to determine the impact of regulatory decisions on exposures to environmental stressors that lead to adverse health outcomes?

B. Long-Term Goals and Performance Measures

This section defines each of the four LTGs for the HHRP. These definitions were developed in conjunction with the review of the HHRP by the BOSC (BOSC, 2005) and the OMB during its review of the HHRP in the summer of 2005. For the purposes of this MYP, LTGs are key outcomes to be achieved from research in support of the mission of ORD and the EPA. APGs are defined as major research outputs that must be achieved in order to meet the LTGs. APMs are a collection of research products (i.e., peer-reviewed methods, models or data) from ORD Laboratories and Centers that contribute to the accomplishment of an APG.

Figures 3-6 are "wiring" diagrams that illustrate the APGs that will be provided for each LTG during the FY 2006-2013 time period. In these diagrams, APGs from the FY03 HH MYP are shown in white blocks, while new APGs are indicated in green. The purpose of this convention is to demonstrate continuity with the previous plan and show areas of new emphasis in the current MYP. Because the HHRA MYP is a significant new recipient of ORD's research, inputs into APGs in LTG 2 of that MYP are indicated by blue blocks. Thematic relationships to other ORD MYPs are discussed in Section VI and summarized in Attachment C.

Each "wiring" diagram consists of 2-4 Research Tracks. Research Tracks describe the research that will be done to address each of the Key Research Questions discussed in Section V for each LTG. Research in each Research Track will usually be based on the efforts of a multi-disciplinary, usually multi-laboratory/center, team (Attachment E contains a list of the research track team leads and the contributing members of each team). In the section that follows, an overview of the research that will be done in each Research Track is described. This overview consists of the rationale for the research to be done, specific research questions to be addressed, and how the proposed research addresses the Key Research Questions for each LTG. A more detailed description of the research for each Research Track can be found in Attachment F. In

addition, each Research Track section contains an overview of the APGs and a brief summary of the research associated with that APG. A list of APMs for each LTG/APG can be found in Attachment D.

The table below provides an indication of the relative emphasis for each LTG over time.

Long-Term Goal	Relative Emphasis in MYP Planning Window
LTG 1	Level
LTG 2	Decreasing
LTG 3	Decreasing
LTG 4	Increasing

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment

a. Definition: Risk assessors and risk managers use ORD's methods, models or data to reduce uncertainty in risk assessment using mechanistic (or mode of action) information. Key Research Questions for this LTG are:

- 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 PK and PD 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?
    - Harmonization of cancer and non-cancer risk assessments?

b. Performance Measures: APGs in each Research Track for LTG 1 are summarized in Figure 3. A description of the research supporting the APGs in each Research Track follows (see Attachment F for a more detailed explanation of the research at the project level):

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment
Research Track 1: Methods and Models to Characterize MOA

A major problem facing risk assessors is an incomplete understanding of the mechanisms by which toxicity is induced. The application of emerging technology to better understand these mechanisms has been catalyzed by the development of large data array based approaches, especially deoxyribonucleic acid (DNA) micro-array analysis. These new technologies can simultaneously measure the expression of thousands of genes (e.g., genomics), accelerating our ability to better characterize adverse responses as well as the cellular and biochemical pathways which underlie these responses.

Proteomics methodology is rapidly becoming available to allow screening of tissues and

biological fluids for changes in hundreds of peptides simultaneously. The application of proteomics to environmental toxicology will allow identification of specific peptides whose expression is altered by xenobiotics and environmental pollutants and/or are associated with an adverse effect. This approach will facilitate identification of protein biomarkers for exposure,

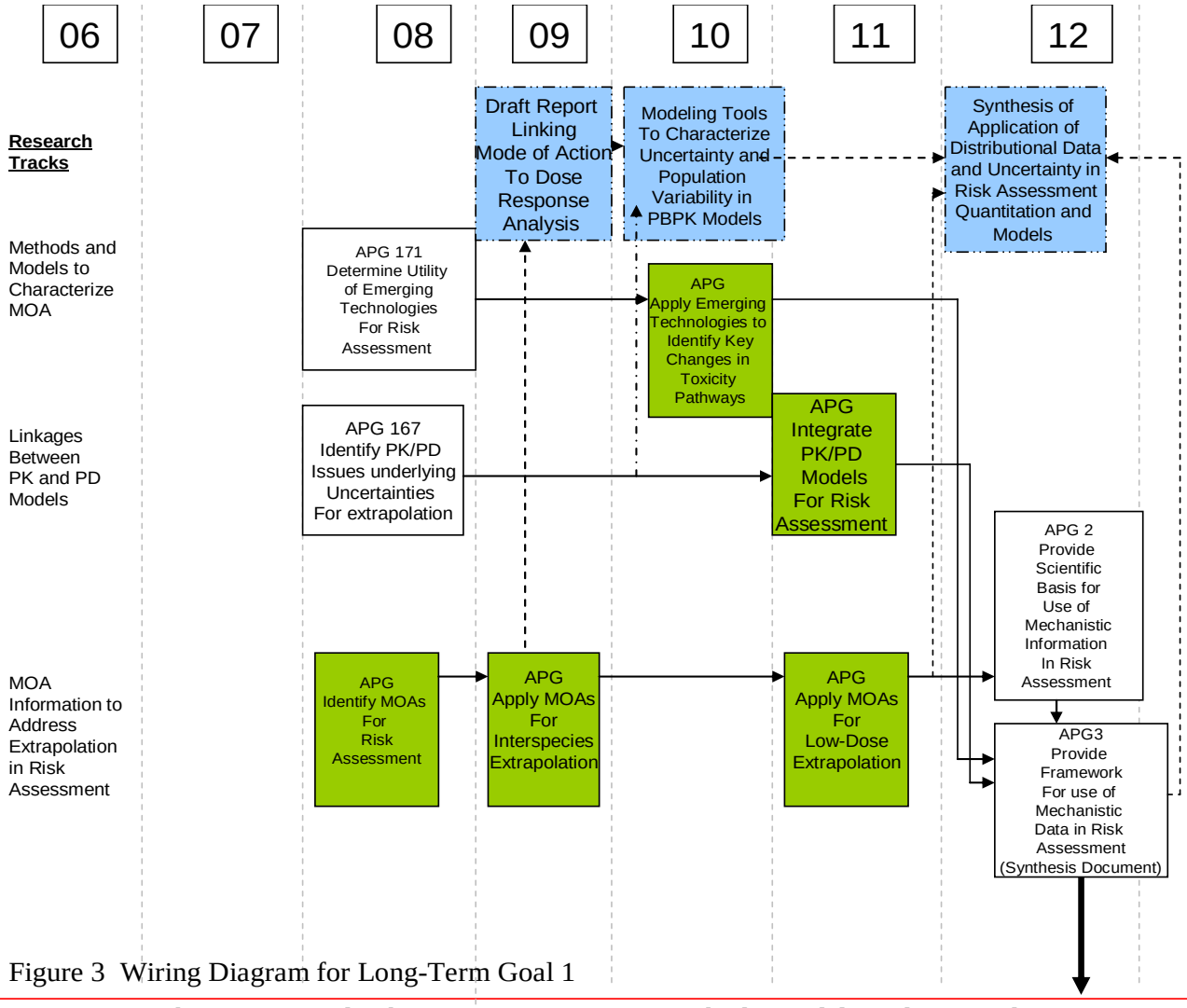


Figure 3 Wiring Diagram for Long-Term Goal 1

Risk assessors and risk managers use ORD's methods, models or data to reduce uncertainty in risk assessment using mechanistic (or mode of action) information

susceptibility, and effect. It also enables the identification of post-translational changes in proteins such as phosphorylation or glycosylation, which are integral to many of the signal transduction pathways that control cellular processes.

Metabolomics is proving useful in simultaneously evaluating changes in levels of small

molecule metabolites which represent the product of biochemical pathways controlled by cellular proteins. Alterations in the activities of proteins due to chemical insults translate into alterations in levels of cellular metabolites that are further reflected in the body fluids (e.g., blood, cerebrospinal fluid, saliva). Metabolic alterations provide clues to the site of action of chemicals, and can facilitate both *in vitro* to *in vivo* and animal to human extrapolations. Methodologies such as genomics, proteomics, and metabolomics as they are applied to toxicology are often referred to as toxicogenomics, toxicoproteomics, or toxicometabolomics. The Agency recently asked the NRC to conduct an independent review and develop a long-term vision strategy for toxicity testing (NRC, 2006). The NRC concluded that emerging techniques such as "omics" may help screen chemicals more rapidly and provide the basis for supporting the need for additional testing. Work in this research track addresses this recommendation.

This Research Track consists of two APGs. APG 171 FY08 "Determine utility of emerging technologies in harmonizing risk assessment" is a continuation of work from the previous MYP. Research in this APG will focus on evaluating the potential for toxicogenomic and related methods to detect key adverse effects used for risk assessment. This research will emphasize work on chemical classes being studied in other Research Tracks such as the conazole fungicides and arsenic (As). Work in APG FY10 "Apply emerging technologies to identify key changes in toxicity pathways" will develop methods to help identify key biological events (modes of action, MOAs) that could be used for possible risk assessment of a wider range of chemical classes, including air pollutants, pesticides, and drinking water contaminants, as well as conazoles and As. The chemicals and MOAs characterized in Research Track 3 were selected after discussions and negotiations with the Program and Regional Offices (Attachment B). The objective of this research is to develop MOA information that can be used to reduce uncertainty in exposure/dose-response extrapolation.

Work in this APG will also focus on transcript profiling to identify early signaling pathways which control key non-cancer (e.g., immune and cardiovascular disease) and cancer outcomes after exposure. It will define alterations in cell signaling pathways and link changes in these pathways to adverse outcomes. The focus of this work will be to develop methods that permit comparing effects across species and identify potential genetic factors responsible for

differential responses in sensitive subpopulations. Results from this work will be important for understanding biological differences between groups that may important for intraspecies extrapolation, as described in LTG 3 Susceptible Subpopulations- Research Tracks 1 and 2. Transcript profiling methods to identify key events will also facilitate research to identify potential biomarkers of exposure and effect in animals and humans. Biomarkers developed on the basis of exposure to a single chemical will be useful in identifying molecular and cellular indicators for cumulative risk, as described in LTG 2 Cumulative Risk- Research Track 1. Sensitive methods to identify MOA and reduce uncertainties in exposure/dose-response extrapolation are essential for developing computational and other approaches to prioritize chemicals for screening and testing. Such methods will make an important contribution to ORD's National Center for Computational Toxicology (NCCT) and the NRC (2006) recommendations.

This Research Track addresses the Key Research Questions by providing methods to:

- Identify key toxicity pathways that underlie cancer and non-cancer outcomes for high priority environmental pollutants
- Identify biomarkers that could be used to identify susceptible subpopulations (linked to LTG 2 Research Tracks 1 and 2, LTG 4 Research Track 1)
- Identify key biological events that could be used to evaluate cumulative risk of chemicals with a similar MOA (linked to LTG 2 Research Track 1, Biomarkers of Cumulative Risk)
- Identify key differences or similarities in response that could improve extrapolation from laboratory animals to human, *in vitro* to *in vivo*, and high to low dose in risk assessment
- Identify possible genetic differences as the basis for intra-human variability, i.e., differential responsiveness of some groups within the human population
- Develop "-omic" methods that could be used to develop approaches to screen and test chemicals based on MOA information

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment
Research Track 2: Develop Linkages between Pharmacokinetic and Pharmacodynamic Models

Assessing risk posed by chemical(s) depends on an understanding of toxicant concentrations or concentration-time pattern and the processes (i.e., MOAs) that result in a toxicological response. PK models allow for a more rational understanding and prediction of toxic effects by accounting for the time-dependent processes of absorption, distribution, metabolism, and excretion. The presumption in these analyses, whether implicit or explicit, is

that a fraction of the toxicant is channeled to biological targets within the organism where toxic action is exerted. The theory and application of PD has been employed to further elucidate critical events that occur at the target site (i.e., receptor binding and post-receptor events such as signal transduction). The integration of these two approaches, PK-PD modeling, provides real-time coordination of kinetic and dynamic processes and therefore has greater potential for extrapolation of response data generated with *in vivo* or *in vitro* models. Research in this track will focus on developing mathematical models to describe effects for several MOAs and classes of compounds of high regulatory interest to the Program and Regional Offices (see Attachment B). Research will address impaired nerve cell function by pyrethroid insecticides, multiple cellular responses to As, cellular consequences of altered thiol redox status, and activation of nuclear receptors by a wide range of chemicals, including conazole fungicides.

This Research Track consists of two APGs. APG 167 FY 08 "Identify PK/PD issues underlying uncertainties for extrapolation" is a continuation from the previous MYP. The focus of this research is on identifying parameters in PK and PD models that could be used to study similarities or differences in responsiveness between species and between different routes of administration. A new APG FY 11 " Integrate PK/PD models for risk assessment" is aimed at developing approaches to using PD data and integrating it into a modeling framework with PK models with the goal of submitting data or data-based modifying factors for the UFs used in risk assessment. Research will also be conducted to identify circumstances in which *in vitro* data could be included in developing PD models. This work will culminate in a report describing research that integrates both PK and PD models for selected MOAs that can be used to reduce uncertainty in risk assessments involving *in vivo* to *in vitro* and cross-species extrapolation in risk assessment.

This Research Track addresses the Key Research Questions by:

- Elucidating critical methodological issues and approaches for linking PK/PD models
- Determining the utility of PK/PD models for high to low dose, interspecies and *in vitro* to *in vivo* extrapolations in risk assessment (linked to LTG2, Research Track 1, Biomarkers for Cumulative Risk)
- Providing models applicable to broad classes of MOAs from several chemical classes expanding the options available for risk assessments based upon MOA (LTG1, Research Track 3, MOA Information to Address Extrapolation in Risk Assessment)

- Providing biological plausibility for substituting data for the UF in interspecies and intrapopulation extrapolation by risk assessors in NCEA, Program (OAR, OW, OPPTS) and Regional Offices

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment
Research Track 3: MOA Information to Address Extrapolation in Risk Assessment

MOA information can be used in risk assessment for several purposes. Key differences between laboratory animals and humans could mean that the animal data are not relevant to humans, e.g., the MOA in animals may be different from humans. This information would be important in determining if a full UF factor for animal-to-human extrapolation should be used in the risk assessment process. MOA information may also provide insight into the shape of the dose-response curve, particularly at the lower end of the curve. Evidence of a threshold may suggest that the dose-response curve is non-linear while the absence of a threshold might suggest a linear response curve. Knowing about the presence of a threshold would help risk assessors determine the appropriate risk assessment methodology. In addition, much MOA information is obtained using *in vitro* procedures. It is crucial to know if the MOA identified *in vitro* exists *in vivo.* The purpose of this Research Track is to address these uncertainties in the risk assessment process by conducting parallel dose-response studies on several chemical classes having putative MOA that are of interest to risk assessors (see Attachment B). It is hypothesized that information obtained on representative chemicals in each class could be extrapolated to other members of the same chemical class. Research in this track focuses on five classes of chemicals having high regulatory interest by Program and Regional Offices (see Attachment B), including conazole pesticides, neuroendocrine-related pesticides, As and related chemicals, air pollutants and other chemicals that may act by increasing OS, and brominated drinking water contaminants. The overall objective of this research is to identify key biological events that may be common for chemicals in each representative chemical class. Once MOA information is obtained using emerging molecular methods or with *in vitro* techniques, research will be done to determine if those changes can be extrapolated to *in vivo* models and humans.

The 2006 NRC report on toxicity testing for assessment of environmental agents indicated that structure-activity information and mechanistic data on environmentally relevant classes of chemicals should be developed to guide the assessment of chemicals that lack

adequate bioassay or human data. MOA research will be important for developing approaches to refine and replace current toxicity testing protocols. The combination of using emerging technologies developed in the first Research Track of this LTG and the MOA information for representative chemicals in environmentally relevant classes of agents is a first step toward evolving a strategy to facilitate the prioritization of chemicals for hazard identification (NRC, 2006). This work will be coordinated with model development research conducted by the NCCT as well as with other research partners such as the National Institute for Environmental Health Sciences (NIEHS).

This Research Track consists of three APGs. APG FY08 "Identify MOAs for risk assessment" will focus on using toxicogenomic, proteomic and *in vitro* methodologies to identify key biological events for representative chemical classes that could be used in more extensive dose-response assessments. Significant information about the biological effects of chemicals producing both cancer and non-cancer effects by different MOAs will be obtained. APG FY09 "Apply MOAs for interspecies extrapolation" will focus on the putative MOAs identified in the previous APG and determine if they can be extrapolated to *in vivo* models and humans. It is crucial that MOA information obtained using toxicogenomic or *in vitro* approaches based on animal models can be extrapolated to humans for the purpose of risk assessment. APG FY11 "Apply MOAs for low-dose extrapolation" will utilize putative MOAs in previous studies to determine effects of representative chemicals in the low dose region of the dose-response curve. These studies using representative chemicals with different MOAs will reduce uncertainties concerning extrapolation from high to low dose and provide guidance concerning the appropriate risk assessment approach. These studies will lead to a greater harmonization of how MOA information is used in all risk assessments (e.g., cancer and non-cancer).

This Research Track addresses the Key Research Questions by:

- Identifying key biological events for representative MOAs that can be used to reduce uncertainty in extrapolation in risk assessment, i.e., high to low dose, from animals to humans, and from *in vitro* to *in vivo* exposures
- Determining if there is a common MOA for chemicals of the same class that could be used for risk assessment (linked to LTG 2, Research Tracks 1 and 3, Biomarkers and Application of Tools for Cumulative Risk)
- Providing MOA at the low end of the dose-response curve for representative chemicals

and MOAs to help inform the choice of risk assessment methodology
- Developing comparable approaches for the use of MOA information in cancer and non-cancer risk assessments
- Identifying methods and models that could be used by other MYPs to determine MOA information for chemicals or classes of chemicals
- Provide MOA data that can be used to refine and replace current testing approaches for environmental agents

Synthesis of Research Tracks 1-3 and Long-Term Goal 1 Use of Mechanistic Data in Risk Assessment

Attachment D contains information on the various APMs that will be produced to support each of the APGs displayed in Figure 3. EPA risk assessors will have access to the peer-reviewed research outputs (i.e., methods, models, data) associated with the APMs as they are completed. Information derived from those studies will help inform specific problem-driven research questions and will be available to support on-going risk assessment of various chemicals or chemical classes of interest to Program and Regional Offices. At the completion of each APG, information derived from the research products will be summarized and communicated to the appropriate Program and Regional Offices. Integration of information from all of the Research Tracks is projected in APG 2 FY12 "Provide scientific basis for use of Mechanistic information in risk assessment." Products in this APG will consist of summary papers related to the use of mechanistic information to reduce uncertainties in risk assessment relative to various default assumptions in exposure/dose-response extrapolation. Principles derived from those products will be used to generate a synthesis document in support of APG 3 FY12 "Provide framework for use of mechanistic data in risk assessment." It is the intent of this document to provide a template for the use of MOA information to reduce or eliminate reliance on default assumptions in exposure/dose-response extrapolation in risk assessments. As indicated in Figure 3, research from the ORD program on the Use of Mechanistic Data in Risk Assessment will contribute to three APGs in the HHRA MYP, including information to support a draft report linking MOA to dose-response analysis in FY09, modeling tools to characterize uncertainty and population variability in PBPK models in FY10, and the synthesis of application and distributional data and uncertainty in risk assessment quantification and models in FY12.

2. Long-Term Goal 2: Cumulative Risk

a. Definition: Risk assessors and risk managers use ORD's methods, models, and data to characterize aggregate and cumulative risk in order to manage risk of humans exposed to multiple environmental stressors. Key Research Questions for this LTG follow:

- How can biomarkers be used in cumulative risk assessment?
  - What tools are needed to identify biomarkers for cumulative risk assessment?
  - How can those biomarkers be applied for cumulative risk assessment?
- What source-to-dose models are needed for cumulative risk?
  - What methods and models are available for assessing cumulative risk?
- How can tools be used to conduct cumulative risk assessments on chemical mixtures?
- How can cumulative risk at the community level be evaluated?
  - What tools are necessary for community-based risk assessments?
  - How can those tools be applied for community-based risk assessments?

b. Performance Measures: Figure 4 contains a wiring diagram of performance measures for research on cumulative risk. A description of the research supporting the APGs in each Research Track follows (see Attachment F for a more detailed explanation of the research at the project level):

Long-Term Goal 2: Cumulative Risk
Research Track 1: Biomarkers for Cumulative Risk

The goal of this research is to develop and demonstrate the processes, tools and information needed to better understand when and how people are exposed to environmental contaminants; the magnitude and timing of these exposures; how exposures translate into tissue dose and relate to potential health effects; how biomarker of exposure results reported from exposure and epidemiological studies can be used by risk assessors to improve aggregate exposures and CRA; and how exposure biomonitoring results can be used to demonstrate that the Agency's policies and regulatory actions have resulted in improved human health. This research is linked with the biomarker of effects research outlined in LTG 1 and the life-stage research described in LTG 3.

Biomarkers of exposure, as defined in this Research Track, are the concentration of a

chemical, its metabolite(s), and/or the biologically active molecule that can be measured in a human biological sample (e.g., blood, urine) following an exposure to the chemical. Biomarkers

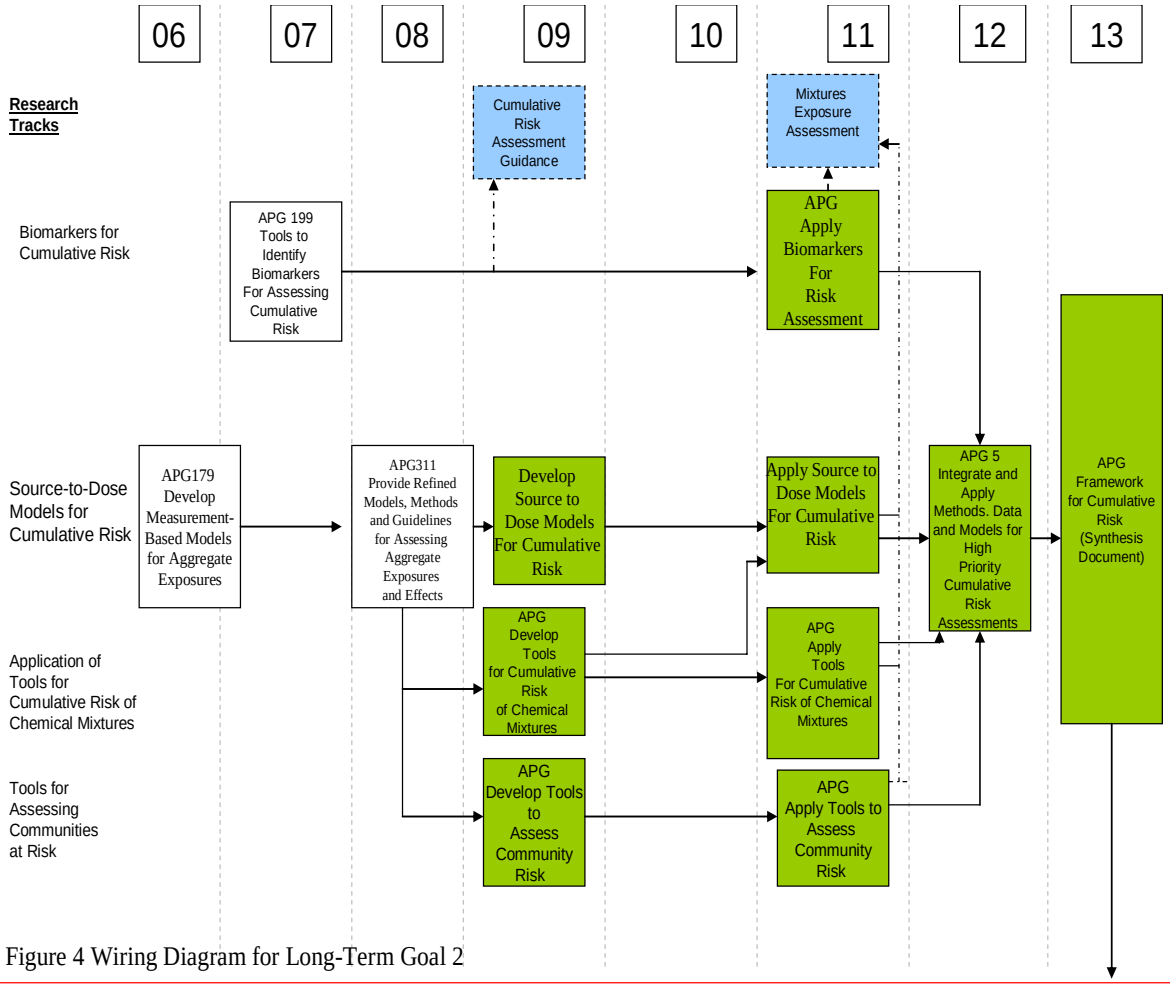


Figure 4 Wiring Diagram for Long-Term Goal 2

Risk Assessors and Risk Managers Use ORD's Methods and Models to Characterize Aggregate and Cumulative Risk in order to Manage Risk of Humans Exposed to Multiple Environmental Stressors

of exposure are used to link real-world human exposures with the corresponding internal dose and ultimately with the biomarker of effects (i.e., early biological response). It is important to note that for some chemicals, the biomarker of exposure may be identical to the biomarker of effect. Ideally, biomarkers of exposure can be used, along with the biomarker of effect and biomarker of susceptibility, to link environmental contamination to the risk of adverse effects in the public's health and to simplify and/or improve CRAs. Unfortunately, at the present time, biomarker of exposure data are difficult to interpret in terms of either human exposure or health risk. The Centers for Disease Control and Prevention (CDC), along with other health

researchers, currently obtains data on a variety of biomarkers of exposure in the US population through the National Health and Nutritional Examination Survey (NHANES). EPA has been called on to interpret the CDC data in terms of both exposure and health outcomes. The research outlined in this area will augment the CDC and other exposure and epidemiological studies that include biomonitoring activities by providing fundamental information to define the appropriate uses and how to interpret the results of biomarkers of exposure. To use biomarkers to their full potential, we must first understand the character and complexity of environmental exposures, the interactions with complex human biochemistry, and the eventual health outcomes.

This research track is designed to answer a number of general scientific questions, including how previous personal exposures can be assessed or reconstructed through a biological measurement and how to determine the range of typical personal exposures and how they relate to observed measures of internal dose through multiple routes. This research also focuses on developing the tools needed to design future exposure/epidemiological studies that will include the collection of biomarker of exposure samples and associated meta data. Other work will determine dose relates to biological availability; the inter- and intra-individual differences in the metabolism of an exogenous substance, and the biologically relevant metabolites, as well as the use of biomarkers of exposure to improve current exposure/risk assessment methodologies and to support accountability.

This research track is closely linked to research tracks in LTG1 and LTG3. For example, research in this track will identify preclinical markers for disease progression and how they relate to metabolism of native compounds of exposure, the changes in the expression of endogenous chemicals that reflect an adverse environmental exposure, early exposure response indicators of predisposition to specific diseases such as cancer, and the range of inter-individual susceptibility and how it compares with the range of exposure variability.

This Research Track is comprised of two APGs. APG 199 FY07 “Provide assessment and analytical tools for region and program offices in using biomarkers for assessing and addressing cumulative risks” is a continuation of the previous MYP. This work is focuses on analyzing existing children’s exposure data to identify factors for characterizing cumulative risk, developing new biomarkers of exposure, and developing methods to devise approaches for using

exposure, biomarker and PK data in CRAs. APG FY11 "Apply biomarkers for risk assessment" will take biomarkers identified using a single chemical/single pathway approach and applying them to CRA. This research will determine if toxicogenomic or toxicoproteomic endpoints can be used as sensitive indicators of exposure to mixtures of environmental chemicals. This research will also develop and demonstrate modeling tools to evaluate and assess exposure-biomarker-dose relationships and report on the development of systems biological approaches to link exposure to health outcome. It will also be important to determine if specific types of biological changes obtained for one chemical in a class can be extrapolated to other chemicals in the same class. Research in this track will also attempt to determine the inter- and intraindividual differences in metabolism to exogenous substances where the exposure occurs through multiple pathways. This research will be linked to LTG 2 Susceptible Subpopulations. Another objective of this research will be to identify preclinical biomarkers that may reflect disease progression, such as asthma. This research will be linked to LTG 2, Research Track 3 Research on Asthma.

This Research Track addresses the Key Research Questions by:

- Providing tools for assessing the cumulative risks from specific classes of environmental pollutants or from complex mixtures, to estimate the risk reduction from various levels of exposure reduction, and to monitor the subsequent efficacy of remediation efforts
- Providing guidance for the appropriate collection and interpretation of biomarkers for multiple uses
- Providing greater accuracy and precision to exposure assessments
- Characterizing and classifying preclinical markers, better estimates of aggregate internal dose, and the understanding of the characteristics associated with diminished or elevated susceptibility to pollutant exposures
- Providing tools for demonstrating policies and regulations that result in improved human health

Long-Term Goal 2: Cumulative Risk
Research Track 2: Source to Dose Models for Cumulative Risk

The goals of this research are to develop, evaluate and apply measurement-based modeling tools to quantitatively describe the ways that people are exposed to multiple environmental pollutants; to predict the target tissue doses that may result from such exposures; and to provide the fundamental science that enlightens risk assessments and policy decisions about the best ways to minimize exposures and to protect human health.

Humans are exposed to varying mixtures of chemicals in real-world environments from multiple sources by multiple pathways and routes. These exposures may result from a single event or they may accumulate over time if multiple exposure events occur. The traditional approach of assessing the risk from a single chemical and from a single route of exposure does not provide a realistic description of exposures and the cumulative risks that result from real-world exposure scenarios. Risk assessments within the Agency are now evolving toward "cumulative assessments" as mandated by new legislation including the FQPA and the SDWA. However, there are considerable uncertainties that remain to be addressed associated with assessing aggregate exposures and cumulative risks. State of the art predictive models can be used to reduce these uncertainties by describing the physical (including personal activity), chemical, and biological processes that lead to exposure and dose of chemical contaminants. Exposure models predict concentrations of pollutants in environmental media as well as describing the activities that bring an individual into contact with the contaminated media. Dose models describe how environmental pollutants, once in contact with humans, are absorbed into the body, distributed to the various organs where they may or may not be metabolized and then contribute to health problems. The research planned in this track is being designed to address the narrow definition of cumulative risk as defined by the FQPA, namely risks from mixtures of chemicals with a common "MOA." Research under the biomarkers and the community cumulative research track will address the broader issues of cumulative risks associated with multiple chemicals or other stressors.

Research in this track will address a number of scientific issues, including determining the environmental pollutants or mixtures of pollutants people are exposed to, the sources for these pollutants, and where and how people are exposed. Work will focus on the number of people exposed to these pollutants, at what levels, and over what time period. Research will also be done to determine the target tissue doses that follow these exposures, the factors that lead to exposure and dose, and the variability and uncertainty associated with these exposure and dose estimates.

This Research Track consists of four APGs. APG 179 FY06 "Develop measurement-based models/components for estimating aggregate exposures and doses" is a continuation of the

previous MYP. The primary focus of this research is to estimate aggregate exposure to indoor air contaminants and develop models to estimate exposure and dose of environmental chemicals for Agency risk assessors. This work will focus on the application of fugacity models that can be used for risk assessment and develop model components to estimate exposure and dose to environmental contaminant to assess aggregate exposure and risk. APG 311 FY08 "Provide refined models, methods, and guidelines for assessing aggregate exposures and effects" is also a continuation of research from the previous MYP. The main thrust of this APG is to apply methods and models from the previous APG to estimate aggregate risk in a risk assessment context. An additional focus of this work is to provide access to model components that can be used by Agency risk assessors and risk managers. APG FY09 "Develop source to dose models for cumulative risk" marks the transition of research from aggregate to cumulative risk. Products for this APG will focus on evaluate temporal variation in exposure to environmental contaminants in longitudinal studies. In addition, research will extend aggregate measurement-based models to assess cumulative exposures and risk. Finally, research in this APG will evaluate, refine and link model components for assessing cumulative exposures and risk. APG FY11 "Apply source to dose models for CRA" will use validated source-to-dose models developed in the previous APG and apply it to CRA. Products from this research will include databases on exposure patterns usage and consumption of high priority chemicals such as pesticides, peer-reviewed modeling tools, and guidance to Program and Regional Offices concerning the application of the models for CRA.

This Research Track addresses the Key Research Questions by:

- Generating data, methods, techniques, and models, and evaluating these under real-world scenarios, that demonstrate the usefulness of ORD's research tools for aggregate exposures and cumulative risk
- Producing fundamental science results that will be used to refine Agency guidance for conducting aggregate and cumulative risk assessments
- Providing opportunities for stakeholders to collaboratively develop new tools and guidance, and to conduct state of the art cumulative risk assessments
- Providing data for developing risk reduction and risk management strategies
- Developing new research hypotheses and for identifying and prioritizing future ORD research

Long-Term Goal 2: Cumulative Risk
Research Track 3: Application of Tools for Cumulative Risk of Chemical Mixtures

Assessing the risks posed by exposure to multiple chemicals is a problem that the Regions and Program Offices face on a daily basis. When OPP, OW, OAR, OSWER, NCEA and the Regional Offices conduct risk assessments on mixtures, they rely heavily on default models that contain a number of uncertainties. The goal of this program project is to reduce the uncertainties surrounding the default assumptions by testing the validity of these assumptions. The elucidation of the limitations of the default assumptions should help assess and predict risk of exposure to mixtures of toxicants. In this Research Track, both *in vivo* and *in vitro* experiments will be conducted. This research will focus on identifying the most sensitive methods for predicting and evaluating interactions of chemicals acting through a common mode of action, dissimilar or unknown MOAs of action. It is also important to determine how to predict interactions of chemicals after repeated exposure scenarios. In addition, to understand the dose-response to mixtures, research will determine how the direction (greater than-, less than-, or additive) and magnitude of effects of chemical mixtures can change as a function of dose level or as the ratio of the chemicals in the mixture changes. This includes the likelihood of non-additive interactions occurring at environmentally relevant exposure levels. Research will also address whether PK and PD mixture models can be used to extrapolate between species, from *in vitro* to *in vivo*, or to characterize intrahuman variability in response to mixtures. This Research Track approaches answering these questions by conducting parallel dose-response acute and repeated dosing studies on chemicals or chemical classes of interest to the Program and Regional Offices, especially those for which there is a regulatory driver, i.e., carbamate and pyrethroid pesticides, halogenated disinfection by-products, and HAPs.

Research in this Track is comprised of two APGs. APG FY09 "Develop tools for cumulative risk of chemical mixtures" focuses on determining sensitive and biologically plausible dose-related effects of chemicals or chemical classes following acute or repeated dosing. One component of the research will focus on identifying possible *in vitro* approaches that could be used to extrapolate to *in vivo* systems, including humans. Research in the APG will also consist of development of PK/PD approaches to estimate cumulative risk of environmental agents such as the pyrethroid pesticides. This work is linked to fundamental research conducted in LTG 1 Research Track 2 Linkage of PK/PD Models. APG FY11 "Apply

tools for CRA" will use the methods and models developed in the previous APG and develop principles and guidance as their application for CRA. Principles will be generated for at least three chemical classes, including carbamate and pyrethroid insecticides, halogenated disinfection by-products and HAPs. One component of this APG will be the development of experimental databases for high priority chemical classes such as the pyrethroid pesticides. This research will also examine the role of external factors such as dosing scenario and ratios of chemicals in mixtures to predicted effects. Other research will summarize research on extrapolation of *in vitro* to *in vivo* models, as well as the integration of PK/PD models to predict the effects of pesticides in mixtures.

This Research Track addresses the Key Research Questions by:

- Developing general principles to improve cumulative risk assessment decisions for a variety of chemicals, including environmental toxicants, chemicals present in water due to environmental contamination and those formed during chemical disinfection of water, pesticides, and the residual risk of HAPs
- Providing data from chemical classes that will directly support on-going risk assessment decisions by Program Offices (OW, OPP, OPPT, OAR) and NCEA, including the carbamates and pyrethroid pesticides (linked to LTG 1 Research Track 2, Linkage of PD/PK Models for Risk Assessment)
- Developing and implementing dose-time-response models for calculating the relative potencies of N-methyl carbamate pesticides, and develop models to assess cumulative risk of N-methyl carbamate exposure in drinking water
- Addressing issues of extrapolating mixture data across dosing scenarios, dose levels, methodologies, and populations (linked to LTG3, Track 1, Life-stage Susceptibility)
- Enabling an understanding of the influence of dose and mixture composition on non-additive interactions and the joint toxic action of mixtures
- Developing *in silico* predictive models based on systems biology approaches that will link *in vitro*, PK, and *in vivo* PD components (linked to LTG 1, Research Tracks 1-3)

Long-Term Goal 2: Cumulative Risk
Research Track 4: Tools for Identifying and Assessing Communities at Risk

The goals of this research are to develop, evaluate, and apply tools for estimating exposures to multiple stressors that will lead to cumulative risks. Research is specifically targeted toward understanding the key elements that lead to groups of individuals and/or community-level exposures and risks.

Individuals have differential chemical exposures and potential risk of adverse health effects, regardless of whether chemical exposure occurs singly or as mixtures of several chemicals. Elevated exposures can result from frequent contact with environmental contaminants and depends on the spatial and temporal variation in chemical concentrations and human time-location-activity-patterns. Progress has been made in estimating aggregate exposure to single chemicals through the development of probabilistic models that account for variations in environmental concentrations and in human activities. However, the traditional approach of focusing on a single chemical does not provide a realistic description of exposures to mixtures of chemicals and the resulting cumulative risk in the real world. Risk assessments within the Agency are now evolving toward cumulative assessments, which in the broadest sense address risks from exposures to multiple chemical and non-chemical stressors accumulated over time.

When considering multiple stressors and their location of occurrence and contact, increased risk may be shared among groups of individuals or within a community. For example, where a community is located will determine the sources, routes, pathways, and magnitude of chemical exposures. Community norms may influence the activity patterns and dietary habits, which will determine the way that individuals come in contact with contaminated media. Finally, community may be defined by other non-chemical stressors that could impact risk, including socioeconomic status, cultural behavior, access to healthcare, and educational level. Focusing on the community, a multidimensional and dynamic classification of individuals defined by geographical and or demographical attributes that are common among the group, provides a rational starting point for developing, evaluating, and applying cumulative risk tools.

This research is designed to addresses a number of scientific questions, including determining exposures to pollutants and other non-chemical stressors that lead to cumulative risks in a community and assessing how to identify and prioritize communities at risk. Other work will focus on assessing if exposures to pollutants and other non-chemical stressors are distributed equally across the community, the relative risk from different sources of pollutants within a community, and the most effective approaches for reducing risks within a community.

This Research Track consists of two APGs both of which are new to the HHRP. APG FY09 “Develop tools to assess community risk” will focus on identifying modeling tools and

approaches and developing a research framework to assess community risk. Research in the APG will produce a research framework outlining tools and approaches to prioritize and assess communities at risk, as well as provide risk assessors and risk managers with new and updated methods and models for characterizing community exposures to both chemical and non-chemical environmental stressors. APG FY11 "Apply tools to assess community risk" will begin to apply the approaches described in the previous APG to real world environmental situations in selected communities. A final report to Program and Regional Offices on the application of such approaches in also planned.

This Research Track addresses the Key Research Questions by:

- Providing the methods, models, and data that will allow risk assessors and risk managers to more accurately estimate risk from multiple stressors accumulated over time, pathways, and routes within a community-level structure (e.g., both demographical and geographical)
- Developing methods and models that can be used in epidemiological research to provide better estimates within a community.
- Providing data that can be used to develop and evaluate the impact or risk management mitigation strategies at the community level

Synthesis of Research Tracks 1-4 and Long-Term Goal 2 Cumulative Risk

Attachment D contains information on the various APMs that will be produced to support each of the APGs displayed in Figure 4. EPA risk assessors will have access to the peer-reviewed research outputs (i.e., methods, models, data) associated with the APMs as they are completed. Information derived from those studies will help inform specific problem-driven research questions and will be available to support on-going risk assessment of various chemicals or chemical classes of interest to Program and Regional Offices. At the completion of each APG, information derived from the research products will be summarized and communicated to the appropriate Program and Regional Offices. Integration of information from all of the Research Tracks is projected in APG 5 FY12 "Integrate and apply methods, data and models for high priority CRAs". Products in this APG will consist of summary documentation of methods, models and data to conduct CRAs for chemical and non-chemical environmental stressors. Principles derived from those products will be used to generate a synthesis document in support of APG FY13 "Framework for cumulative risk". The intent of this document is to

provide a template for conducting CRA and reduce or eliminate reliance on default assumptions in assessing multiple chemical/multiple pathway exposures. As indicated in Figure 4, research in this Track will contribute to two APGs from the HH RA MYP, including Guidance for Cumulative Risk in FY09 and Mixtures Exposure Assessment Guidance in FY11.

3. Long-Term Goal 3: Susceptible Subpopulations: Interspecies Extrapolation

a. Definition: Risk assessors and risk managers use ORD's methods, models, and data to characterize and provide adequate protection for susceptible subpopulations. The Key Research Questions for this LTG are as follows:

- Is there differential life-stage responsiveness or exposure to environmental agents
  - What are the long-term effects of developmental exposure to chemicals?
  - How does aging affect responsiveness to environmental chemicals?
  - How can we model exposure and effects to protect susceptible subpopulations?
- Which methods and models are appropriate for longitudinal research with children?
- What are predisposing factors for asthma as a function of life-stage and how do they interact with indoor air environments?

b. Performance Measures: Figure 5 contains the "wiring" diagram for the performance measures for LTG 3. An description of the research supporting the APGs in each Research Track follows (see Attachment F for a more detailed explanation of the research at the project level):

Long-Term Goal 3: Susceptible Subpopulations
Research Track 1: Research on Life-Stage

Work in this Research Track addresses the concern that exposure to and resulting biological effects of environmental agents can have differential effects as a function of life-stage. This research will determine if there are key critical developmental windows that are associated with increased susceptibility or vulnerability to environmental agents. It is important to know if age-related exposures or effects are generalized phenomena or agent or class-specific. If there are differential life-stage dependent responses to environmental chemicals, it will be important to determine the PK or PD basis for those effects. If MOA information is being used with greater frequency in risk assessment, it will be important to know if MOAs vary as a function of life-stage. This Research Track will focus on three general approaches, including research on the long-term effects following developmental exposure, tools to measure exposure and effects in older populations, and studies on exposure and effects in children.

There are five APGs in this Research Track. APG 14 FY09 "Long-term effects following developmental exposure" will address the observation that clinical and

epidemiological studies

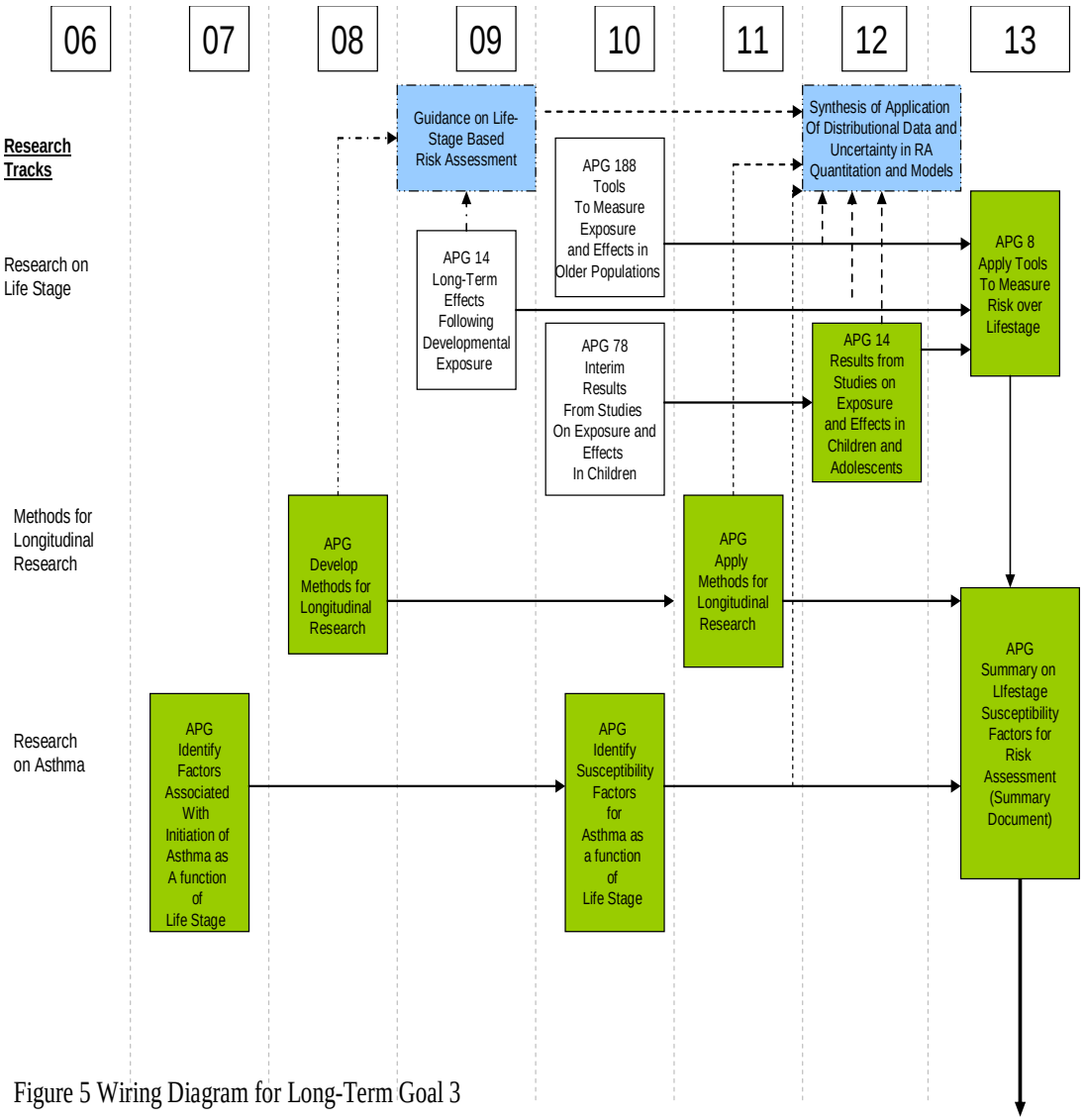


Figure 5 Wiring Diagram for Long-Term Goal 3

Risk Assessors and Risk Managers Use ORD's Methods and Data to Characterize and Provide Adequate Protection for Susceptible Subpopulations

have shown significant correlations between the *in utero* and early-life environments (using birth weight and early growth as indicators) and disease states later in life, including hypertension, coronary heart disease, diabetes, obesity, schizophrenia, early onset chronic renal failure, cancer and compromised reproduction. Recent studies suggest that some of these effects may involve epigenetic changes that can persist through multiple generations. The most common adverse effect seen in developmental toxicology bioassays with rodents is reduced fetal weight. Current developmental study designs do not assess long term morbidity in offspring. This APG will

include studies that utilize animal models to define the causal factors and identify long-term effects under controlled experimental conditions that are impossible to duplicate in epidemiology studies. The focus on this research will be on developmental exposures in rodents and evaluation of outcomes later in life, although reproductive toxicity will be emphasized.

APG 188 FY10 "Tools to measure exposure and effects in older populations" will address the fact that the average of the population of American adults older than 65 is rapidly increasing. There is a need to determine if and how environmental factors may interact with increased health risks as a function of aging. While the susceptibility of the aging population is explicitly recognized in amendments to the CCA and the SDWA, the risks of environmental exposures to older adults could significantly impact decision-making in all of the Agency's Program and Regional Offices. This research will take a highly integrated approach to identifying and understanding the factors leading to the increased susceptibility of older adults to environmental pollutants. The overarching goal is to reduce uncertainty in risk assessment by characterizing both the hazardous exposures and biological basis of susceptibility of the aging population in relation to the general population. One significant output in this APG is the development of a framework to guide ORD's research on aging. Laboratory-based studies will focus on assessing the PK and/or PD changes in capacity that occurs with aging and the potential for differential life-stage sensitivity to environmental chemicals.

APG 78 FY 10 "Interim results from studies on exposure and effects in children" and APG FY12 "Results from studies on exposure and effects in children and adolescents" responds to concerns about risks to children from exposures to chemicals. This Track conducts research to fill critical gaps in our understanding of children's exposures, susceptibility, and differential risk. Products for APG 78 consist of determining the dietary intake of high priority environmental chemicals such as pesticides and developing models to determine exposure patterns associated with children's exposure to these chemicals. Research will also determine how current risk management practices reduce or prevent exposure of children to hazardous pollutants in indoor environments. Differential responsiveness of younger animals to other chemical classes will be studied in the out-years and will focus on the developing nervous system. This research provides fundamental science needed for the development of testing methods to provide more sensitive

and cost-effective screening approaches for assessing developmental neurotoxicity. Products for APG14 FY12 will consist of long-term longitudinal and epidemiological studies assessing exposure patterns of children and adolescents in a variety of environmental scenarios. Attempts will be made in coordinated intramural and extramural research products to link such exposures to adverse health outcomes.

APG 8 FY13 "Apply tools to measure risk over life-stage" will consist of a number of summary documents that describe the relationship between early exposure to environmental chemicals and the development of adverse health effects such as reproductive toxicity, as well as research on risk management approaches. This APG will also produce summary reports on models for differential exposures to environmental chemicals as a function of life-stage and on the biological basis (PK and PD) for differential responsiveness to environmental chemicals as a function of life-stage. Output also include guidance on using potentially high-risk consumer products, reports on risk management opportunities in schools and evaluation of the effectiveness of the risk management methods for solving indoor air quality problems in schools.

This Research Track addresses the Key Research Questions by:

- Elucidating early biological indicators of effect, MOAs and potential biomarkers that vary as a function of life-stage
- Identifying methods and models that could be used by other MYPs to assess life-stage susceptibility
- Developing efficient study designs (e.g., age groups for exposure assessments) to study effects of and exposure to chemicals as a function of life-stage
- Identifying potential susceptible subpopulations based on life-stage dependent exposures, activity patterns, and health status that could significantly change current risk assessment practices and policies
- Developing integrative exposure-dose-response models for quantitatively characterizing susceptibility to environmental pollutants in susceptible subpopulations and minimizing reliance on default assumptions in assessing risk
- Developing and verifying information to support an Exposure Factors Handbook for the aging and children that can be used by Regional, State and local agencies, as well as community associations, for evaluating the potential risks of environmental pollutants
- Providing guidance to Program and Regional Offices concerning the appropriate use of safety factors to protect potentially sensitive subpopulations based on life-stage
- Developing both qualitative and quantitative exposure assessment methods that could be applied to longitudinal methods in Research Track 2 of this LTG
- Developing broadly applicable risk management solutions that will allow schools to carry out practical action plans to improve indoor air quality and protect children's health at

reasonable cost

Long term Goal 3: Susceptible Subpopulations
Research Track 2: Methods for Longitudinal Research

Current efforts to identify environmental factors associated with important public health outcomes like childhood asthma and neurobehavioral development are limited by retrospective epidemiology study designs. The NCS was intended to be a large federally-sponsored prospective study of children's environmental health authorized under the Children's Health Act of 2000 (for more information see: www.nationalchildrensstudy.gov). The legislation named the Agency as a partner with CDC and National Institutes of Health (NIH) to plan, implement, and conduct this comprehensive epidemiology study following approximately 100,000 children and their families from before conception to age 21. Primary health endpoints were pregnancy outcomes, asthma, injury, obesity and physical development, and neurobehavioral development. Exposures to be measured included biological, chemical, psychosocial and physical factors. In addition, gene environment interactions were to be assessed as they relate to multiple outcomes. However, due to the relatively high cost of conducting such an extensive longitudinal study in children over several years, funding for the NCS was not provided in the FY07 budget. However, methods and models for designing and conducting longitudinal studies are still needed.

Research in this Track will focus on three general areas: 1) determining if repeated, low-level exposure to non-persistent pesticides, including carbamates, organophosphates, and pyrethroids, *in utero* or postnatally increases risk of poor performance on neurobehavioral cognitive examinations during infancy and later in childhood among those with genetic polymorphisms, 2) assessing if exposure to bioaerosols including allergens, endotoxins, and mold is associated with increased risk of onset of asthma and 3) elucidating the biological basis for critical periods of development as it relates to neuroendocrine disruption.

This Research Track consists of two APGs, both of which are new to the HH MYP. APG FY08 "Develop methods for Longitudinal Studies in Children" will focus on experimental design for the longitudinal studies, as well as developing recruitment approaches and sampling methods. Products for APG FY11 Apply methods to associate exposure and environmental

disease" will consist of observations made from the pilot study that will screen several thousand children starting in March 2006. Outputs from the extramural program will identify early biological indicators of environmentally induced disease in young children.

This Research Track addresses the Key Research Questions by:

- Maintaining collaborative efforts of the Agency and the DHHS, including a study team at the Agency that includes ORD, OCHP and Office of Environmental Information (OEI)
- Identifying factors that are harmful, harmless and helpful so that prevention and intervention efforts can be targeted appropriately
- Providing to the scientific and risk assessment community a dataset that can be used to address questions on children's health and development
- Providing longitudinal data with measures of exposures and exposure factors for women of child-bearing age, pregnant women, as well as infants and toddlers
- Providing an opportunity to assess the relationship between community level ambient exposure measures and individual household measures on a national scale.
- Providing linkage to corresponding international efforts developed with the World Health Organization, including developing a set of common core measures to help study rare outcomes such as childhood cancer
- Providing unique approach data on antecedents of widely occurring childhood diseases, such as asthma (linked to LTG 2 Susceptible Subpopulations-Research Track 3 Research on Asthma)
- Providing access to biologic and environmental samples for intramural research collaboration
- Developing novel methods of exposure or health assessment at different stages of child development (linked to LTG 2, Research Track 1, Biomarkers for Cumulative Risk)

Long-Term Goal 3: Susceptible Subpopulations
Research Track 3: Research on Asthma

Asthma is the most common chronic respiratory disease in children growing up in western societies, and is understood to have both genetic and environmental influences. In 1995, the prevalence of asthma has reached 7.5%, or approximately 5 million children. Although children appear to be the population most at risk, there is growing concern that new cases are also arising in adults. ORD has developed a targeted asthma research program, outlined by a peer reviewed 2002 Asthma Research Strategy (US EPA, 2002a). ORD's research focuses on the role of common air pollutants and bioaerosols in the onset and exacerbation of asthma in susceptible populations, the underlying mechanisms involved, and the development of improved risk management methods. The objectives of this research are to determine the diverse

responsiveness of life-stages to air pollution exposure, the different factors responsible for the differential responsiveness and the predisposing factors for asthma. The intended beneficiaries of this research program are primarily Agency Program Offices, especially OAR; OCHP; Office of Prevention, Pesticides and Toxic substances (OPPTS); and Regional Offices. Research in this Track will determine how exposure to air pollutants, bioaerosols (molds), and allergens affect the incidence and severity of asthma. The factors responsible for susceptibility and vulnerability to asthma relative to life stages, and the populations most affected will also be studied. Also of concern are the underlying mechanisms for induction and exacerbation of asthma and the best risk management strategies to reduce the burden of asthma.

This Research Track contains two new APGs. APG FY07 "Identify factors associated with initiation of asthma as a function of life-stage" will focus on the development of animal models of asthma to study how environmental pollutants such as diesel exhaust particles and molds initiate asthma, particularly in younger populations. APG FY10"Identify susceptibility factors for asthma as a function of life-stage" builds on the previous APG to determine if *in utero* diesel exposure increases the potential to develop allergic asthma. Research will also be done to determine if certain species of mold are associated with childhood asthma in water-damaged homes

This Research Track addresses the Key Research Questions by:

- Providing data demonstrating the association between early-life exposure to mobile source emissions and their role in induction of asthma in children and in elderly which will be applied to risk assessment activities
- Improving the understanding of the mechanisms underlying differential susceptibility to pollutants leading to an improved design of strategies to protect asthmatics from air pollutants and buttress the current standards for ambient air pollutants
- Providing data for the improved prediction of human health risk to air pollutants, identify potentially susceptible populations, and provide guidelines for exposures to classes of air toxics
- Demonstrating the impact of exposure to different types of diesel and molds on the development of allergic asthma needed to reduce the risk of exposure to air contaminants
- Providing the scientific basis and tools to improve the identification and quantification of molds leading to better guidance to parents of asthmatic children on mold types, their exposures, potential health effects and relative priorities for mitigation strategies

Synthesis of Research Tracks 1-3 and Long-Term Goal 3 Susceptible Subpopulations

Attachment D contains information on the various APMs that will be produced to support each of the APGs displayed in Figure 5. Agency risk assessors will have access to the peer-reviewed research outputs (i.e., methods, models, data) associated with the APMs as they are completed. Information derived from those studies will help inform specific problem-driven research questions and will be available to support on-going risk assessment of various chemicals or chemical classes of interest to Program and Regional Offices. At the completion of each APG, information derived from the research products will be summarized and communicated to the appropriate Program and Regional Offices. Integration of information from all of the Research Tracks is projected in APG FY13 "Summary on life-stage susceptibility factors for risk assessment." This document will consist of summary documentation of methods, models and data that can be used to protect susceptible groups in the human populations and reducing reliance on the default assumption for intra-species extrapolation in the risk assessment process. As indicated in Figure 5, research in this Track will contribute to the APG from the HH RA MYP FY12 "Integrate and synthesize a risk assessment framework for risk assessment across life-stages."

4. Long-Term Goal 4: Assessment of Risk Management Decisions

a. Definition. Risk assessors and risk managers use ORD's methods and models to evaluate the effectiveness of risk management decisions. Key Research Questions for this LTG are:

- What are the trends in health status in the US?
- What tools are available to determine the impact of regulatory decisions on exposures to environmental stressors that lead to adverse health outcomes?

b. Performance Measures: Figure 6 contains the "wiring" diagram for the performance measures for LTG 4. A description of the research supporting the APGs in each Research Track follows (see Attachment F for a more detailed explanation of the research at the project level):

Long-Term Goal 4: Evaluation of Risk Management Decisions
Research Track 1: Approaches to Evaluate Risk Management Decisions

The objective of this research track is to develop and validate EPHIs. These indicators are intended to reflect more closely the actual impact of environmental decision-making on public health and help clarify the health benefits and financial costs associated with further incremental environmental improvements. The current label applied to this overall effort is accountability, i.e., the Agency's desire to be more accountable to the public in demonstrating true environmental progress. The key to using outcome-based indicators is a clear understanding of the sequence of events that link changes in the environmental conditions to health. This Research Track is a primary recipient of fundamental research conducted in LTGs 1-3.

Understanding the determinants of the events that comprise the exposure-dose-effect continuum (Figure 1) and the linkages between them has always been a key priority for the Agency (US EPA, 2003b). In fact, these determinants underlie the science upon which the Agency bases the risk assessment process (NAS, 1983) for making regulatory decisions and implementing risk management actions for a given pollutant and/or condition. The Agency will also use these determinants to proactively identify opportunities to protect public health. In this process, all available exposure, toxicological and epidemiological data are assembled,

synthesized and analyzed in formulating the risk assessment. Risk assessments, to a large degree,

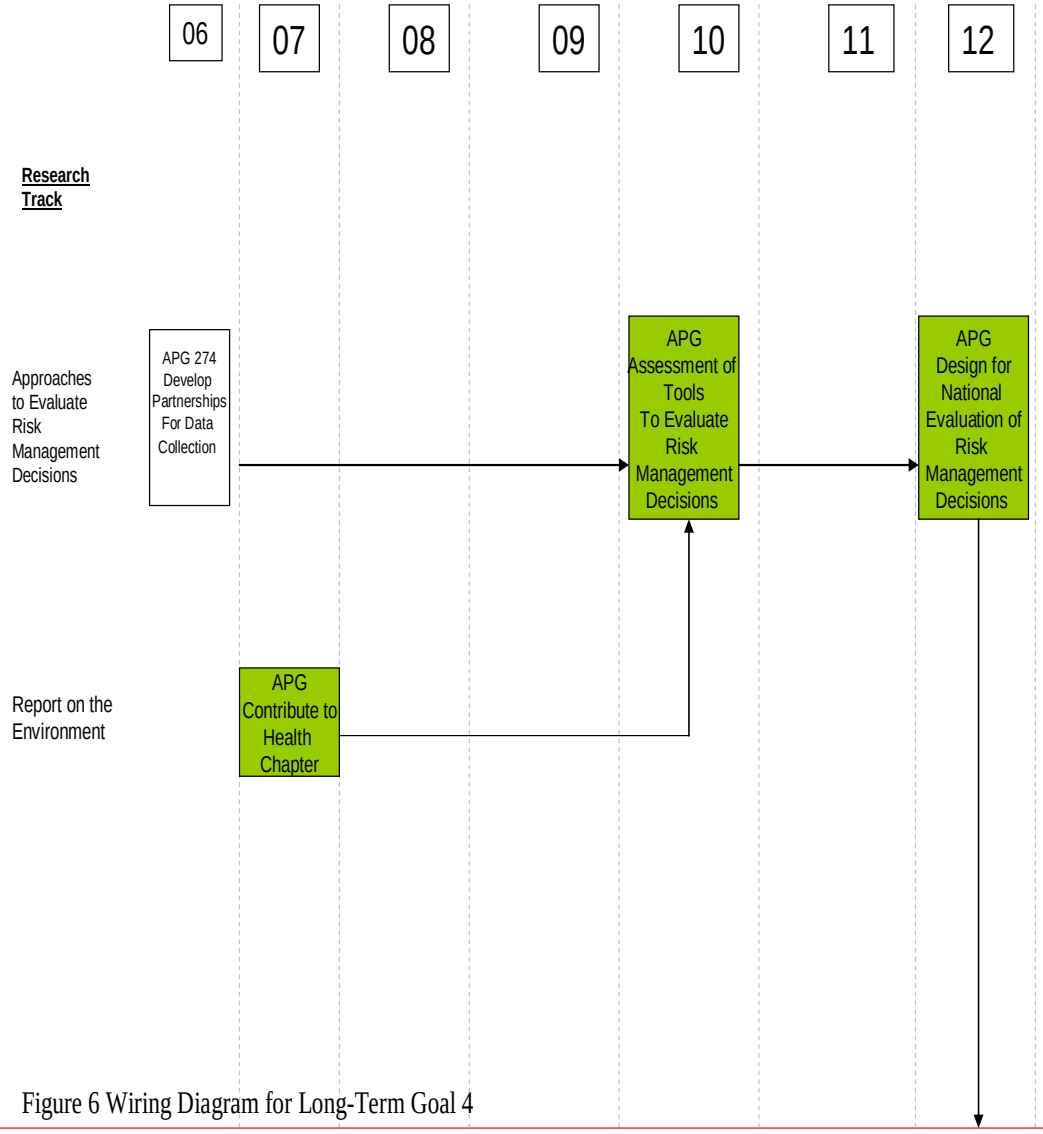


Figure 6 Wiring Diagram for Long-Term Goal 4

Risk Assessors and Risk Managers Use ORD's Methods and Models to Evaluate Risk Management Decisions

estimate these linkages to assess the probability and magnitude of outcomes. This research will address approaches to demonstrate the relationship between Agency action, outcomes such as exposure reduction and health benefits, and the methods, models or data that currently exist to evaluate Agency actions for public health benefit. The goal of this research program is to better understand the impact of past Agency decisions and to better estimate the impact of future Agency decisions.

This Research Track consists of two APGs. APG 274 FY06 from the previous HH MYP will provide information on public health and public exposure indicators that reflect early detection of public health effects. APG FY10 "Assessment of tools to evaluate risk management decisions" will describe results from two proof-of-concept studies focusing on developing approaches to assess changes in health parameters as a function of changes in exposure due to regulatory actions by the EPA.

Research in this Track addresses the Key Research Questions by:

- Providing a matrix of local health data to convey the health status of vulnerable populations
- Developing questionnaire data on activity patterns for vulnerable populations for OAQPS
- Developing GIS maps of air quality and modeled exposures for air toxics, ozone and particulate matter (PM) in New Haven, CT
- Applying and evaluating Industrial Source Complex modeling approaches
- Determining exposure predictors of health outcomes for vulnerable populations
- Providing case studies demonstrating how measurements, models and health effects analysis tools might be used in other communities and at the national level
- Linking surrogate monitoring information to public health outcomes
- Providing tools for risk assessment methodologies in estimating public health impacts of drinking water regulations
- Aiding the Agency in refining assumptions used to estimate waterborne disease
- Improving estimates of public health effects associated with recreational water criteria

Long-Term Goal 4 Evaluation of Risk Management Decisions
Research Track 2: Health Chapter for Report on the Environment

The purpose of this program is to identify potential EPHIs. These indicators, while complementing traditional process indicators such as decreases in emissions, discharges and pollutant levels in environmental media, are intended to reflect more closely the actual impact on public health that result from environmental decision-making and to help clarify the benefits and costs associated with further incremental environmental improvements. The *Report on the Environment (ROE) 2007* is the product of a continuing Agency-wide effort to compile and assess information that helps answer broad questions important to the Agency concerning the state of the nation's whole environment – air, water, land, human health, and ecological condition. The ROE began with the release of the Draft RoE in 2003. The report selects environmental indicators that help answer the ROE question, and highlights important gaps indicator data and/or understanding that prevent the questions from being fully answered. This

dual objective positions the ROE as a potential tool for strategic research planning within the Agency. This Research Track has one APG "Health Chapter for RoE in FY07.

This effort addresses the Key Research Questions by:

- Determining trends in health status in the United States.
- Determining trends in human disease and conditions for which environmental pollutants may be a risk factor, including across population subgroups and geographic regions
- Determining trends in human exposure to environmental pollutants including across population subgroups and geographic regions

Synthesis of Research Tracks 1-2 and Long-Term Goal 4 Evaluation of Risk Management Decisions

Attachment D contains information on the various APMs that will be produced to support each of the APGs displayed in Figure 6. Agency risk assessors will have access to the peer-reviewed research outputs (i.e., methods, models, data) associated with the APMs as they are completed. At the completion of each APG, information derived from the research products will be summarized and communicated to the appropriate Program and Regional Offices. Integration of information from all of the Research Tracks is projected in APG FY12 "Design for national study to evaluate risk management decisions". This document will integrate principles derived from demonstration projects at the regional level and information on human health trends in the US to develop a national approach to evaluate the effectiveness of environmental legislation or health advisories.

VI. Relationship to Other Multi-Year Plans

Linkages between the newly developed HHRA MYP and the HHRP MYP are noted in the "wiring" diagrams (Figures 3-6). The HHRA MYP receives methods, models and data from ORD laboratories, including research covered by the HHRP. As a client of the laboratories, the HHRA MYP helps prioritize research in the ORD laboratories by identifying critical data gaps and scientific needs, but does not conduct or fund this work itself. In contrast, the HHRP plans and coordinates the performance of primary laboratory work on the health effects of environmental pollutants, emphasizing longer-term, cross-cutting, or multimedia research questions. It is anticipated that, in implementing the HHRA MYP, ORD-NCEA will identify

research needs during the course of conducting risk assessments and will contact the appropriate National Program Directors to develop strategies for obtaining crucial information for specific risk assessments. It is also anticipated that ORD-NCEA and the ORD laboratories will meet on a regular basis to determine how general principles derived from research can be used to develop guidance documents and other products for the HHRA MYP. Attachment C provides a cross-walk between research themes in the HHRP MYP and human-related topics in other ORD MYPs. This cross-walk was developed after discussions with the National Program Directors for Air, Drinking Water, Endocrine Disruptors, and Safe Pesticides/Safe Products.

VII. Relationship to the Research & Development (R&D) Investment Criteria

As part of the President's Management Agenda (http://www.whitehouse.gov/omb/budintegration/pma_index.html), explicit criteria were developed for managers to use for assessing R&D programs. The R&D Investment Criteria consist of three categories, including:

- Relevance- R&D programs must have clear plans and demonstrate relevance to national priorities, agency missions, and "customer" needs
- Quality-programs should maximize the quality of the research through the use of clearly stated, defensible methods for awarding a majority of their funding
- Performance- programs should maintain a set of high priority, multi-year R&D objectives with annual performance outputs and milestones that show how one or more outcomes will be reached

The R&D Investment Criteria were used by OMB in the evaluation of the HHRP using the Program Assessment Rating Tool (PART) during FY05. OMB rated the HHRP as "Adequate" and had the following comments:

- The program has an unambiguous, focused design, and there is no evidence of major flaws that would limit the program's effectiveness or efficiency
- The program has meaningful annual and long-term performance measures
- The program's research results are being used to reduce uncertainty in risk assessment

OMB also noted that the HHRP needed to develop verifiable ambitious long-term measures and define what outcomes would represent a successful program. OMB also noted that the HHRP needs more data and clearer long-term targets to show that it is making continued progress. The HHRP is taking steps to improve the ability to link budget resources to annual and

long-term performance targets, develop ambitious long-term performance targets that clearly define what outcomes would represent a successful program, and continue to use independent expert external reviews to assess program planning, performance and implementation of OMB's recommendations. The OMB process led to the identification of two performance metrics for the HHRP, including the development of bibliography of externally peer-reviewed scientific products that will be evaluated for impact on the field using a bibliometric analysis and documentation of how such products have been used by risk assessors and risk managers to reduce reliance of defaults assumptions in human health risk assessments.

On February 28-March 2, 2005, the Human Health Subcommittee of ORD's BOSC reviewed the HHRP. The Subcommittee was asked to comment specifically on how the program met the R&D Investment Criteria. Their comments (http://www.epa.gov/osp/bosc) are as follows:

Relevance- the overall purpose of the HHRP was clear, i.e., it addresses limitations in human health risk assessment with a focus on biological modes of toxicity, aggregate and cumulative risk, susceptible subpopulations and evaluations of public health outcomes resulting from risk management decisions. The BOSC found that the program provides broad fundamental scientific information that will improve understanding of problem-driven human health issues arising from Agency's program and regional offices, other federal agencies, international health organizations, the regulated community, and the academic community. The BOSC also found that the HHRP was designed to address specific needs identified by external advisory bodies and clients and stakeholders of the program. The BOSC reported that the outputs of the program were designed to address customer needs. The HHRP was also found to be multidisciplinary and displayed good stakeholder participation in the planning of the program.

Quality- the BOSC found that 1) the HHRP program was free of major flaws that would limit the program's effectiveness or efficiency, 2) the program was designed so that resources address the program's purpose directly and will reach intended beneficiaries, 3) grants were awarded on a clear competitive process that includes a qualified assessment of merit, and 4) the program used a prioritization process to guide budget requests and funding decisions.

Performance- the BOSC noted that HHRP program 1) had a limited number of specific measures that can demonstrate progress toward achieving the program's LTGs and APMs, 2)

had in place a process of independent evaluations of sufficient scope and quality to evaluate on a regular basis the effectiveness and relevance of the program, and 3) regularly collected timely and credible performance information to manage the program and improve performance. The BOSC noted that the HHRP was a leader in developing research to support Agency risk assessments, which has allowed the Agency to conduct credible, nationally/internationally accepted risk assessments of chemicals of environmental concerns. It was also noted that the program displayed a good balance between the extramural and intramural research programs and that the Agency had successfully utilized its extramural grants program to advance its research agenda.

At a meeting with the Executive Committee of the BOSC on September 13, 2005, the HHRP responded to the recommendations of the HH Subcommittee and outlined 27 specific action items that will be addressed over the next four years. An interim review of the HHRP by the BOSC is scheduled for 2007, which will be followed by a full review of the HHRP in 2009.

VIII. Communication

Communication of products from this MYP is considered to be a high priority. It is not sufficient that research be performed and papers or documents produced or published without providing adequate feedback to stakeholders. One crucial aspect of our communication strategy is the decision to link an ORD scientist to each APM in the MYP (See Attachment D). The person identified with the APM is expected to work with ORD management to provide reports on the progress of the APM. Such an evaluation will be included as a performance measure in the annual evaluation of the program. Contacts for the APMs are responsible for answering questions by stakeholders concerning specific research products and for providing feedback to appropriate stakeholders at various milestones during the life of the APM. When papers are published or when a body of work is completed, contacts are responsible for informing the appropriate stakeholder about the work. The research described in this MYP is also dependent on research teams (see Attachment E). As a body of research is completed or progress made, the team is responsible for informing the appropriate stakeholder. In many cases, completing APGs involves generating a summary document describing the original risk assessment problem, the

research that was done, and how the research addressed the problem. Additional transmission of information for ORD scientists to stakeholders may occur in one of several ways, including:

- Direct one to one contact between ORD scientists and stakeholders
- Direct communication of ORD and stakeholders in the Human Health Working Group
- Transmission of published work and supporting materials to stakeholders, especially upon completion of the APM or APG
- Scientist to scientist meetings involving stakeholders
- Participation in seminars and workshops for stakeholders
- Developing and maintaining an internet website for the HHRP

IX References

Board of Scientific Counselors (BOSC). Report of the Human Health Research Program Review. May 18, 2005.
http://www.epa.gov/osp/bosc

Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), 1980.
http://www.epa.gov/superfund/action/law/cercla.htm

Children's Health Act, 2000.
http://www7.nationalacademies.org/ocga/laws/PL106_310.asp

Clear Air Act, 1990.
http://www.epa.gov/air/caa/caa103.txt

Department of Health and Human Services. Healthy People 2010, Vol II (second edition), Chapter 24. Respiratory Diseases, 2001.
http://www.healthy people.gov

Federal Insecticide, Fungicide and Rodenticide Act, 1996
http://www4.law.cornell.edu/uscode/7/136r.html

Food Quality Protection Act, 1996.
http://www.epa.gov/oppfead1?fqpa/backgrnd.htm

National Research Council (NRC). *Risk Assessment in the Federal Government: Managing the Process.* National Academy of Sciences, Washington, DC, 1983.

National Research Council (NRC). *Pesticides in the Diets of Infants and Children*. National Academy of Sciences, Washington, DC, 1993.

National Research Council (NRC). *Science and Judgment in Risk Assessment*. National

Academy of Sciences, Washington, DC, 1994.

National Research Council (NRC). *Building a Foundation for Sound Environmental Decisions*. Committee on Research Opportunities and Priorities for EPA. National Academy of Sciences, Washington, DC, 1997.

National Research Council (NRC). *Toxicity Testing for Assessment of Environmental Agents: Interim Report.* National Academy Press, Washington, DC, 2006.

Presidential/Congressional Commission on Risk Assessment and Risk Management. Final Report. Volume 2, *Risk Assessment and Risk Management in Regulatory Decision-Making*, 1997.

Safe Drinking Water Act, 1996.
http://www.epa.gov/safewater/sdwa/text.html

Science Advisory Board (SAB). *Future Risk: Research Strategies for the 1990s*. SAB-EC-88-040, 1988.

Seed,J, Carney, EW, Corley, RA, Crofton, KM, DeSesso, JM, Foster, PMD, Kavlock, R, Kimmel, G, Klaunig, J, Meek, ME, Preston, RJ, Slikker, Jr, W, Tabacova, S, Williams, GM. Overview: Using mode of action and life-stage information to evaluate the human relevance of animal toxicity data. **Critical Reviews in Toxicology** 35:663-672, 2005.

US EPA. *The Role of Human Health Research in Support of EPA's Regulatory Programs*, 1990. EPA/600/0-90/034.

US EPA. *Strategic Plan for the Office of Research and Development*, 1996. EPA 600/R-96/059.

US EPA. *1997 Update to ORD's Strategic Plan*, 1997. EPA/600/R-97/015.

US EPA. *Research Plan for Endocrine Disruptors.* Office of Research and Development, US EPA, 1998. EPA/600/R-98/087.

US EPA. *Strategy for Research on Environmental Risks to Children.* Office of Research and Development, US EPA, 2000a. EPA/600R-00/068

US EPA. *Strategic Plan*, 2000b. EPA/190/R-00/002.

US EPA. *Supplemental Guidance for Conducting Health Risk Assessment of Chemical Mixtures.* ORD, US EPA, 2000c. Risk Assessment Forum. EPA/600/R-00/062.

US EPA. Office *of Research and Development Strategic Plan.* ORD, US EPA, 2001a. EPA/600/R-01/003.

US EPA. *Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity.* Office of Pesticide Programs, US EPA, 2001b.

US EPA. *Asthma Research Strategy.* Office of Research and Development, US EPA, 2002a. EPA/600/R-01/061.

US EPA. *A Review of the Reference Dose and Reference Concentration Processes*. Risk Assessment Forum, US EPA, 2002b. EPA/630/P-02/002F.

US EPA. *2003-2008 EPA Strategic Plan: Directions for the Future.* US EPA, 2003a.

US EPA. *Human Health Research Strategy*. Office of Research and Development, US EPA, 2003b. EPA/600/R-02/050.

US EPA. *A Framework for a Computational Toxicology Research Program*. Office of Research and Development, US EPA, 2003c. EPA/600/R-03-065.

US EPA. *Human Health Research Multi-Year Plan*, US EPA, 2003d. http://intranet.epa.gov/ospintra/Planning/myp.htm

US EPA. *Draft Report on the Environment.* Office of Research and Development, Washington, DC, 2003d. EPA 600/R-03/050.

US EPA. *Guidelines for Carcinogen Risk Assessment.* Office of Research and Development. Washington, DC, 2005. EPA 600/P-03/001F.

X. Attachments

ATTACHMENT A
Examples of Major Collaborative Research Efforts

Research Agency or Group	Research Theme or Effort
Agency for Toxic Substances and Disease Registry	Collaborates in developing background technical information and guidance concerning environmental health-related issues
American Chemistry Council	Collaborative research to examine risks associated with exposure to pesticides
Centers for Disease Control and Prevention	Collaborative ties with the National Center for Environmental Health to study health problems associated with human exposure to lead, radiation, air pollution and other toxicants, as well as hazards resulting from technological or natural disasters
Centers for Disease Control and Prevention	Collaboration in large-scale epidemiological and exposure research programs, including the National Health Exposure Assessment Survey (NHEXAS)
Centers for Disease Control and Prevention	Exposure studies along the US/Mexico Border (North American Free Trade Act)
Centers for Disease Control and Prevention	With the National Center for Health Statistics (NCHS) conduct the National Health and Nutrition Examination Survey (NHANES), which is a population-based survey including data on potentially sensitive subpopulations such as the elderly and children
Cumulative and Aggregate Risk Evaluation System	Collaborates in developing background technical information and guidance concerning issues related to aggregate and cumulative risk
Health Effects Institute	Collaborates with ORD to support research programs to evaluate exposures to environmental agents and develop strategies for assessing public health indicators
Housing and Urban Development	Collaboration of ORD and NIEHS on the National Allergen Study; American Healthy Homes Survey
International Life Sciences Institute	Collaborates in developing background technical information and guidance concerning environmental health-related issues
National Heart, Lung and Blood Institute	Collaborates in developing background technical information and guidance concerning environmental health-related issues
National Institute of Allergy and Infectious Diseases	Collaborates in developing background technical information and guidance concerning environmental health-related issues; conduct of the Inner-City Asthma Study
National Institute of Child Health and Human Development	Collaborates with NICHD and other Federal agencies in the design and implementation of the National Children's Study, which focuses on following children from birth throughout childhood and adolescence
National Institute for Environmental Health Sciences	Joint RFAs and co-sponsoring of Children's Environmental Health and Disease Prevention to define environmental influences on asthma and other respiratory diseases, childhood learning, and growth and development
National Institute for Environmental Health Sciences	Collaborations between the National Center for Computational Toxicology (ORD) and the National Center for Toxicogenomics to develop informatics infrastructure for toxicogenomic data
World Health Organization	Collaboration between the International Program on Chemical Safety and ORD in developing background technical information and guidance on issues related to environmental exposures and health

ATTACHMENT B

Summary of Regional and Program Offices Needs

Research Need	P/R Office[a]	ORD Research Program
Aging and Interaction with the Environment	OCHP	HH LTG 2[b] Tools for Identifying Communities at Risk HH LTG 4 Develop and Apply Tools too Evaluate Risk Management Decisions
Asthma-predisposing factors	OAR, OCHP	HH LTG 3 Research on Asthma in Children
Asthma-basis for hospital admissions	Regions, OAR	HH LTG 3 Research on Asthma in Children
Asthma-triggers for asthma in children	OAR	HH LTG 3 Research on Asthma in Children
Asthma-mechanisms of sensitization	OAR, OCHP	HH LTG 3 Research on Asthma in Children
Biomarkers Based on Mechanistic Information	OPPTS, Regions	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment HH LTG 2 Tools for Using Biomarkers in Risk Assessment HH LTG 3 Research on Susceptibility Factors
Biomarkers for Children	OCHP, OW. OAR	HH LTG 3 Research on Susceptibility Factors
Biomarkers for Evaluation of Risk Management Decisions	OPPTS, Regions	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment HH LTG 2 Tools for Using Biomarkers in Risk Assessment EDC MYP
Child-Specific Exposure Factor Handbook (data gaps)	OCHP, OAR OPPTS, OW	HH LTG 3 Research on Susceptibility Factors HH LTG 3 Research on Life-Stage HH Risk Assessment MYP
Cross-species Extrapolation	OPPTS, OW, OAR	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment HH LTG 2 Tools for Cumulative Risk HH LTG 3 Research on Life-Stage
Cumulative Risk-Community Risk	OPPTS, OAR, Regions	HH LTG 2 Tools for Identifying Communities at Risk
Cumulative Risk-Chemicals with Different Modes of Action	OPPTS	HH LTG 2 Tools for Cumulative Risk
Exposure and Dose Models -Pesticides	OPPTS	HH LTG 2 Tools for Risk Management Approaches
Exposure and Dose Models-1 HR SHEDs	OAR	No research proposed by ORD
Exposure and Dose Models-estimating local and personal air exposures	Regions	No research proposed by ORD
Exposure and Dose Models-Asbestos	OSWER	No research proposed by ORD
Exposure and Dose Models-Long-Term Multi-Pathway	OW, OSWER	HH LTG 2 Tools for Cumulative Risk
Immunotoxicity Risk Assessment Guidelines	OCHP, OW	No Research Conducted by ORD in Support of Risk Assessment Guidelines HH Risk Assessment MYP-Guideline Development Research is being supported by SP MYP on datagaps related to testing guidelines for immunosuppression
Life- Stage and Risk Assessment	OCHP, OPPTS, Regions	HH Risk Assessment MYP
Life-Stage Sensitivity to Carcinogens	OCHP, OW, OAR	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment

		HH LTG 3 Research on Life-Stage HH LTG 3 Research on Susceptibility Factors
Long-Term Effects of Early Exposure	OCHP, OAR OPPTS, OW, Regions	HH LTG 3 Research on Life-Stage HH LTG 3 Research on Susceptibility Factors EDC MYP
Mechanistic Research-Endocrine Disruptors	OPPTS	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment EDC MYP
Mechanistic Research-Conazoles	OPPTS	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment
Mechanistic Research-CCL compounds	OW	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment (specific compounds were not identified, but could be included on a case by case basis)
Mechanistic Research-Air Pollutants PM and related compounds Aldehydes PAHs VOCs	OAR	HH LTG 3 Research on Asthma HH LTG 3 Research on Asthma Air Toxics MYP Air Toxics MYP
Mechanistic Research-Arsenic	OW	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment DW MYP
Mechanistic Research-PFOA/PFOS	OPPTS	SP2 MYP
Mechanistic Research-PCBs and related compounds	OPPTS, OSWER, OAR	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment (flame retardants) HH LTG 3 Research on Life- Stage
Mechanistic Research-Oxygenates	OSWER	No research proposed by ORD
Mechanistic Research-Asbestos	OSWER	Effects research supported by SP2 MYP
Microbial Pathogens and Vulnerable Populations	OW, Regions	HH Risk Assessment MYP HH LTG 4 Develop and Apply Tools to Evaluate Risk Management Decisions (Beaches Surveillance Project)
Mixtures Research-Pyrethoids, Carbamates	OPPTS	HH LTG 2 Tools for Cumulative Risk
Mixtures Research-Air pollutants	OAR	HH LTG 3 Research on Asthma (Diesel) Air Toxics MYP-VOCs
Mixtures-Goitrogens	OW	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment (flame retardants)
Mixtures-Endocrine Disruptors	OCHP OPPTS	HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment (chloroatrazines) HH LTG 2 Tools for Cumulative Risk EDC MYP
Mixtures-Disinfection By-Products	OW	HH LTG 2 Tools for Cumulative Risk
National Children's Study	OCHP, OAR OPPTS, OW, Regions	HH LTG 3 Research on Methods for Longitudinal Research
"Omics" Technology for Effects	OCHP, OPPTS, OW	HH LTG 1 Develop Methods, Models to Characterize MOA Model Development Supported by the Computational Toxicology Research Program
"Omics" Technology for Developmental Markers	OCHP	HH LTG 3 Research on Life- Stage HH LTG 3 Research on Methods for Longitudinal Research

		HH LTG 1 Model Development Supported by the Computational Toxicology Research Program
Provisional Risk Assessment Values	OWSER, Regions	HH Risk Assessment MYP
Physiologically Based Pharmacokinetic Models	OAR, OPPTS, OW	HH LTG 1 Develop Linkages Between PK and PD Models HH LTG 1 Develop MOA Information to Address Extrapolation in Risk Assessment HH LTG 2 Tools for Cumulative Risk HH LTG 2 Tools for Using Biomarkers in Risk Assessment HH LTG 3 Research on Life- Stage
Probabilistic Risk Assessment Methods	Regions	HH Risk Assessment MYP
Public Health Outcomes-approaches, biomarkers, socioeconomic approaches	OCHP, OEI, OPPTS, OW, Regions	HH LTG 4 Evaluation of Risk Management Decisions
Statistical Approaches to Determine Critical Effect	OW	HH Risk Assessment MYP
Susceptible Subpopulations- Differential sensitivity to air pollutants	OAR	HH LTG 3 Research on Asthma (Aldehydes, Molds) PM MYP
Susceptible Subpopulations Differential exposure to air pollutants	OAR	HH LTG 3 Research on Asthma
Susceptible Subpopulations Differential Mechanisms	OW, OAR	HH LTG 3 Research of Life-Stage
Susceptible Subpopulations Indoor air environments and schools	OSWER	HH LTG 2 Tools for Cumulative Risk

[a] Program/Regional Office

[b]Denotes the LTG in the HHRP where this research is described. There are some research needs that will be met by other ORD MYPs (i.e., Particulate Matter, Human Health Risk Assessment, Safe Pesticides/Safe Products, Endocrine Disruptors).

ATTACHMENT C

Summary of Crosswalk between Human Health and Other ORD Multi-Year Plans

ORD MYP	Long-Term Goal	HH Long-Term Goal	HH Research Track	Related Themes
Air Toxics	LTG 1 Reducing uncertainties in risk assessment	LTG 1 Mechanistic Research	Develop linkages between PD/PK models	PKPD models-ingestion vs inhalation VOCs
	LTG 1 Reducing uncertainties in risk assessment	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Cross species extrapolation for toluene/VOC and Cl^- respiratory irritants
	LTG 1 Reducing uncertainties in risk assessment	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Low-dose research on PAHs
Particulate Matter	LTG 1 Progress toward reducing uncertainty in standard setting and air quality management decisions	LTG 3 Susceptible Subpopulations	Research on asthma	"Omics" methods to study MOA of diesel; MOA information on diesel; Information on interaction of components of diesel; Susceptible populations exposed to diesel
	LTG 1 Progress toward reducing uncertainty in standard setting and air quality management decisions	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Apply MOA information to study relative toxicity for air pollutants and characterize PM components; Interpretation of MOA information
	LTG 1 Progress toward reducing uncertainty in standard setting and air quality management decision	LTG 3 Susceptible Subpopulations	Research on asthma	Biomarkers for children, Detroit Children Health Study
	LTG 1 Progress toward reducing uncertainty in standard setting and air quality management decision	LTG 3 Susceptible Subpopulations	Research on asthma	Long-term effects of early exposure to air pollutants-Detroit's Children Health Study
	LTG 1 Progress	LTG 2 Cumulative	Tools for risk	Differential

	toward reducing uncertainty in standard setting and air quality management decision	Risk	management approaches	exposure in children/adults-activity patterns
	LTG 2 Progress in assessing source to health linkages	LTG 2 Cumulative Risk	Tools for using biomarkers in risk assessment	Biomarkers for evaluating risk management decisions (accountability)
	LTG 2 Progress in assessing source to health linkages	LTG 4 Evaluate Risk Management Decision	Evaluate risk management decision	Biomarkers for evaluating risk management decisions; Relationship to near roadway exposures; Accountability
Computational Toxicology	Development and Implementation of Advanced Biological Models and Systems Biology	LTG 1 Mechanistic Research	Develop linkages between PK and PD models	Chemical data for developing statistical methodology to provide framework for PK/PD modeling
	Development and Implementation of Advanced Biological Models and Systems Biology	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Mechanistic research on diesel exhaust PM for systems biology model
	Development and Implementation of Advanced Biological Models and Systems Biology	LTG 3 Susceptible Subpopulations	Research on asthma	Mechanistic research on diesel exhaust PM for systems biology model
	Development and Implementation of Advanced Biological Models and Systems Biology	LTG 3 Susceptible Subpopulations	Research on asthma	Exposure information from Detroit Study
	Advanced Computational Toxicology Approaches to Improve Cumulative Risk Assessment	LTG 2 Cumulative risk	Tools for cumulative risk	Data and models for predicting interactions between chemicals based on MOA; Qualitative relationship

				between exposure and dose
	Advanced Computational Toxicology Approaches to Improve Cumulative Risk Assessment	LTG 3 Susceptible Subpopulations	Research on asthma	Development of tools and concepts for the Detroit Children's Study
Drinking Water	LTG 3 Prioritization of contaminants for CCL-innovative methods	LTG 1 Mechanistic Research	Develop methods and models to characterize MOA	Molecular approaches to study MOA that can be applied to prioritization of drinking water contaminants for screening
	LTG 1 Regulated contaminants: Arsenic MOA	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Research on arsenic MOA; cross species extrapolation
	LTG 2 Unregulated waterborne pathogens	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Research on cyanobacteria
	LTG 1- Regulated Contaminants: MOA of DBPs	LTG 2 Cumulative Risk	Tools for cumulative risk	Component-based models for drinking water mixtures; multi-route, chemical mixture risk estimates using internal dosimetry and knowledge of MOA for 13 major DBPs
Endocrine Disruptors	LTG 1 Improving scientific understanding	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Research on neuroendocrine MOAs for risk assessment
	LTG 1 Improving scientific understanding	LTG 2 Cumulative Risk	Tools for cumulative risk	Research on interactions between EDCs in mixtures
Human Health Risk Assessment	LTG 1 Integrated risk assessment and other priority health hazard assessments	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Provide data to reduce uncertainty in extrapolation default

				assumptions
	LTG 1 Integrated risk assessment and other priority health hazard assessments	LTG 2 Cumulative Risk	Tools for cumulative risk; Tools for risk management approaches	Provide data to support additivity default assumption in risk assessment
	LTG 1 Integrated risk assessment and other priority health hazard assessments	LTG 3 Susceptible Subpopulations	Research on life-stage; Research on Methods for Longitudinal Research	Data to support application of default assumptions for susceptible subpopulations
	LTG 2 State-of-the-science risk assessment models, methods and guidance	LTG 1 Mechanistic Research	Develop Methods and Models to Characterize MOA	Mode of action to refine risk assessment and extent beyond the range of data
	LTG 2 State-of-the-science risk assessment models, methods and guidance	LTG 1 Mechanistic Research	Develop Linkages Between PK and PD Models	Integrate risk assessment advances into quantitative frameworks: PBPK models
	LTG 2 State-of-the-science risk assessment models, methods and guidance	LTG 1 Mechanistic Research	Develop Linkages Between PK and PD Models	Guidance on risk assessment models and uncertainty analysis: PBPK models
	LTG 2 State-of-the-science risk assessment models, methods and guidance	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Integrate and synthesize progress in risk assessment models and methods: dose-response methods and models; Harmonization of uncertainty factors
	LTG 2 State-of-the-science risk assessment models, methods and guidance	LTG 2 Cumulative Risk	Tools for cumulative risk; Tools to measure community risk; tools for risk management approaches	Guidance for cumulative risk; Guidance for cumulative risk; Mode of action to refine risk assessment and extend beyond the range of data: Exposure levels

				and environmental levels
	LTG 2 State-of-the-science risk assessment models, methods and guidance	LTG 3 Susceptible Subpopulations	Research on life-stage; Research on Methods for Longitudinal Research	Guidance on risk assessment models and uncertainty analysis: appli-cation to children's risk assessment
Safe Pesticides/Safe Products	LTG 1 Provide EPA with Predictive Tools for Prioritization	LTG 1 Mechanistic Research	Develop methods and models to characterize MOA	Molecular methods to study MOA
	LTG 1 Provide EPA with Predictive Tools for Prioritization	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Research on neuroendocrine MOA; Research on P450 MOA (conazoles)
	LTG 3 Provide OPPTS with scientific underpinnings for guidance to prevent or reduce risks of human environments with communities, homes, workplaces	LTG 2 Cumulative Risk	Tools for identifying communities at risk	Research to develop and apply tools to assess community risk
	LTG 4 Provide OPPTS with strategic scientific information and advice concerning novel or newly discovered hazards	LTG 1 Mechanistic Research	Develop methods and models to characterize MOA	Molecular methods to study MOA
	LTG 4 Provide OPPTS with strategic scientific information and advice concerning novel or newly discovered hazards	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Research on neuroendocrine MOA; Research on P450 MOA (conazoles)
Sustainability Research Strategy	Research Theme 3 Long-Term Chemical and Biological Impacts	LTG 1 Mechanistic Research	Develop MOA information to address extrapolation in risk assessment	Research to determine which chemicals are persistent or bioaccumulative
		LTG 2 Cumulative Risk	Tools for using biomarkers in risk assessment	Research to determine which indicators can be used to determine if acceptable levels have been

				exceeded
		LTG 2 Cumulative Risk	Tools for risk management approaches	Research to determine the acceptable levels of human exposure to chemicals
		LTG 2 Cumulative Risk	Tools for identifying communities at risk	Research to develop metrics and indicators to measure and track progress toward sustainability goals

ATTACHMENT D

Tables of Long-Term Goals with Annual Performance Goals and Annual Performance Measures

TABLE 1

Long-Term Goal 1: Risk Assessors and Risk Managers use ORD's Methods, Models and Data to Reduce Uncertainty in Risk Assessment using Mechanistic (or Mode of Action) Information

Annual Performance Goals and Measures		Year	Lab/Center
APG 171 Determine utility of emerging technologies in harmonizing risk assessment		**2008**	**ORD**
APM 144	Papers on the importance of receptor-mediated metabolism of chemicals to improving risk assessment	2004	NCER Saint
APM 437	Report on the use of toxicogenomic and related technologies to define common modes of action of P450 modulating chemicals	2007	NHEERL Nesnow
APG Apply emerging technologies to identify key changes in toxicity pathways		**2010**	**ORD**
APM	Identification of genetic polymorphisms associated with susceptibility to environmental toxicants	2010	NHEERL Devlin
APM	Use of transcript profiling and proteomics to identify biomarkers of exposure and effect in animals and humans	2010	NHEERL Devlin
APG 167 Identify PK/PD issues underlying uncertainties for extrapolation		**2008**	**ORD**
APM 141	Interim report on PK/PD model for interspecies extrapolation in risk assessment	2006	NCCT Barton
APM 465	Development of multi-route PBPK model	2007	NHEERL Simmons
APM 62	Summary report on PK/PD for interspecies extrapolation in risk assessment	2008	NCCT Barton
APG Integrate PK/PD models for risk assessment		**2011**	**ORD**
APM	Report on approaches for incorporating *in vitro* mode of action information into developing pharmacodynamic models	2009	NHEERL DeVito
APM	Report on linking pharmacokinetic and pharmacodynamic models for selected modes of action to address *in vitro*/*in vivo* and cross-species extrapolations	2011	NHEERL DeVito
APG Identify MOAs for Risk Assessment		**2008**	**ORD**
APM 148	Report on the mechanisms involved in altering luteinizing hormone	2006	NHEERL Cooper
APM 150	Report on the role of oxidative stress in toxicant specific target organ effects	2006	NHEERL U Kodavanti
APM 151	Report from workshop demonstrating how mechanistic data can be used in risk assessment	2006	NCER Saint
APM	Develop and evaluate methodologies for detecting	2006	NHEERL

523	intracellular signaling activation in cells obtained from human subjects exposed to pollutants in vivo		Samet
APM 524	Develop and validate a method for using human breath condensate to measure respiratory tract responses to air pollutants	2006	NHEERL Madden
APM 525	Develop and validate a "lipomics" approach to characterizing a comprehensive lipid profile in humans and cells exposed to pollutants	2006	NHEERL Madden
APM 526	Demonstrate the mechanism by which metals injure respiratory tract cells	2006	NHEERL Ghio
APM 527	Development and validation of a perfused lung and isolated vascular ring model to screen for vascular toxicity of pollutants	2006	NHEERL Huang
APM 528	Identify single nucleotide polymorphisms in humans that predict susceptibility to pollutants that cause oxidative stress	2006	NHEERL Devlin
APM 606	Genetic and environmental determinants of interindividual variation in arsenic metabolism	2006	NHEERL Thomas/Kitchin
APM	Report on genetic and environmental determinants of interindividual variation in arsenic metabolism: Relation to modes of action of arsenic as a carcinogen and toxicant	2007	NHEERL Thomas
APM 492	Report on arsenical modes of action studies employing gene expression and genotoxicity endpoints in carcinogenicity	2007	NHEERL Thai
APM	Characterize the state of the science of oxidative stress and establish database on relationship between oxidative stress and exposure to environmental agents	2008	NHEERL Sams/Hatch
APM	Provide guidance concerning the possibility that oxidative stress is a primary mode of action based on a systems biological approach	2008	NHEERL P. Kodavanti
APM	Develop *in vitro* models reflecting multiple pathway effects induced by chemicals with demonstrated oxidative stress as a primary or secondary effect for toxicity testing	2008	NHEERL P Kodavanti/J Royland/B Veronesi
APM	Report on factors modifying the metabolism and modes of action of arsenic as toxic and carcinogen	2008	NHEERL Allen/Kligerman/Thomas
APM	Report on characterization of mechanistic and hierarchical (e.g., genome to tissue) oxidative stress endpoints due to inhaled chlorine	2008	NHEERL Jarabek
APM 65	Report on the use of cell signaling data for extrapolation of mode of action information from in vitro to the whole animal	2008	NHEERL P. Kodavanti
APG Apply MOAs for Interspecies Extrapolation		**2009**	**ORD**
APM 67	Report on characterization of cancer and non-cancer reproductive effects following modulation of luteinizing hormone secretion	2008	NHEERL Cooper
APM	Report on the integration of toxic effects, structure activity analysis and gene expression profiling for interspecies extrapolation for conazoles and data on MOA	2008	NHEERL Nesnow/Wolf
APM	Report on the development of a quantitative (Bayesian hierarchical) model to describe oxidative stress due to inhaled chlorine and characterize the degree of confidence in interspecies extrapolation and intrahuman extrapolation	2009	NHEERL Jarabek

APM	Identify and characterize factors that contribute to species differences in adverse toxicological responses mediated by oxidative stress	2009	NHEERL U Kodavanti
APM	Report on the use of oxidative stress markers in surrogate fluids/cells in rodent and humans exposed to air pollutants	2009	NHEERL Gallagher
APG Apply MOAs for Low-Dose Extrapolation		**2011**	**ORD**
APM 399	Report on comparative dose-response toxicity data for susceptible hypertensive rats and roles of oxidative stress	2007	NHEERL U Kodavanti
APM	Human pharmacokinetics of bromodichloromethane: development of data and models for use in route-to-route, rodent to human, and high to low dose extrapolation for risk assessment	2009	NHEERL Pegram/Kenyon
APM	Information to OW on the modes and mechanisms of action of priority halogenated drinking water contaminants that produce adverse reproductive effects	2009	NHEERL Hunter/Narotsky/Kleinfelter
APM	Report(s) establishing biological plausibility of cancer effects associated with human exposure to chemical contaminants in drinking water	2009	NHEERL DeAngelo/Delker
APM 15	Report on evaluation of risk associated with multiple exposures to chemicals having differential effects on secretion of luteinizing hormone	2010	NHEERL Cooper
APM	Determination of the biological plausibility of reproductive and developmental epidemiological effects associated with chemical contaminants in drinking water	2010	NHEERL Hunter
APG 2 Provide scientific basis for use of mechanistic information in risk assessment		**2012**	**ORD**
APM 459	Report on critical evaluation of mode of action research to identify and assess potential biomarkers of effect and exposure for use in human population-based studies	2007	NHEERL Thomas/Calderon
APM	Report on genotype-phenotype correlations and susceptibility to the toxic and carcinogenic effects of arsenic	2009	NHEERL Thomas
APM	Deliver to OW a biologically based dose response model for arsenic	2010	NHEERL Kenyon
APM	Comparison of ability of short-term *in vivo* screens to predict developmental neurotoxicity of thyrotoxic agents	2010	NHEERL Crofton/Gilbert/DeVito
APM	Synthesis document on the use of genomics in determining mode of action in determining mode of action for a group of hepatotoxic and carcinogenic conzaoles in support of risk assessment	2010	NHEERL Wolf/Hester
APM 1	Report summarizing harmonized risk assessment for chemicals modifying luteinizing hormone secretion	2012	NHEERL Cooper
APM 464	Identify interventional dietary or pharmaceutical strategies to mitigate the effects of air pollutants in humans.	2012	NHEERL Samet
APM 2	Report summarizing risk assessment for chemicals acting by oxidative stress	2012	NHEERL/NCEA Hatch/Sams
APM	Report on the potential modes of action of arsenicals as toxicants and carcinogens	2012	NHEERL Kitchin/Blackman
APM	Characterize the dose-response curves of selected prototype environmental chemicals that act through oxidative stress and investigate the background levels of	2012	NHEERL Kitchin

	oxidative stress		
APM	Summary report on chemicals with multiple modes of action	2012	NHEERL Thomas
APG 3 Provide framework for use of mechanistic data in risk assessment		**2012**	**ORD**
APM	Synthesis document for use of mechanistic information in risk assessment	2012	ORD NPD for HH

ATTACHMENT D
TABLE 2

Long-Term Goal 2: Risk Assessors and Risk Managers use ORD's Methods, Models and Data to Characterize Aggregate and Cumulative Risk in order to Manage Risk of Humans Exposed to Multiple Environmental Stressors

Annual Performance Goals and Measures		Year	Lab/Center
APG 199 Provide assessment and analytical tools for regional and program offices in using biomarkers for assessing and addressing cumulative risk		**2007**	**ORD**
APM 33	Analysis of existing children's exposure data to identify important factors for characterizing cumulative exposure to pesticides and other environmental contaminants	2006	NERL Egeghy
APM 97	Papers on new biomarkers methods for risk assessment	2007	NCER Saint
APM 23	Summary of biomarker studies utilizing pharmacokinetic data to interpret their applications to cumulative and aggregate risk assessment	2007	NCER Saint
APM 377	Report on approaches for using exposure, biomarker and pharmacokinetic data in risk assessments	2007	NERL Morgan
APM Apply biomarkers for risk assessment		**2011**	**ORD**
APM 158	Report on promising new biomarkers of exposure and effect	2006	NCER Saint
APM	Report on the use of blood gene expression data as sensitive bioindicator of exposure to inhaled pollutants in rodent strains	2007	NHEERL Gallagher
APM	Develop and demonstrate modeling tools to evaluate and guide the use of biomarkers to assess exposure	2008	NERL Okino
APM	Report on assessments of the exposure/biomarker/dose relationship for priority chemicals within the agency	2009	NERL Dary
APM	Papers on biomarkers of PAH exposure and asthma in an inner city birth cohort	2009	NCER Saint
APM	Papers on pulmonary biomarkers based on alterations in protein expression following exposure to arsenic	2009	NCER Saint
APM	Report on the development and evaluation of a systems biology approach to link exposure to health outcome	2010	NERL Pliel
APM 13	Develop/refine biomarker methods that can be used to evaluate measurement data on multiple exposures which will enhance, refine and verify the Agency's cumulative risk assessments	2011	NERL Morgan
APM	Report on refined approaches for applying biomarkers in cumulative risk	2011	NERL Okino
APG 179 Develop measurement-based models/components for estimating aggregate exposures and doses		**2006**	**ORD**
APM 173	Develop and demonstrate a method for assessing exposure to particle-borne contaminants in indoor air due to resuspension from flooring	2005	NRMRL Guo

	surfaces		
APM 174	Evaluate prototype version of Source Modules for aggregate exposure/modeling of indoor sources/source types, using available models/data, including non-indoor sources as possible	2005	NRMRL Guo
APM 32	Develop model components to estimate exposure and dose to environmental contaminants for EPA to use in conducting assessments of aggregate exposure and risk	2005	NERL Zartarian
APG 311 Provide refined models, methods and guidelines for assessing aggregate exposures and effects		**2008**	**ORD**
APM 98	Papers on novel analyses of existing human exposure data for assessing aggregate exposure to environmental toxins	2007	NCER Saint
APM 69	Provide access to refined, easy-to-use human exposure and dose model components that can be used by Program Offices, Regions, States, exposure modelers and other stakeholders for conducting improved exposure assessments as part of environmental decision-making	2008	NERL Schultz
APG Develop source-to-dose models for cumulative risk		**2009**	**ORD**
APM 48	Evaluate the temporal variation in the exposure of selected populations to pesticides based on longitudinal case studies of pesticide exposure	2006	NCER Saint
APM 22	Publish longitudinal data on the temporal variation in the exposure of selected populations to pesticides in a publicly available format	2007	NCER Saint
APM 75	Papers on the feasibility of novel sampling platforms for collecting behavioral data for exposure assessors in EPA, industry and state and local governments	2008	NCER Saint
APM	Extend aggregate measurement-based models and model components to assess cumulative exposures and doses	2008	NERL Zartarian
APM	Evaluate, refine and link (coordinate) model components for assessing cumulative exposures and doses	2009	NERL Dary
APG Apply source-to-dose models for cumulative risk		**2011**	**ORD**
APM	Summary report on research to develop approaches for assessing toxicity and risk of exposure to chemical mixtures	2008	NCER Saint
APM 70	Report on critical review of indoor chemistry and indoor chemistry models: compile existing information and models, identify information gaps and recommend the best indoor chemistry model for use in cumulative risk models	2008	NRMRL Guo
APM	Develop an indoor air quality simulation program for implementing indoor chemistry models, which predict the formation of secondary pollutants due to interactions of multiple pollutants and their interactions with interior surfaces	2009	NRMRL Guo
APM 13	Publicly available databases of human activity patterns, pesticide and product usage, and dietary consumption patterns for risk assessors in EPA, state and local governments, and industry	2010	NCER Saint
APM	Peer review and publish refined source-concentration-exposure-dose modeling tools to provide improved cumulative exposure assessments for environmental decision making	2011	NERL Schultz
APG Develop tools for cumulative risk of chemical mixtures		**2009**	**ORD**
APM 27	Evaluate studies to provide the basis to compare the acute and sub chronic toxicities of a mixture of high volume usage carbamate pesticides	2006	NHEERL Padilla/Moser
APM 28	Evaluate age-related differences in response to repeated pesticide	2006	NHEERL

	exposure, using behavioral and neurochemical endpoints		Moser
APM 40	Develop dose response data on the adverse developmental effects of exposure to phthalates to address the 10X safety factor	2006	NHEERL Gray
APM 597	Reports on effects of disinfectant by product mixtures	2006	NHEERL Simmons
APM 440	Develop parameters to model dose-additivity for mixtures of organophosphate and/or carbamate pesticides	2007	NHEERL Moser/ Herr/ Gordon
APM 340	Dose-response and time to recovery modeling for several N-methyl carbamate pesticides	2008	NCCT Setzer
APM	Develop methods to predict interactions between persistent environmental toxicants	2008	NHEEL P. Kodavanti
APM	Demonstrate influence of altering the ratios of the constituent chemicals within defined chemical mixtures on effects of mixtures of air toxics, water contaminants and pesticides	2008	NHEERL Moser/ Shafer/ Gordon
APG Apply tools for cumulative risk of chemical mixtures		**2011**	**ORD**
APM 434	Develop experimental database of pharmacokinetic parameters for pyrethroid pesticides after oral and dermal exposure	2007	NHEERL Hughes/DeVito
APM 435	Develop experimental database of neurotoxicological effects for pyrethroid pesticides after oral exposure	2007	NHEERL Crofton/DeVito
APM 439	Develop *in vitro* preparations to study interaction of pyrethroid pesticides *in vitro*	2007	NHEERL Shafer
APM 287	Develop experimental database for in vivo and in vitro neurotoxicity data for pyrethroids	2008	NHEERL Shafer/ Crofton
APM	Develop experimental pharmacokinetic database for tissue dosimetry of pyrethroids	2008	NHEERL Hughes/ Devito
APM 45	Integrate physiologically based pharmacokinetic models with neurotoxicity data for pyrethroids	2009	NHEERL Hughes/DeVito
APM 46	Develop experimental database of the pharmacokinetic and pharmacodynamic interactions of pyrethroid pesticides	2009	NHEERL Crofton/DeVito
APM	Evaluate the contribution of critical exposure and mixture composition parameters to the toxicity of mixtures for pesticides, water contaminants, and air pollutants	2010	NHEERL Simmons/Herr /Moser
APM	Use PBPK modeling to predict interaction thresholds for mixtures of chemicals that act through a common mode of action for mixtures of water contaminants, air toxics, or pesticides	2010	NHEERL EL-Masri/ DeVito
APM	Final report on the ability of combined PK and PD models to predict adverse effects of combined exposure of environmentally relevant environmentally relevant mixtures of pyrethroids	2011	NHEER Crofton/ DeVito
APM	Link *in vitro* data with in vivo physiological and behavioral data to define underlying biological mechanisms of chemical mixtures using a systems biology approach	2011	NHEERL Herr/Moser
APM	Integrate PBPK and BBDR models with biological data to predict the effects of mixtures of pesticides, water contaminants or air toxics	2011	NHEERL El Masri/ Simmons/ Moser/ Herr
APG Develop tools to assess community risk		**2009**	**ORD**

APM	Produce a research framework outlining tools and approaches needed to prioritize and assess communities at risk	2008	NERL Graham
APM	Report on current modeling tools and approaches used in the conduct of community based risk assessments	2008	NERL Graham
APM	Provide program, regional, states and tribal offices with new/updated tools and/or approaches for characterizing community exposures to environmental contaminants and non-chemical stressors that lead to cumulative risks	2009	NERL Graham
APG Apply tools to assess community risk		**2011**	**ORD**
APM	Deliver provisional assessment of application of tools and approaches used in selected communities	2009	NERL Graham
APM	Final report to program, regional, state and tribal offices on application of community-based tools and approaches for assessing exposures to environmental contaminants and non-chemical stressors	2011	NERL Graham
APG 5 Integrate and apply methods, data and models for high priority cumulative risk assessments		**2012**	**ORD**
APM 281	Develop, evaluate and provide improved field and laboratory exposure methods to ORD for use in characterizing cumulative exposures to one or more selected classes of current use pesticides	2010	NERL Medina-Vera
APM	Report on proceedings of a workshop on the use of dose- and response additivity to predict interaction of chemicals with similar and dissimilar modes of action, respectively	2010	NHEERL Simmons/ Padilla
APM 70	Report on important activity patterns and exposure factors and how they change over time	2010	NERL McCurdy
APM 66	Provide analysis and critical measurement data needed for exposure models that will be used by the agency to conduct cumulative risk assessments	2011	NERL Schultz
APM 3	Incorporate new data on time activity patterns, exposure factors, and exposure into HEDS so that program offices, regions, states, exposure modelers, and other stakeholders have access to high quality data for cumulative exposure assessments	2011	NERL Crogan
APM 14	Develop protocol for characterizing cumulative exposures in field studies that will provide high quality exposure data to be used by the agency in conducting cumulative risk assessments	2012	NERL Fortmann
APM 5	Apply, evaluate, and publish refined versions of human exposure and dose modeling tools to provide improved cumulative exposure assessments for environmental decision-making	2012	NERL Sheldon
APG Framework for cumulative risk		**2013**	**ORD**
APM	Synthesis document on cumulative risk assessment	2013	ORD NPD for HH

ATTACHMENT D
TABLE 3

Long-Term Goal 3: Risk Assessors and Risk Managers use ORD's Methods, Models and Data to Characterize and Provide Adequate Protection for Susceptible Subpopulations

APG 14 Long-term effects following developmental exposure		**2009**	**ORD**
APM 192	Report on gene expression changes correlated with latent adverse health effects of developmental exposures	2006	NHEERL Rogers
APM 608	Report on long-term effects of *in utero* insult on adult health and reproduction to assess adequacy of current testing guidelines for reproductive toxicity	2006	NHEERL Rogers
APM 402	Report on development of principles to be used to assess cancer risks in children	2007	NHEERL Preston
APM	Report on the effects of developmental toxicant exposure on physiological indicators of adult health	2008	NHEERL Rogers
APG 188 Tools to measure exposure and effects in older populations		**2010**	**ORD**
APM 536	Produce research framework on aging and the environment	2006	NHEERL Geller
APM 102	Report on the types of environmental exposures and activity patterns, physiological conditions, and additional stressors that characterize the aging population	2008	NERL K Thomas
APM	Provide database for physiological parameters used in PBPK models for the older adult	2008	NCEA Sonawane
APM	Proceedings of a workshop on risk assessment and research priorities in understanding the susceptibility of older adults to environmental pollution	2008	NCEA Moya/Sonawane NHEERL MacPhail
APM	Report on the influence of aging on pharmacokinetics and its impact on exposure-to-dose relationships for environmental chemicals	2009	NHEERL DeVito/Evans
APM	Report on differences between genomic profiles in tissues from young adults and the aging population and how these differences results in altered sensitivity to environmental chemicals	2010	NHEERL Corton/Royland
APM 59	Report on mechanisms of susceptibility to environmental insult in models of aging	2010	NHEERL DeVito/MacPhail
APM	Report on differential responses of older subjects and cells to environmental agents	2010	NHEERL Gordon/MacPhail
APM	Development of a physiologically based model for susceptibility to environmental agents in the aging population	2010	NHEERL Benignus
APM	Provide the agency with new/updated tools for characterizing exposures/dose for environmental contaminants in the aging population	2010	NERL K Thomas
APM	Develop of an Exposure Factors Handbook for the Aging	2010	NCEA

	Populations		Moya
APG 78 Interim results from studies on differential exposure and effects in children		**2010**	**ORD**
APM 171	Provide new models of longitudinal dietary intake of pyrethroid and organophosphate insecticides by children	2006	NCER Saint
APM 328	Develop and demonstrate methods that will enable school systems to reduce the exposure of susceptible children to indoor contaminants from a third source	2007	NRMRL Guo
APM 85	Report on two assessments of the relationships between pre and post natal exposures to neurotoxic chemicals in the environment and brain development and injury (including autism) among children in New Jersey and California	2008	NCER Saint
APM	Provide tools (e.g., protocols, best practices, methods, study design) for conducting observational exposure studies to assess cumulative risks over life-stage	2008	NERL Fortmann
APM	Guidance document on risk assessment associated with developmental exposure to neurotoxicants	2010	NHEERL Moser
APM	Integration of human epidemiological studies with animal models of developmental neurotoxicity	2010	NHEERL Moser
APM 81	Provide an analysis of cumulative exposures of infants and toddlers in residences	2010	NERL Fortmann
APG 14 Results from studies on differential exposure and effects in children and adolescents		**2012**	**ORD**
APM 170	Complete a longitudinal characterization of permethrin concentrations in a multipathway study of young children	2006	NCER Saint
APM 458	Evaluate the utility of non-invasively obtained biological samples for the measurement of cholinesterase and its application in evaluation of cholinesterase inhibition	2007	NHEERL McMaster/Padilla
APM 83	Complete a comprehensive epidemiological study of the relationship between PCB and mercury exposure and adverse health outcomes in a population of Hmong and Laotian in Northwestern Wisconsin	2008	NCER Saint
APM	Report on the distribution of pesticide concentrations measured from residential surfaces during the American Healthy Home Survey	2008	NERL Bradham
APM 84	Report on a study of the exposure of children in Cincinnati, Ohio, to lead, mercury, pesticides, PCBs, and environmental tobacco smoke	2008	NCER Saint
APM	Complete and report on environmental health indicator proof-of-concept projects to determine improvements in public health as related to interventions in UT-Mexico Border Region	2009	NHEERL McMaster
APM	Comparisons of health status and environmental exposure to pesticides and other chemicals in an urban community in New York City	2010	NCER Saint
APM	Comparisons of health status and environmental exposure to pesticides in agricultural communities in California and Washington State	2010	NCER Saint
APM	Report on analysis of exposure factors for young children to chemicals to further reduce uncertainties in exposure and risk assessment	2011	NERL Tulve
APG 8 Apply tools to measure risk over life-stage		**2013**	**ORD**

APM 401	Report on age-related PK and PD changes in developing animals	2007	NCCT Barton
APM 454	Report on rodent mammary tumor susceptibility following early-life exposures during critical periods of gland development	2007	NHEERL Fenton
APM 297	Report on the ability of animal models to predict human life-stage susceptibility to agent exposure resulting in organ system dysfunction	2008	NHEERL
APM	Complete comprehensive evaluation on "low-VOC" paint used in schools and other types of buildings and provide information to risk managers	2008	NRMRL Guo
APM	Survey county school system on purchases and practices to identify high risk consumer products and other factors affecting indoor air quality and develop risk management solutions	2009	NRMRL Guo
APM	Develop and demonstrate broadly applicable risk management solutions in a county school system for reducing/preventing children's exposure to hazardous pollutants in schools	2010	NRMRL Guo
APM 8	Provide ORD and program offices with an assessment of the results of 1-2 exposure studies to identify critical factors influencing exposures of for different life-stages	2012	NERL Fortmann
APG Develop methods for longitudinal research		**2008**	**ORD**
APM 607	Report on methods for collection and storage of breast milk samples for accurate detection of endogenous milk components	2006	NHEERL Fenton
APM 610	Report on the validation of a human blood ex vivo model to evaluate dose, genetic and age specific factors impacting inter- and intra-individual phenotypic response measurements	2006	NHEERL Gallagher
APM	Papers on developmental toxicity as an indicator of childhood susceptibility to environmental toxins	2007	NCER Saint
APM 455	Report on transfer of environmental compounds to the milk of pregnant and lactating rodents	2007	NHEERL Fenton
APM 403	Report on reliability of assays to measure endogenous and exogenous constituents of breast milk that are implicated in altering health status of women or their breast-fed children	2007	NHEERL Fenton
APM	Report on the use of nails as a measure of metal exposures in rodents and children	2008	NHEERL Gallagher
APG Apply methods to associate exposure and environmental disease for longitudinal research		**2011**	**ORD**
APM	Report on the feasibility of validating and implementing early indicators of environmentally induced diseases in large-scale birth cohort studies	2009	NCER Fields
APM	Report on pregnancy outcomes in relation to environmental pollutants	2010	NHEERL Mendola
APM	Report on the association of endogenous or exogenous components of human milk as markers of human health and environmental exposure	2010	NHEERL Fenton
APG Identify factors associated with initiation of asthma as a function of life-stage		**2007**	**ORD**

APM 605	Report on health effects associated with exposure to diesel exhaust particles in asthma animal model	2006	NHEERL Gilmour
APM 609	Report on the assessment of the relative potency of several indoor fungal allergens to obtain quantitative information for risk assessments	2006	NHEERL Ward
APM 400	Report on the characterization of physicochemical properties of the allergenic protein from selected indoor fungi and compare to other well-characterized proteins for hazard identification	2007	NHEERL Ward
APG Identify susceptibility factors for asthma as a function of life-stage		**2010**	**ORD**
APM 456	Report on the morbidity in children with various asthma phenotypes associated with environmental exposures	2007	NHEERL Neas
APM 406	Characterize the response of asthmatics to biological components found in the air and indoors	2007	NHEERL Devlin
APM	Reports on the differential response of young versus old asthmatics to air pollution	2008	NHEERL Devlin
APM	Reports on the cardiopulmonary response of asthmatics and healthy individuals to air pollutants	2008	NHEERL Devlin
APM	Determine relative potency of carbonyl air toxics (including aldehydes) in the induction and/or exacerbation of allergic asthma using animal and human data	2009	NHEERL Gilmour
APM 107	Report on prevalence of asthma and low pulmonary function and biological markers of exposure, early effects, and susceptibility among 9-12 years old school children in Detroit	2009	NHEERL Neas/Gallagher
APM 405	Report on the relative potency putatively asthmagenic and non-asthmagenic molds ranked against indoor allergens and other molds to obtain quantitative information for risk assessment	2009	NHEERL Ward
APM	Identify genetic polymorphisms and biomarkers in healthy and asthmatic humans that predict susceptibility to air pollutants	2009	NHEERL Devlin
APM	Comparisons of asthma incidence and severity and environmental exposure to air pollutants and allergens in an urban community in Maryland and California	2010	NCER Saint
APM	Develop an *in utero* allergen exposure model and report on developmental windows of vulnerability	2010	NHEERL Ward
APM	Report on the effect of *in utero* diesel exposure on normal growth, immune development and the development of allergic lung disease	2010	NHEERL Gilmour
APM	Develop guidance for the Office of Air and Radiation to provide parents of asthmatic children about mold exposure	2010	NERL Vesper
APG Summary on life-stage susceptibility factors for risk assessment		**2013**	**ORD**
APM	Summary on availability of measures for aging-related susceptibility for field use	2012	NHEERL McMaster
APM	Report on exposures during pregnancy and the impact of exposure on infant development	2012	NHEERL Mendola
APM	Provide integrative exposure-dose-response model for risk estimation in the aging population	2013	NHEERL MacPhail
APM	Summary document on life-stage susceptibility factors for risk assessment	2013	ORD NPD for HH

ATTACHMENT D
TABLE 4

Long-Term Goal 4 Risk Assessors and Risk Managers use ORD's Methods, Models and Data to Evaluate Risk Management Decisions

APG 274 Develop partnerships for data collection and new indicators and metrics for exposure and health effects		**2006**	**ORD**
APM 611	Publish new suites of public health and public exposure indicators that reflect early detection of public health effects	2006	NHEERL
APG Assessment of tools to evaluate risk management decisions		**2010**	**ORD**
APM	Report on 2 case studies using large publicly available databases for the purpose of validating methods applicable to accountability and evaluating health effects of pesticides	2008	NHEERL Schreinemacher
APM	Develop approaches for assessing effectiveness of voluntary and regulatory air pollution reduction actions on public health outcomes	2008	NHEERL Lodbell
APM	Provide to Regional Offices a comparison of the incidence of waterborne infections before and after the implementation of a state-of-the-art drinking water treatment in Lawrence, MA	2009	NHEERL Lodbell
APM	Provide to Regional Offices a methodology and criteria to select communities for future studies of waterborne infections to address the effectiveness of US drinking water regulations	2010	NHEERL Lodbell
APG Health chapter for Report on the Environment		**2007**	**ORD**
APM 506	Provide health chapter for the report on the environment	2007	NHEERL Lodbell
APG Design for national study to evaluate risk management decisions		**2012**	**ORD**
APM	Design for national level study	2011	NHEERL Calderon

ATTACHMENT E

Team Leads and Writing Teams for Research Tracks

LTG	Research Track	Team Lead(s)	Contributing Team Members
1	Methods and Models to Characterize MOA	Robert Devlin (NHEERL)	C. Corton, S. Nesnow, W. Mundy, S. Hunter, I. Gilmour, G. Klinefelter, R. Ramabhadran (NHEERL)
1	Linkages Between PK and PD Models	Hugh Barton (NCCT)	M DeVito, M Evans, E Kenyon (NHEERL); C Thompson, K Guyton, W Chiu (NCEA); M Tornero (NERL)
1	MOA Information to Address Extrapolation in Risk Assessment	Oxidative Stress Team Reeder Sams (NCEA) and Gary Hatch (NHEERL) Conazole Team: Stephen Nesnow (NHEERL) Arsenic Team: David Thomas (NHEERL) Neuroendocrine Team: Ralph Cooper (NHEERL) Brominated Disinfection By-Products Team: Rex Pegram (NHEERL)	A DeAngelo, D Delker, R Devlin, J Gallagher, S Hester, K Kitchin, P Kodavanti, U Kodavanti, R Macphail, J Ross, S Nesnow, J Royland, B Veronesi, W Winnik (NHEERL); A Jarebek, A Rooney (NCEA) J Allen, LClaxton, D Delker, S Hester, L King, M Narotsky, J Ross, S Thai, W Ward, D Wolf (NHEERL); H Barton, D Dix, A Richard (NCCT); D Ekman (NERL); S Barone (NCEA); D Juberg (Dow-Elanco-US Triazole Task Force); V Dellarco (OPP) D Wolf, S Nesnow, K Kitchin, D Demarini, A Kligerman, S Thai, D Delker, B Adair, M Hughes E Kenyon (NHEERL); J Creed, P Creed, H Ozkaynak (NERL); R Sams (NCEA); R Connelly (NCCT) E Gray, T Stoker, J Goldman, S Laws, K Crofton, M Devito, M Gilbert (NHEERL) S Hunter, M Narotsky, T DeAngelo (NHEERL)
2	Biomarkers for Cumulative Risk	Joachim Pleil (NERL)	M Morgan (NERL); M Dellarco (NCEA); C Saint (NCER); R Devlin, K Crofton (NHEERL)
2	Source-to-Dose Models for Cumulative Risk	Valerie Zartarian (NERL)	Z Guo (NRMRL); M Tornero, F Power, C Dary, M Okino, D Vallero (NERL); C Saint (NCER); H Ozkaynak (ORD)
2	Application of Tools for Cumulative Risk of Chemical Mixtures	Jane Ellen Simmons and Stephanie Padilla (NHEERL)	D Herr, G Moser, H El-Masri, I Gilmour, JE Simmons, K Crofton, M Madden, M Devito, P Bushnell, P Kodavanti, S Hunter, S Padilla, T Shafer, W Boyes (NHEERL); W Setzer, J Blancato (NCCT); M Tornero-Velez (NERL); R Hertzberg (NCEA)

2	Tools for Assessing Community Risk	Stephen Graham (NERL)	K Thomas (NERL); V Benignus (NHEERL)
3	Research on Life-Stage	Long-Term Effects: John Rogers (NHEERL)	C Lau, N Chernoff, S Fenton, M Rosen, E Massaro, B Abbott, J Andrews, M Gilbert, D Schreinemachers (NHEERL); S Barone (NCEA)
		Effects and Exposure in Children: Nicole Tulve (NERL)	S McMaster, R Daniels, G Moser (NHEERL); R Fortmann, K Thomas, D Stout (NERL), C Saint, (NCER); J Moya, S Makris (NCEA); M Firestone (OCHP); J Evans (OPP); E Hubal (NCCT); Z Guo (NRMRL)
		Aging: A Geller, L Birnbaum, R MacPhail (NHEERL)	K Thomas (NERL); A Geller, M DeVito, J Royland, C Corton, C Gordon, V Benignus, L Birnbaum (NHEERL); B Glenn, J Moya (NCER); B Sonawane (NCEA)
3	Methods for Longitudinal Research	Pauline Mendola (NHEERL)	J Gallagher and S Fenton (NHEERL); J Quackenboss (NERL); B Sonawane and R Brown (NCEA); L Blackburn (OCHP); N Fields (NCER)
3	Research on Asthma	Hillel Koren (NHEERL)	I Gilmour, L Neas, S Gavett, M Ward, R Devlin (NHEERL); S Vesper, R Williams (NERL); J Jetter, M Menetrez, T Dean (NRMRL); C Saint, T Katz (NCER)
4	Approaches to Evaluate Risk Management Decisions	Rebecca Calderon (NEERL)	H Ozkaynak, V Zartarian, P Egegy (NERL); D Lobdell, D Schreinemachers (NHEERL); D Petersen (NRMRL), P Murphy (NCEA); C Saint (NCER); M Smuts (OAQPS)
4	Report on the Environment	Danelle Lobdell (NHEERL)	D Shaw, P Murphy (NCEA)

ATTACHMENT F
Detailed Description of Research for Each Research Track

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment
Research Track 1: Methods and Models to Characterize MOA

Toxicogenomic and toxicoproteomic technical approaches are currently being developed as a key part of research approaches within ORD. Transcript profiling is currently used to identify early signaling pathways which control the immune and cardiovascular systems and may be involved in immune dysregulation or cardiovascular disease after exposure to air pollutants, experimental allergens, or infections. Toxicogenomic approaches are also being used in conjunction with laser capture microdissection to examine mechanisms by which air pollutants affect the pulmonary and cardiovascular system. Transcript profiling is being used to characterize age-dependent changes on control of metabolizing gene expression in human liver cells, to identify networks of co-regulated genes, and to determine inherent variability in the pattern of gene expression. Transcript profiling is also being used to differentiate xenobiotics within chemical classes that exhibit different toxicity profiles including carcinogenicity. This profile-based research is resulting in our ability to differentiate carcinogenic from non-carcinogenic compounds within the same chemical class. Micro-array approaches are being used to define the molecular pathways critical to acute to chronic neurotoxicity of volatile organic compounds (VOCs), and to identify genetic "fingerprints" that can be used as biomarkers of exposure to a specific air pollutants, or individual components of air pollutants. High throughput single nucleotide polymorphism (SNP) analysis is being used to identify human genetic polymorphisms associated with increased and decreased sensitivity to air pollutants. Since many of these studies use *in vitro* toxicology approaches it will be necessary to validate the results using *in vivo* models in which pollutant concentrations that are closer to real-world exposure scenario are used.

Proteomic approaches, including protein microarrays and mass spectroscopy, will be used to define alterations in cell signaling pathways, link changes in these pathways with pathophysiology, and correlate protein expression changes with those identified by transcriptional profiling. In addition, two-dimensional gel electrophoresis will be used to identify and characterize specific protein changes associated with exposure to environmental contaminants including air toxics, drinking water contaminants, and pesticides. These techniques are used to better describe effects in human serum, adult rodent fluids and tissues, and from rodent embryos. Use of SELDI-TOF technology is also being used to identify biomarkers of exposure or effect in tissues of humans exposed to air pollutants.

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment
Research Track 2: Develop Linkages between Pharmacokinetic and Pharmacodynamic Models

Nerve cell function impairment by Pyrethroids: The signals used by the nervous system to process information and transmit information are electrochemical in nature. Nerve cells have a resting potential across their membranes that may be perturbed by the movement of ions across their membrane, resulting in action potential (nerve firing). Pyrethroid insecticides bind to voltage-sensitive sodium channels and modify their gating kinetics, thereby disrupting nerve function. Pyrethroids may be classified into two groups, those that lack a cyano group in the α-position (type I) and those that have one (type II). Both types prolong sodium channel current thereby reducing the threshold for nerve firing, a condition termed hyperexcitability. Type I compounds prolong channel opening only long enough to cause repetitive firing of action potentials (repetitive discharge), whereas type II compounds hold open the channels for such long periods of time that the membrane potential ultimately becomes depolarized to the point at which generation of action potentials is not possible (depolarization-dependent block). These differences in prolongation of channel open times are hypothesized to contribute to the differences in syndromes occurring after exposure to type II and I pyrethroids, respectively. A physical and mathematical model has been employed to describe the voltage-dependence of sodium and potassium conductance of the nerve membrane. This research will attempt to model the induction of the action potential by a larger suite of pyrethroids, singly or as a mixture, as well as to evaluate options for linking this modeling to pharmacokinetic models also being developed for pyrethroids.

Cellular Responses to As: Epidemiologic studies have established that relatively high level inorganic As exposures cause cancer in multiple organs (skin, bladder, lung). However, the risk associated with the lower exposure levels common in the US is uncertain. Low dose extrapolation for As is confounded by limited understanding of both the quantitative and mechanistic relationship between arsenical target tissue dosimetry and subsequent development of adverse effects. Evaluation of this relationship is complex due to (1) limited tissue disposition data for the multiple valence states and metabolites of inorganic As [i.e., AsV, AsIII, monomethylarsenic acid V (MMAV), MMAIII, dimethylarsenic acid (DMA) III, DMAV), (2) data indicating that the individual arsenicals have intrinsic and unique toxic effects, and (3) potential for both kinetic and dynamic interactions among the metabolites to produce toxic effects. As is known to induce effects on the cell regulatory network that are highly concentration dependent. The goal of this research is two fold: (1) to develop pharmacodynamic representations of key events in specific target organs (e.g., bladder, skin, lung) and, (2) develop PK-PD linkages to existing models of arsenical metabolism in both specific cell types and the whole organism. PK information on As and related chemicals will be crucial for develop MOA information for risk assessment (LTG1, Research 3, MOA Information to Address Extrapolation in Risk Assessment)

Thiol Redox Status and Cell Function: Many proteins present on cell surfaces and located

in extracellular fluids contain cysteine and methionine residues that are subject to oxidation. These proteins (including transporters, receptors, and enzymes) respond to subtle changes in the intra- and extracellular thiol/disulfide redox environment, which may occur at concentrations below those causing damage to proteins, lipids and DNA (i.e., cytotoxicity). Changes in the ratios of reduced and oxidized glutathione (GSH/GSSG) regulate the post-translational modification of many proteins, thus this ratio may serve as a starting point for modeling other pharmacodynamic processes. This research will address several issues. How can the impact of xenobiotics (e.g., methanol or formaldehyde) on redox potential be modeled? Important factors include the physical properties of a compound or its metabolites, pharmacokinetic properties such as rates of enzyme-mediated clearance or activation of the compound, and baseline redox states? What are the normal ranges of redox potential (e.g. GSH/GSSG ratio) in cell types of interest, and how do either transient or sustained redox changes within this range affect cell function and rates of proliferation, differentiation, and apoptosis? What are the signaling pathways activated by changes in redox status that lead to changes in cell function? What are the implications of mild oxidation (within or near the physiologic range), leading to protein modification/regulation, on low dose extrapolation for cancer and non-cancer endpoints (e.g., leukemia and developmental toxicology, respectively)?

Nuclear Receptor Activation-Induced Responses: Nuclear receptors are transcription factors activated by endogenous and exogenous chemicals. These include the peroxisomal proliferator activated receptors (PPAR), the constitutive androstane receptor (CAR), and the pregnane-X-receptor (PXR). A wide range of environmental chemicals including toxics, pesticides such as conazole fungicides, and air toxics may have similar MOAs in that they bind or otherwise activate these transcription factors. Activation results in changes in the expression of genes regulating growth and differentiation in the liver and genes involved metabolism of xenobiotics and endogenous substances. Many liver tumor promoters and thyroid hormone disruptors are nuclear receptor ligands. There are also known species differences in the structure activity relationship for ligand binding, particularly for CAR and PXR. Suggestive evidence indicates there are species differences in the role of these receptors in regulation of cellular functions of growth and differentiation. Because of the similar MOAs, it is likely that environmental chemicals that activate nuclear receptors in a similar fashion across species. A combination of systems biology and PBPK modeling approaches will be of value in developing pharmacodynamic models of these receptor systems. Several PBPK models for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is a potent ligand for the aryl hydrocarbon receptor, describe the pharmacokinetics of chemicals resulting in receptor-binding and activation of genes for hepatic xenobiotic metabolizing enzymes (XMEs) including CYP1A1, CYP1A2 and UGT1A6. This model structure could be used to describe the expression of XME's regulated by other nuclear receptors. It also may be possible to use this model structure to incorporate genomic data on the induction of XME's by any environmental chemical that is a ligand for a nuclear receptor. This modeling approach could then be expanded to include mode of action models for liver carcinogenesis, thyroid hormone disruption, or other toxicities induced by environmental chemicals that are ligands for nuclear receptors. A better understanding of the role of these receptors in toxicity could have broad implications for screening and testing as well as the development of quantitative pharmacodynamic models.

Long-Term Goal 1: Use of Mechanistic Data in Risk Assessment
Research Track 3: MOA Information to Address Extrapolation in Risk Assessment

Conazoles: The conazole program is a demonstration project aimed at using state-of-the science molecular tools supported by traditional toxicology to reduce uncertainties in interspecies extrapolation, develop a model approach for the use of toxicogenomic data to identify MOAs, and identify MOAs that may allow for harmonized approaches for cancer and non-cancer risk assessments, as well as inform CRA of mixtures of conazole pesticides.

Previous ORD research has shown promise for understanding the modes of toxic action of conazole fungicides for identifying key events as a means for extrapolations from high to low dose, from laboratory animals to humans, and from *in vitro* data to *in vivo* exposures. This highly integrated research is designed to apply state-of-the-art molecular tools (genomics, proteomics and metabolomics) supported by traditional toxicological methods to study the mode(s) of action of conazoles that have toxicologically adverse outcomes. A basic tenet of this research is to select activity-inactivity pairs of conazoles for comparison of their effects (i.e., carcinogens and non-carcinogens; reproductive toxicants and non-reproductive toxicants). Tissues are collected from rats and mice who were administered selected conazoles and these tissues subjected to a battery of biochemical, hormonal, molecular, and histological evaluations. Global changes in gene expression (genomics) were compared across species, conazole compounds, dose, and time to reveal those alterations associated with toxicity. Those genes and cellular and molecular ontological pathways identified as candidates were further explored at the protein, enzyme, and biochemical intermediate levels. These molecular beacons or roadmaps of MOAs will be further studied using proteomics and metabolomics, including identifying markers of exposure. Interspecies comparisons (rat, mouse, and human) will be investigated using both *in vitro* and *in vivo* approaches.

Future research will focus on extending the toxicogenomic analyses on the hepatotoxic tumorigenic triazole-based conazoles to a wider conazole class, the imidazole-containing conazoles (e.g. tumorigenic and non-tumorigenic imidazole-containing conazoles, climbazole, prochloraz, and oxypoconazole). Other studies will apply the strategy of an integrated toxicogenomic approach to identifying the mode(s) of action of other key environmental agents, particularly found in Air Toxics. This research will also develop analyses that explore the links between toxic exposures and epigenetic regulated gene expression. Epigenetic dysregulation is central to cancer development and progression, including hypomethylation leading to oncogene activation and chromosomal instability, hypermethylation, tumor suppressor gene silencing, and chromatin modification to modify gene expression. Research will be conducted using environmentally relevant concentrations and tissues derived from both animal and human cell lines to promote laboratory animal-to-human extrapolation. Dose-response relationships for a select group of 4-5 conazoles will be determined before moving on to other chemicals in this class.

Neuroendocrine Mechanisms: The overall objective of this research is to develop MOA

information to reduce uncertainty in interspecies extrapolation and use MOA to identify key events underlying multi-system, life-stage-dependent toxicity. This research focuses on developing the fundamental science needed to identify and evaluate the impact of environmental compounds having a neuroendocrine MOA. The ultimate goal is to develop animal models that provide the means to identify those cellular mechanisms altered by exposure to endocrine disrupting chemicals (EDCs) and the ensuing cascade of events that lead to an adverse outcome. Once established, these models can be used to evaluate the relevance of such effects to human health (i.e., exposure/dose response extrapolation and intraspecies extrapolation) and to harmonize the cancer and non-cancer risk assessments. Past research was successful in characterizing the effect of antiandrogens on reproductive tract development in the rat and establishing NOAELs and LOAELs for the antiandrogen vinclozolin. This research also identified the effect of phthalates on reproductive tract development. Research also contributed to evaluating the cumulative effect of antiandrogens and working with OPPTS on the cumulative effects document for antiandrogens. Other research characterized the dose response relationship and the effect of perinatal exposure to environmental estrogens on ovarian function in the offspring, the dose response relationship, critical windows of exposure, and functional consequences of developmental hypothyroidism induced by environmental toxicants.

Future research will focus on four areas. Two of these areas address the effect of environmental chemicals on male and female reproductive development, in which animals are exposed perinatally and evaluated during development and/or in adulthood. The third area is designed to identify and characterize the functional consequences of developmental hypothyroidism induced by environmental toxicants on brain structure and function during development and in the adult. A fourth area focuses on evaluating the effect of environmental compounds on the regulation of Luteinizing Hormone (LH) secretion in the female. Various chemicals can alter circulating levels of the LH, impair fertility in both sexes, and lead to reproductive pathology or tumor development. ORD research has identified a number of compounds that modify the secretion of this key hormone and is currently developing the methods/approaches necessary to characterize the cellular mechanisms affected following toxicant exposure and the mode of action by which these adverse outcomes develop. The principles derived from these efforts are expected to aid in developing a generalized approach for examining a range of related, chemically-induced disorders of the neuroendocrine control of the reproductive and thyroid axes. Research will be conducted using environmentally relevant concentrations and tissues derived from both laboratory animal and human cell lines to promote animal-to-human extrapolation.

As and Related Compounds: Humans are chronically exposed to arsenicals from various sources; ingestion of drinking water containing inorganic As and exposure to methylated arsenical pesticides are probably the major sources. Although arsenicals are recognized as carcinogens and toxicants, relatively little is known about the MOAs by which these adverse effects are exerted. Understanding these MOAs would reduce uncertainties in risk assessments for arsenicals by clarifying process underlying cell injury. To date this program has made several important contributions to understanding the mechanistic basis for the actions of arsenicals as toxicants and carcinogens. Major accomplishments include elucidation of the role

for biomethylation of arsenicals in their activity, identification of the generation of reactive oxygen species by arsenicals as a potential mode of action, critical investigations of potential MOAs of asenicals including their genotoxic activity and their role in the generation of reactive oxygen species, and development of a comprehensive PBPK model that reflects biological reality for the variety of arsenicals that are produced by biomethylation. Each of these accomplishments has been described in scientific communications. This body of research has focused new attention on MOA research for arsenicals and provides critical information in the evaluation of the risk for cancer and non-cancer health effects associated with exposure to these agents.

The critical features of research on As are to promote harmonized approaches for cancer and non-cancer risk assessment, develop approaches to evaluate multi-media mixtures of environmental agents with comparable MOAs, and assess susceptibility to As based on genetic polymorphisms. ORD research will address two topic areas for mechanistic research. First, work on MOAs of arsenical is critical to evaluating the adverse health effects that may be attributed to these agents. This effort includes studies on the linkage between the metabolism of arsenicals and their actions as toxins and carcinogens. Second, a significant effort is devoted to the development of models that link the kinetic and dynamic behaviors of arsenicals at the systemic and cellular levels. Development of comprehensive models will provide a powerful tool for integration of dosimetric studies and research on MOAs. PK information from LTG1 Research Track 2 (Develop Linkage between PK and PD Models) will be critical for determining tissue levels of parent compounds and metabolites and relating them to critical health effects for risk assessment.

Chemicals that Act by Oxidative Stress (OS): OS is a ubiquitous event in biological systems associated with normal physiological changes such as ageing; it is also the result of diverse stimuli including exercise, disease, and exposure to environmental pollutants. OS occurs when there is an imbalance in the production of oxidants (endogenous or exogenous stimuli) and the cell's ability to reduce them with antioxidant defenses (*e.g.* catalase, glutathione, dietary antioxidants). Reactive nitrogen species, reactive oxygen species, and antioxidants have duel roles, functioning in OS and normal physiological processes (*e.g.*, cellular signaling, second messenger pathways, and apoptosis). OS has been implicated as playing a major role in the MOA resulting in adverse health effects from exposure to a wide range of environmental pollutants by both inhalation and systemic routes of administration. These agents include radiation, diesel exhaust particles and PM, ozone , chloroform, carbon tetrachloride, polychlorinated biphenyls (PCBs), As, organometals, pesticides, and dioxin. ORD researchers have investigated the role of OS for epithelial perturbations in the respiratory tract caused by ozone. More recently, ORD scientists have turned their investigations to the role of PM-mediated cardiopulmonary health effects. These efforts have strengthened the science required to support implementation of regulatory actions for the criteria pollutants, PM and ozone, and helped establish the biological plausibility for various undetected emerging health effects. The database amassed on PM and ozone represents a rich resource with which to pursue an in-depth understanding of the health consequences of OS. In addition, key research regarding the role of OS in As-induced toxicity has been conducted within ORD. This research provides a strong

foundation for the hypothesis that OS may be a generic MOA for many organ-specific toxicities and that specific biological changes associated with OS (e.g., inflammatory cell recruitment) may serve as predictor changes in the exposure-dose-response paradigm.

Future research will focus on further developing the concept that OS may serve as a generic MOA underscoring adverse effects in a number of target tissues. If this is the case, OS may have potential as a biomarker of exposure or effect for assessing the consequences of exposure to environmental agents. Elucidation of OS effects and their dose-response characterization might also be useful in the risk assessment process, particularly if effects can be measured at various levels of biological organization and if these effects are similar in laboratory animals and humans. Research regarding OS has generated a comparatively large literature base over the past 10-15 years.

The first step in this research strategy is to organize a workshop of expert scientists to evaluate the state of the science in OS, including: dose-response characterization, species extrapolation, extrapolation of acute to chronic studies, and common OS events occurring in both cancer and non-cancer adverse health effects. Simultaneously, a separate effort will focus on compiling a comprehensive database for OS analogous to the Transgenic Rodent Assays Information Database for the purposes of identifying OS research gaps, highlighting undefined relationships attributed to OS in the current literature, and providing direction for an efficient research strategy. Communication with other federal agencies (National Institute of Aging, National Institutes of Health, National Cancer Institute, and Food and Drug Administration) will be conducted throughout this effort due to shared interests in OS resulting from human exposures. This approach will not only result in a focused research strategy for OS within EPA, but likely yield advancements toward providing key data for: (1) aggregate/CRA, (2) risk to susceptible subpopulations, (3) use of common MOAs for cancer and non-cancer toxicity pathways, and (4) *in vitro* models based on MOA for toxicity testing.

Another aspect of this research strategy is to develop a quantitative model of the consequences of OS due to inhaled chlorine and the resultant epithelial perturbation in the respiratory tract in order to refine interspecies extrapolation methods for inhaled irritant gases. The biological responses in the respiratory tract will be characterized at various levels of organization (i.e., for different units of analysis or at different scale. Chlorine has been chosen for development of this model because of its proposed MOA as OS due to its hydrolysis to HOCl, and in order to base the model on the experience, knowledge and database on ozone as an inhaled irritant gas. The project involves both experimental and computational components. The targeted experimental component will obtain critical mechanistic data on chlorine that update its existing comprehensive traditional database to one of contemporary standards and comparable to ozone for characterizing OS responses. The computational component will use the previous data on ozone and the new data on chlorine together to develop a quantitative (Bayesian hierarchical) model to describe the effects of OS in the respiratory tract epithelium. Inhaled dose in the model is estimated from a combined species-specific computational fluid dynamics model of airflow with physiologically-based pharmacokinetic (PBPK) descriptions of tissue reactions. The goal is to produce a semi-empirical systems biology model to integrate and

quantify the degree of OS damage and transition among different states of epithelial tissue damage (e.g., adaptive, inflammation, cytotoxic) integrates the diverse data on OS at various levels of organization and thereby obviate the reliance on a single endpoint for dose-response analysis required in risk assessment. Comparison of the predictive power and accuracy of performing interspecies extrapolation using the model versus default algorithms to estimate human effect levels will be evaluated to arrive at a quantitative expression of confidence in the model. These expressions of confidence can serve as a new approach for mechanistic motivation for the magnitude of interspecies and intrahuman extrapolation factors applied in risk assessment.

Brominated Drinking Water Contaminants: Increased need for decontamination of drinking water has led to concerns about the potentially toxic effects of brominated disinfection byproducts (BrDBPs). Previous research at ORD has suggested possible reproductive/ developmental toxicity and colon cancer may be associated with exposure to BrDBPs. Research is needed to establish biological plausibility of these effects and reduce uncertainties in exposure-dose extrapolation to strengthen risk assessments of BrDBPs by the OW. The critical aspects of this project are to develop harmonized approaches for cancer and non-cancer risk assessments and characterize effects of BrDPBs following multiple routes of exposure (ingestion, inhalation, and dermal).

This research will focus on the reproductive and developmental toxicity of brominated haloacetic acids and trihalomethanes, the pharmacokinetics of brominated trihalomethanes, and adverse reproductive and developmental effects. Mechanisms by which bromodichloromethane (BDCM) induces pregnancy loss will be studied using *in vivo* and *in vitro* techniques. These studies will include an assessment of the effects of BDCM on human placental differentiation and the mechanisms that perturb its development. BDCM-induced pregnancy loss following exposure via routes other than oral will also be assessed, and a route-to-route extrapolation model will be developed for BDCM. BDCM is an appropriate candidate for full development of a human PBPK model, because it has been implicated in both reproductive and carcinogenic effects. In another study, a model will be developed for identification of low-dose effects of dibromoacetic acid and the effects on semen quality in men exposed to DBPs. Alterations in fetal growth and induction of birth defects have been reported to be associated with DBPs. In animal models, the brominated haloacetic acids are more potent than the chlorinated molecules. Bromochloroacetic acid (BCA), which is one of the most potent haloacetic acids, produced embryonic death, birth defects and alterations in fetal growth in laboratory animals. Mechanistic studies following exposure to low doses of DBA and BCA will utilize toxicogenomic and proteomic tools to better understand the potential for these compounds to adversely affect human health. Work will also include studies on the pharmacokinetics of brominated trihalomethanes and the effect of individual and mixtures of trihalomethanes on the development of colon carcinoma (such as development of preneoplastic aberrant crypt foci). The use of colon cell lines in this research is also being proposed. These studies will address the mode of action of brominated DBPs as it pertains to their carcinogenicity in the colon and precancerous outcomes.

Long-Term Goal 2: Cumulative Risk

Research Track 1: Biomarkers for Cumulative Risk

With advanced technologies, it is now possible to measure very low levels of many environmental chemicals and/or their metabolites in biological fluids. However, the appropriate use and interpretation of these measurements will depend upon many factors, such as the exposure concentration and duration; the adsorption, deposition, metabolism, and elimination of these chemicals; and personal and activity related information pertaining to the individual or population being examined. Developing a framework and modeling tools to guide future biomarker of exposure applications is central to this research theme. ORD exposure and dose modeling tools will aid in determining approaches for collecting biomonitoring data and identifying data gaps for interpretation. Focused exposure measurement studies, modeling activities, and data analysis will be conducted to address these knowledge gaps and to quantify the relationship between measurements of biomarkers of exposure, environmental concentrations, and internal dose. Modeling and advanced statistical analysis will be used to define the relationship between environmental concentrations and biomarkers of exposure, and to also determine changes in biomarker concentrations that may results from changes in various environmental measures.

In this research track, we will also address the risk incurred from combined chemicals and routes through an integrated study of systemic biological changes that retrospectively may indicate previous exposures, or prospectively may indicate a precursor to an adverse effect. Such markers could be comprised of pattern shifts in the normal expression of proteins or simpler endogenous chemicals, of exogenous chemical adducts with DNA, glutathione, or proteins of exogenous compounds, or simply of a representative suite of the native compounds of exposure found in body fluids. The ultimate goal is to acquire sufficient detailed knowledge of complex environmental exposures and the resulting systems biology to determine an individual's cumulative risk with a simple suite of blood, breath, or urine measurements. Biomarkers can also serve to address the concept of individual susceptibility in response to interaction with a common set of environmental agents or stressors. Differences among individuals' activity patterns influences the route and amount of uptake; their health state and phenotype can influence the distribution, biologically available dose and elimination mechanisms, and their genotype affects the defense mechanisms and repair functions. As such, biomarkers allow us to understand why there is a range of effects from ostensibly common exposures.

Long-Term Goal 2: Cumulative Risk
Research Track 2: Source to Effect Modeling

The Stochastic Human Exposure and Dose Simulation model (SHEDS) is a physically-based, probabilistic model that was developed by ORD to predict multimedia, multipathway single chemical (aggregate) exposures for user-specified populations. It combines information on chemical use, human activity data, environmental concentrations, and other important exposure factors using probabilistic sampling methods. The model has been used to simulate children's aggregate exposures to several pesticides including chlorpyrifos and CCA. Future research will focus on refining, evaluating, and releasing a user-friendly version of SHEDS to

the public. Improved source to concentration modules will be developed that use fugacity principals to predict fate and transport of primary pollutants and that also incorporate indoor chemistry algorithms to predict the formation of secondary pollutants. A refined dietary module will be incorporated into the model. Procedures for employing SHEDS to estimate exposures to mixtures of chemicals (cumulative) and longitudinal exposures over time will be developed to provide inputs for CRAs. SHEDS will be modified, as needed, and applied to address specific Agency exposure assessment needs.

SHEDS and other exposure models provide mathematical equations to estimate exposure using available data on environmental concentrations, human activities and exposure factors. Research activities are underway to ensure that high quality databases containing this critical information are continually updated and readily available to risk assessors both within and outside of EPA. The HEDS incorporates data from all of NERL's exposure measurement studies. The CHAD contains data describing individuals (sex, age, etc.) and their personal activities obtained from survey questionnaires administered in both internal ORD and externally conducted human activity studies collected at city, state, and national levels. These data are used to update ORD's Exposure Factors Handbooks and provide a compilation of information useful as inputs to the models necessary for conducting probabilistic exposure assessments.

The Exposure Related Dose Estimating Model (ERDEM) is a physiologically-based pharmacokinetic (PBPK) modeling system developed by ORD that describes internal doses resulting from human exposures to single or multiple chemicals through multiple pathways. Recently a physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model has been added to provide predictions of actual organ level doses for single chemicals and mixtures. ERDEM is fundamental to studies of aggregate exposure and cumulative risk because it allows for the examination of multiple exposure routes (e.g. oral, dermal and respiratory) simultaneously. It has been used to estimate doses resulting from aggregate exposure scenarios to methyl tertiary-butyl ether, trichloroethylene, chlorpyrifos, malathion, and carbaryl. Planned research will provide enhancements that improve both the ease of operation and additional modeling capabilities. The ERDEM front end will be modified to include an exposure time history repository that will take inputs from various exposure models, such as SHEDS, so that a Monte Carlo simulation can be run. The system will also be modified to add an user-defined uncertainty analysis interface that will enable researchers to perform sensitivity and Monte Carlo analyses including correlated parameters such as volumes and blood flows. ERDEM components will be modified or new ones added as necessary to meet the specific Agency's needs. These include intracellular modeling approaches, multiple compartment organs, and the development of Quantitative Structure Activity Relationship (QSAR) databases to make predictions for chemicals where data are lacking.

The resulting modeling tools and databases will be applied to identify critical data needs and prioritize future exposure/epidemiological research studies. For example, the models will be used to define the appropriate timing for collecting environmental and biological samples (see Research Track "Biomarkers of Exposure"). They will also be used to support of important Agency risk assessments. As an example, a cross-ORD research team is developing methods,

exposure data, exposure and dose models and toxicity data to support OPP's CRAs for pyrethroid pesticides and N-methyl carbamates. The application of these modeling tools in support of these risk assessments is described in the Research Track "Application of Tools for Risk Assessment." This research will not only provide tools and data for conducting an important agency risk assessment but, more importantly, it will elaborate the general scientific principles and knowledge base for considering cumulative exposure and dosimetry models.

Long-Term Goal 2: Cumulative Risk
Research Track 3: Application of Tools for Cumulative Risk of Chemical Mixtures

This research will investigate common uncertainties that have an integral impact upon the risk assessment of mixtures. The issues to be addressed in this research track are the default risk assessment assumptions for chemical mixtures described in the Risk Assessment Guidelines for Chemical Mixtures (US EPA, 1986) and the recent Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (US EPA, 2000, *Erratum* in 2001). Over the past three years, ORD has investigated principles of dose- and response-additivity, supplied the Program Offices with data on the interaction of chemicals in mixtures of regulatory interest, and developed and implemented dose-response models for use in CRAs. For example, in support of the CRA required under the FQPA, the team supplied the OPP with data on mixtures solely of organophosphorus pesticides or carbamate pesticides, and on a mixture of organophosphorus and carbamate pesticides combined. ORD developed the dose-response model for organophosphate exposure used to compute relative potency factors in the organophosphate CRA. ORD provided the OW with data on mixtures of trihalomethanes, and the OPP and OW with data on a mixture of thyrotoxic compounds. ORD has also published a series of papers on statistical methods for designing and analyzing data from mixture experiments. These activities have served to influence directly regulatory decisions or to reinforce the confidence of existing risk assessment decisions.

Future research will develop general principles for predicting the interaction of chemicals in a mixture. This research will focus on responding to strong programmatic needs articulated by the Regions and Program Offices. ORD will study chemicals and chemical classes as model mixtures and mixtures of interest to the Regions or Program Offices, including the OW, OPP, and OAR. Because one factor that has a marked influence on the toxicity of a mixture is the composition of the mixture, exposure data from ORD will allow examination of mixtures that are environmentally relevant, *i.e.*, so that real world exposure conditions are driving the experimental design. A collaborative team of researchers from NHEERL, NERL, NCCT, and NCEA will interact to conduct integrated, interdisciplinary research to address the generic issues of mixtures risk assessment. Through a coordinated research program, we will use common experimental designs and similar methods with multiple classes of chemicals allowing us to eventually integrate the data into global predictive models.

Long-Term Goal 2: Cumulative Risk
Research Track 4: Tools for Identifying and Assessing Communities at Risk

Research will be conducted to identify, refine, evaluate and apply tools for assessing exposures and effects to multiple chemical and non-chemical stressors to individuals and across communities. Studies will be conducted to examine the combined effects resulting from acute exposures to single or multiple chemicals (e.g., toluene, CO) and one or more non-chemical stressors (e.g., noise, heat) over a continuum of physical exercise/activity levels. The results will provide insights regarding the composite relationships among chemical and non-chemical stressors in terms of exposure, effects, and other important endpoints used in risk assessment (e.g., safety, accidents). Existing community-based assessment tools and approaches will be compiled, reviewed, and evaluated. Hypotheses will be generated regarding how to address spatial and temporal patterns of exposure to multiple chemical and non-chemical stressors (e.g., physical, biological and psychosocial) and how to incorporate individual human attributes (e.g., health status, behaviors, life-stage) reflective of the general community structure. Collaborations will be established with scientists within and outside the Agency who are engaged in community risk research to better understand the approaches and skills needed to design, plan and implement community-based cumulative research, and to learn from their experiences. Specific tools will be used/modified/designed for project specific applications to demonstrate the initial utility of the tools and, when supplemented with appropriate measures, to determine the value added to the assessment. These will include State, Region, Tribal, etc. collaborations to address real-world issues within their geographic areas (e.g., auto body shop and air toxics emissions in Region 1; port related emissions (shipping, railroad, automotive) in Region 10; community risk issues within selected communities). Through these collaborative research activities, existing approaches/protocols for the conduct of community-based assessments will be evaluated in addition to identifying new methods/protocols that need to be developed. Finally research will be conducted on approaches that effectively implement and communicate prevention/intervention strategies to communities.

Long-Term Goal 3: Susceptible Subpopulations
Research Track 1: Research on Life-Stage

Long-Term Effects of Developmental Exposures: Research to date has produced preliminary data indicating that prenatal chemical exposure [perfluorinated alkyl acids (PFAAs), atrazine, dexamethasone] in rodents, as well as maternal under nutrition, results in elevated blood pressure in young adult offspring. This effect is more prominent in male offspring, although the mechanism underlying this gender difference in sensitivity is unknown. Our ongoing research is designed to assess the effects of adverse developmental environments on life-long health**.** The so-called ABarker Hypothesis@ states that the developmental environment plays a key role in setting physiological parameters (“programming”) that affect later risk of disease. This has been well established in terms of developmental under nutrition, but it is unknown if toxic exposures can have similar effects. The cardiovascular system, glucose regulation, obesity and reproduction have received the most attention in human studies, and will be the primary foci of this project. There is emerging evidence that other aspects of health may be vulnerable as well. Thus, we will also include studies on the central nervous system, kidneys, and the induction of cancer. Pregnant rats and mice will be exposed to toxicants at dosages known to affect fetal weight. Choice of toxicants will be made to maximize connection to other

human health-related research, but will include Peas, atropine, at least one arsenical, agents putatively acting via reactive oxygen species Offspring will be assessed throughout life to determine their health status and reproductive capacity. Measures to be carried out include blood pressure (tail cuff plethysmography), carbohydrate metabolism (glucose challenge followed by time-course of blood glucose and insulin levels), body composition (adiposity), renal histology, serum chemistries, behavioral testing, reproduction and longevity. In order to identify mechanisms of action for significant effects, we will carry out perinatal gene expression analyses and global and gene-specific genomic methylation profiling.

Tools to Measure Exposure and Effects in Older Populations: The research spans the continuum from environmental exposures to adverse health outcomes, using epidemiological, clinical and laboratory approaches. Information will be collected to identify exposures, activity patterns, confounding stressors and subpopulations of concern in the older-adult community; this effort will also identify gaps in our current understanding, which are expected to be numerous. Knowledge bases will be constructed to provide quantitative descriptions of the changes in organ-system reserve capacity and metabolic function that accompany aging. Laboratory and clinical studies will focus on characterizing susceptibility in terms of (1) frailty, or the efficacy and potency of environmental pollutants in producing adverse effects, (2) resilience, or the speed and extent of functional recovery following exposure, and (3) the breadth of individual differences in susceptibility. Collectively, these studies will determine the mechanism(s) underlying susceptibility at the genomic, molecular and tissue levels, and evaluate the relative importance of PD and PK influences on risk. It is anticipated that biomarkers of susceptibility will be identified that can then be validated and deployed through clinical and epidemiological investigations. Survey, laboratory and clinical data will be integrated to create predictive models of exposure, activity patterns, metabolism and physiology that can be used to strengthen the assessment of health risks for older adults.

*Studies on Exposures and Effects in Children***:** The research involved characterizing the differential response of the young to the neurobehavioral and neurochemical effects of cholinesterase-inhibiting pesticides (carbamates and organophosphates) and determining the biological mechanisms for these differences. A set of highly focused research studies was developed by ORD researchers to fill critical data gaps related to children's exposures to chemicals in their everyday environments. Exposure measurement studies were performed to identify important exposure pathways and exposure factors for a wide range of persistent and non-persistent chemicals, including polycyclic aromatic hydrocarbons (PAHs), PCBs, phthalates, phenols, acid herbicides, organochlorine pesticides, organophosphate pesticides, and current-use pyrethroid pesticides. In the area of children's pesticide exposure measurements, ORD researchers focused on the following four priority research areas: pesticide use patterns, spatial and temporal distribution of pesticides in indoor environments, dermal and non-dietary ingestion exposure pathways, and dietary exposures. Pilot studies were designed to evaluate aggregate exposure measurement methods and a draft protocol for measuring children's non-occupational exposures to pesticides was developed. The data from these research studies have been used by ORD to develop a state of the art aggregate exposure and dose model, the Stochastic Human Exposure and Dose Simulation (SHEDS) model, to examine children's exposure to a variety of

multi-media multi-pathway chemicals. The SHEDS model is designed to interface with more sophisticated source-to-concentration and exposure-to-dose models. ORD has also been formulating appropriate PBPK by evaluating both human and laboratory animal data sets that are relevant to chemicals and exposure scenarios of concern for children. ORD routinely makes child-specific exposure factor data available through the Child-Specific Exposure Factors Handbook.

ORD research has been focused on reducing the data gaps for children in order to better understand their exposures, susceptibilities, and differential risks. ORD research is now moving toward supporting the age groupings proposed and adopted by the Risk Assessment Forum in its new "Guidance on Selecting Age Groups for Assessing and Monitoring Childhood Exposures to Environmental Contaminants," including gestation, very young children (<3 years of age) and children up to adolescence. Differential risks for very young children (under 3 years of age) are not well understood and will be addressed in this research. Data will be collected to determine differential exposures and risks to both persistent and non-persistent chemicals that occur in everyday environments that children occupy. Research will encompass differential exposures, responses, and long-term outcomes, by means of collaborations between NHEERL, NERL, NCEA, and the NCER grant recipients. In addition, the systematic approach developed for aggregate exposure to pesticides will be used to develop the approaches, tools, and methods for assessing the cumulative exposures and risks to other classes of chemicals routinely found in children's everyday environments. Classes of chemicals under consideration include phthalates, brominated flame retardants, and perfluorinated chemicals.

ORD research concerning children will also focus on developing guidance for potentially high-risk products and broadly applicable risk management solutions for schools by prioritizing consumer products based on their chemical composition and emissions under use conditions, and developing tools and guidance to allow school managers to procure products and services with reduced risk to children and develop practical plan of action to reduce indoor air pollution in school buildings. This research will complete evaluation on "low-VOC" paints commonly used in schools and other buildings, and provide guidance to school managers and the public on the benefits and risks associated with these products. Marketed as green products, low VOC paints usually contain less "common" VOCs than conventional paints, but may contain new chemicals, especially polar compounds. Since their potential health benefits and risks have not been fully evaluated, there is a great deal of confusion about these products among the stakeholders such as state regulators, manufacturers, school managers, building owners, green building designers, and builders. Data generated from this study will allow a comprehensive evaluation of this widely used consumer product that affects a large population, including school children. This research will also complete survey in a county school system on purchasing and use of consumer products (such as cleaning products, dry erase markers, and paints) and estimate the potential risks associated with those specific products. Work will also include on-site investigations on factors affecting air quality in school buildings and ways to improve indoor air quality. Finally, ORD will develop broadly applicable risk management solutions and demonstrate in a county school system that the methods can produce measurable improvement to indoor air quality in schools through Buy Clean practice, building maintenance, air cleaning, and other measures.

Long term Goal 3: Susceptible Subpopulations
Research Track 2: Methods for Longitudinal Research

A pilot study that will screen approximately 10,000 in North Carolina is led by EPA and is expected to be in the field in March 2006. This pilot study provides an opportunity to test data collection methods, recruitment and retention strategies and may address the impact of common environmental factors on variations in child growth and development. Women who reside in defined geographic areas will be enrolled prior to pregnancy or anytime during their pregnancies and their children will be followed with repeated visits up to 18 months of age. A variety of environmental stressors and conditions will be assessed including exposures to chemicals on the job and at home, home environmental conditions, stress, and access to medical care. Biologic and environmental samples will be collected at each study visit.

The Science to Achieve Results (STAR) grants program will support 4-5 university-based studies that aim to develop early biological indicators of environmentally induced disease in young children. The investigators will use a suite of biological makers of exposure, effect and susceptibility along with environmental and questionnaire data to determine which set or combination of indicators provides predictive evidence of high risk or onset of disease. Potential adverse health outcomes include asthma, neurodevelopmental delay, skin lesions, and cancer. This research may ultimately provide an important new tool for pediatricians, epidemiologists and health scientists to discover or even prevent disease onset in preschool aged children.

Long-Term Goal 3: Susceptible Subpopulations
Research Track 3: Research on Asthma

To date, EPA's asthma research program has had an impact on regulatory, educational, and outreach activities critical to protect public health by: 1. Providing critical data for partial explanation of the differential susceptibility to air pollutant, reducing key areas of scientific uncertainty, and supporting regulatory programs including the criteria documents for ozone, PM, and the health assessment for diesel emissions; 2. Contributing significantly to a better understanding of the underlying mechanisms responsible for the causation and exacerbation of asthma; and 3. Developing innovative tools to characterize exposures to indoor and ambient bioaerosols leading to improved prevention and intervention techniques.

Asthma studies are an important component of population studies that assess real world exposures to different pollutants (or their mixtures) at different concentrations. The Detroit Children's Study is a major epidemiology study currently underway or in planning to provide data on the association between exposure to environmental agents and adverse health outcomes. These will contribute to our understanding of whether long-term, early-life exposures to mobile source emissions, particularly diesel exhaust particles, play a key role in the induction of allergic asthma in school children, and are of interest to OAR and OCHP.

Laboratory research will address the response of humans to air toxics (e.g., aldehyde) by

developing a data base that will support extrapolation between animal exposures and human health effects, establish QSAR models for aldehydes, and determine susceptibility factors including examination of age-related development of aldehyde detoxification enzymes (OAR, OCHP). *In utero* organogenesis represents a critical life-stage when exposure to pollutants has the potential to produce long-lasting effects. Models are being developed to study how *in utero* exposures to different kinds of diesel (e.g., organic rich vs. organic poor) affect birth weight and the development of allergic asthma (in support of high priority needs of OAR, OCHP). This life-stage model will later be expanded to address similar issues related to molds and pesticides (OAR, OPPTS).

Identification and quantification of molds holds great promise for mitigating childhood asthma. ORD research will develop innovative diagnostic tools that will be employed to design better prevention and intervention strategies to improve the health of asthmatic children (OAR, OCHP). Findings to date suggest that specific molds are directly associated with water-damaged homes of asthmatic children; removal of these molds significantly improves asthma symptoms. Further research will be undertaken in collaboration with planned or ongoing epidemiology studies to corroborate these findings. This project will also address aspects of source-to-effect modeling of asthma by developing biomarkers for exposure of children to molds, assessing the relative potency of molds for assessment of cumulative risk, and determine the role of molds in the development of asthma *in utero*.

Long-Term Goal 4: Evaluation of Risk Management Decisions
Research Track 1: Approaches to Evaluate Risk Management Decisions

This research track has both an extramural (grants) and intramural component. Currently, ORD's National Center for Environmental Research (NCER) is developing an RFA to examine the feasibility of using existing databases of environmental (ambient) and/or biological for linking environmental conditions with health outcomes. The intramural program has completed a solicitation of Program/Regional Office proposals to support demonstration projects that focus on developing principles that could be used to develop a national strategy to evaluate the effectiveness of risk management decisions. One project will focus on assessing the cumulative impact of a suite of air pollution reduction programs on environmental public health indicators for children and older populations in New Haven, Connecticut. This research will provide guidance about which models are most useful in assessing public health impacts in response to provisions of the Clear Air Act. This research involves input and collaborations with Region 1, OAR/OAQPS, ORD, the Connecticut Department of Health, University of Connecticut Health Center, New Haven Fire Department, New Haven Asthma Initiative, and Yale Medical School. A second project will focus on evaluating the potential use of direct health measures for assessing the impact of drinking water regulations targeting microbial pathogens. This research will assess the health impact of drinking water regulations and focus on health effects measurements in communities where water treatment changes have been made to comply with the SDWA to minimize endemic waterborne infectious disease. This research involves input and collaborations with OW, CDC, University of Maryland School of Medicine, VA Medical Health Care System, and Yale University School of Medicine. Additional

demonstration projects may be included depending on the availability of funds in FY06.

Long-Term Goal 4 Evaluation of Risk Management Decisions
Research Track 2: Health Chapter for Report on the Environment (RoE)

The ORD Health Chapter team reviewed the current US indicators of human disease and exposure based on key data sources. For the 2007 report indicators are based on national data. The relationship among and between environmental pollution, exposure, and disease is complex. The relationship between and environmental contaminant, exposure and a health outcome will be established through a compilation of epidemiological, toxicological, exposure and clinical studies. The RoE is an ongoing effort to use existing data and coordinate with other federal and state partners in the collection of exposure and health data to support the development of EPHIs. In assessing the current data available, key data gaps and emerging health and exposure issues will be identified and discussed.

XI. Appendices

Appendix 1 Potential Additional Work if Resources Increased 10-20 Percent

In 2005, Administrator Johnson announced the Agency's Action Plan which included three principles to accelerate the pace of environmental protection – (1) Results and Accountability, (2) Innovation and Collaboration, and (3) Best Available Science. These principles clearly support earlier Agency statements concerning the importance of holding the Agency accountable to the American public and reporting to them progress in addressing its mission to protect human health and the environment. In addition, the Government Performance and Results Act (GPRA) requires the Agency to set strategic goals, measure performance, and report on the degree to which the goals were met. The Government Accountability Office (GAO) noted that the Agency's GPRA strategy could be improved by including more outcome goals (i.e., those that reflect actual environmental or health improvement) to complement process goals, thus providing greater public confidence in the validity of the performance measures. Where outcomes have been proposed, both GAO and the Agency have frequently found that measurement systems are absent, of insufficient quality, of improper design, lack sufficient specificity or interpretability to provide credible data on impacts of Agency actions. Recent reviews of ORD's research programs by the OMB have also raised questions concerning the contribution of the some of the research to the Agency's mission to protect human health and the environment.

In response to these needs, ORD developed an initiative to verify the protective benefit of environmental decisions and to maintain public confidence in those decisions and their associated costs. Through the annual planning process, resources were made available through the HHRP to develop principles for demonstrating improvements in human health following risk management decisions. In 2005, the HHRP funded a project that 1) engaged the program and regional offices in identifying and submitting proposals on ongoing/anticipated decisions and actions appropriate for assessing public health impact; and 2) from those proposals, two proof-of-concept projects were selected and studies were initiated. If additional resources were available, they would be used to fund additional proof-of-concept projects to evaluate effectiveness of risk management decisions. The proposals funded during the FY05 competition included "Assessing Reductions in Waterborne Illness from Safe Drinking Water Act Regulations" and "Evaluation of the Impact of New Haven, CT, 'Clean Air Initiative' Cumulative Air Pollution Reduction Programs on EPHIs for Children and the Elderly". Other compelling, but lower ranked, proposals "Using Biomarkers to Quantify Changes in Diesel-Powered School Bus Driver's Exposure to PAHs in Diesel Exhaust Before and After their Vehicles are Equipped with Emission Retrofit Technologies" and "Effects of Lowering As in Drinking Water and Playground Equipment on Children's Urinary As" could be funded with additional resources. Alternatively, a new competition could be developed and new proposals reviewed by the ORD Accountability Steering Committee. These projects are estimated to cost approximately $400K each.

Appendix 2 Acronyms and Abbreviations

APG	Annual Performance Goal
APM	Annual Performance Measure
As	Arsenic
BCA	Bromochloroacetic acid
BDCM	Bromodichloromethane
BOSC	Board of Scientific Counselors
BrDBPs	Brominated Disinfection By-Products
CAA	Clean Air Act
CAR	Constitutive Androstane Receptor
CCA	Chromated Copper Arsenate
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CDC	Centers for Disease Control and Prevention
CHAD	Consolidated Human Activity Database
CRA	Cumulative Risk Assessment
DHHS	Department of Health and Human Services
DMA	Dimethylarsenic acid
DNA	Deoxyribonucleic acid
EDCs	Endocrine Disrupting Chemicals
EPHIs	Environmental Public Health Indicators
ERDEM	Exposure Related Dose Estimating Model
FY	Fiscal Year
GAO	Government Accountability Office
GPRA	Government Performance and Results Act
GSH	Glutathione
GSSG	Oxidized Glutathione
HAPs	Hazardous Air Pollutants
Heeds	Human Exposure Database System
HH MYP	Human Health Multi-Year Plan
HHRA MYP	Human Health Risk Assessment Multi-Year Plan
HHRP	Human Health Research Program
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
LH	Luteinizing Hormone
LOAEL	Lowest Observed Adverse Effect Level
LTG	Long-Term Goal
MAA	Monomethylarsenic acid
MOA	Mechanism or Mode of Action
MYP	Multi-Year Plan
NAS	National Academy of Sciences
NCCT	National Center for Computational Toxicology
NCEA	National Center for Environmental Assessment
NCER	National Center for Environmental Research
NCS	National Children’s Study

NHANES	National Health and Nutrition Examination Survey
NHEERL	National Health and Environmental Effects Research Laboratory
NERL	National Exposure Research Laboratory
NHEXAS	National Health Exposure Assessment Survey
NICHD	National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NRC	National Research Council
NRMRL	National Risk Management Research Laboratory
NOAEL	No Observed Adverse Effect Level
OAR	Office of Air and Radiation
OAQPS	Office of Air Quality Planning and Standards
OCHP	Office of Children's Health Protection
OEI	Office of Environmental Information
OMB	Office of Management and Budget
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORD	Office of Research and Development
OS	Oxidative Stress
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PAHs	Polycyclic Aromatic Hydrocarbons
PBPK	Physiologically Based Pharmacokinetic
PCBs	Polychlorinated Biphenyls
PD	Pharmacodynamic
PFAA	Perfluorinated Alkyl Acids
PK	Pharmacokinetic
PM	Particulate Matter
PPAR	Peroxisomal Proliferator Activated Receptors
PXR	Pregnane-X-Receptor
QSAR	Quantitative Structure Activity Relationship
RA	Risk Assessment
R&D	Research and Development
RfC	Reference Concentration
RfD	Reference Dose
RoE	Report on the Environment
SAB	Science Advisory Board
SDWA	Safe Drinking Water Act
SELDI-TOF	Surface-Enhanced Laser Desorption Ionization - Time of Flight
SHEDs	Stochastic Human Exposure and Dose Simulation
SP2	Safe Pesticides/Safe Products
STAR	Science to Achieve Results
TCCD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
UF	Uncertainty Factor

US	United States
VA	Veterans Affairs
VOCs	Volatile Organic Solvents
XMEs	Xenobiotic Metabolizing Enzymes