

OVERVIEW OF THE HEALTH RESEARCH PROGRAM AT THE ENVIRONMENTAL PROTECTION AGENCY

INTRODUCTION

The purpose of this Overview is to provide the basis for evaluating the Human Health Research Program at the Environmental Protection Agency (EPA) in the context of the Office of Science and Technology/Office of Management and Budget (OSTP/OMB) Research and Development Investment Criteria. These investment criteria include relevance, quality, performance and leadership. The charge questions provided to the Board of Scientific Counselors were designed to help evaluate these criteria.

RELEVANCE

Relevance refers to the contextual framework for the identification of priority research questions related to EPA's regulatory mission and how research is planned and prioritized. This section attempts to develop an overall conceptual framework for the Human Health Research Program that is consistent with Agency strategic goals, the *Human Health Research Strategy*, and recommendations by the National Research Council for core research. This section also tries to articulate the potential benefits of the research program and the involvement of the various stakeholders, particularly the Program and Regional Offices, in the planning and prioritization of the program. Finally, this section aims to illustrate the relationship of the program with outside research organizations, nationally and internationally.

Evaluation Criteria for Program Reviews

Relevance

Quality

Performance

Scientific Leadership

Overall Conceptual Framework for Human Health Research at EPA

The overall conceptual framework for Human Health Research Program is illustrated in Figure 1. This framework is based on input from various stakeholders concerning the past and future directions of the research program. EPA has identified as its clients risk assessors in EPA's Program and Regional Offices within EPA, States, other Federal agencies, international health organizations, the regulated community, and the academic community. EPA conducts research to develop the knowledge, skills or attitudes so that risk assessors and decision-makers can use mechanistic data to reduce uncertainty in risk assessment, conduct aggregate/cumulative risk assessments in a scientifically defensible manner, identify and protect susceptible subpopulations, and evaluate the effectiveness of public health decisions. The ultimate outcome of their activities is to reduce or prevent exposure of humans to environmental stressors posing a high risk and to demonstrate that the EPA is acting to protect human health.

Figure 1 also shows that one highly crucial feature of the research program at EPA is that

Figure 1 Overall Conceptual Framework for Human Health Research at EPA

Specific Clients	Short-Term Outcomes (knowledge, skills, attitudes)	Short-Term Outcomes (decisions, actions)	Intermediate Environmental Human Health Outcomes	Long-Term Outcomes
<ul style="list-style-type: none"> •EPA-OW, OAR, OPPTS, OCHP, OEI •Risk assessors ,e.g. IRIS, RAF •EPA-Regions •Other Federal Agencies (e.g., FDA, ATSDR, NIH, CDC) •International Health Organizations (e.g., WHO, IPCS) •Regulated Community (e.g., drug or chemical companies) •Academic Community •US Public 	<p>As a result of ORD research, scientists and decision makers have the knowledge, skills and tools to:</p> <ul style="list-style-type: none"> •Use mechanistic data in risk assessments •Conduct aggregate/cumulative risk assessments in scientifically defensible manner •Identify and protect susceptible subpopulations (e.g., children, the aged) in risk assessments •Evaluate effectiveness of Agency public health decisions <p>ORD is recognized as a scientific leader; as measured by leadership roles, citations, applications, scientific quality, and decision-making value.</p>	<p>As a result of ORD research, scientists and decision-makers:</p> <ul style="list-style-type: none"> •Utilize methods, measures and models in a more efficient and cost-effective manner to screen, prioritize and test environmental stressors for potential human health risk •Incorporate sound science for human health risk assessment and for making scientifically sound risk management decisions •Apply methods, measures and models that allows the Agency to focus on legitimate risks and solve Agency problems •Evaluate the results of risk management decisions based on a sound scientific foundation •Avoid unnecessary regulation 	<p>As a result of action by stakeholders:</p> <ul style="list-style-type: none"> •Environmental stressors that pose an unreasonable risk are identified and assessments are prioritized •Exposure to environmental stressors that pose an unreasonable risk to humans is prevented or reduced •Susceptible subpopulations such as children and the aged are protected from unreasonable risk •Effectiveness of regulatory and risk management decisions is improved 	<p>As a result of action by stakeholders:</p> <ul style="list-style-type: none"> •Exposure of humans to environmental stressors posing high risk is reduced or prevented •EPA actions demonstrate that it is protecting human health

it provides the basis for its scientists to be recognized as scientific leaders, both inside and external to the Agency. This is the basis for establishing the credibility of EPA's scientists to provide the expertise to help support the mission of the Agency. How outputs from the Human

Health Research Program at EPA have been used by our clients is discussed in greater detail in the topic entitled Progress to Meet the Long-Term Goals in the Section on Performance.

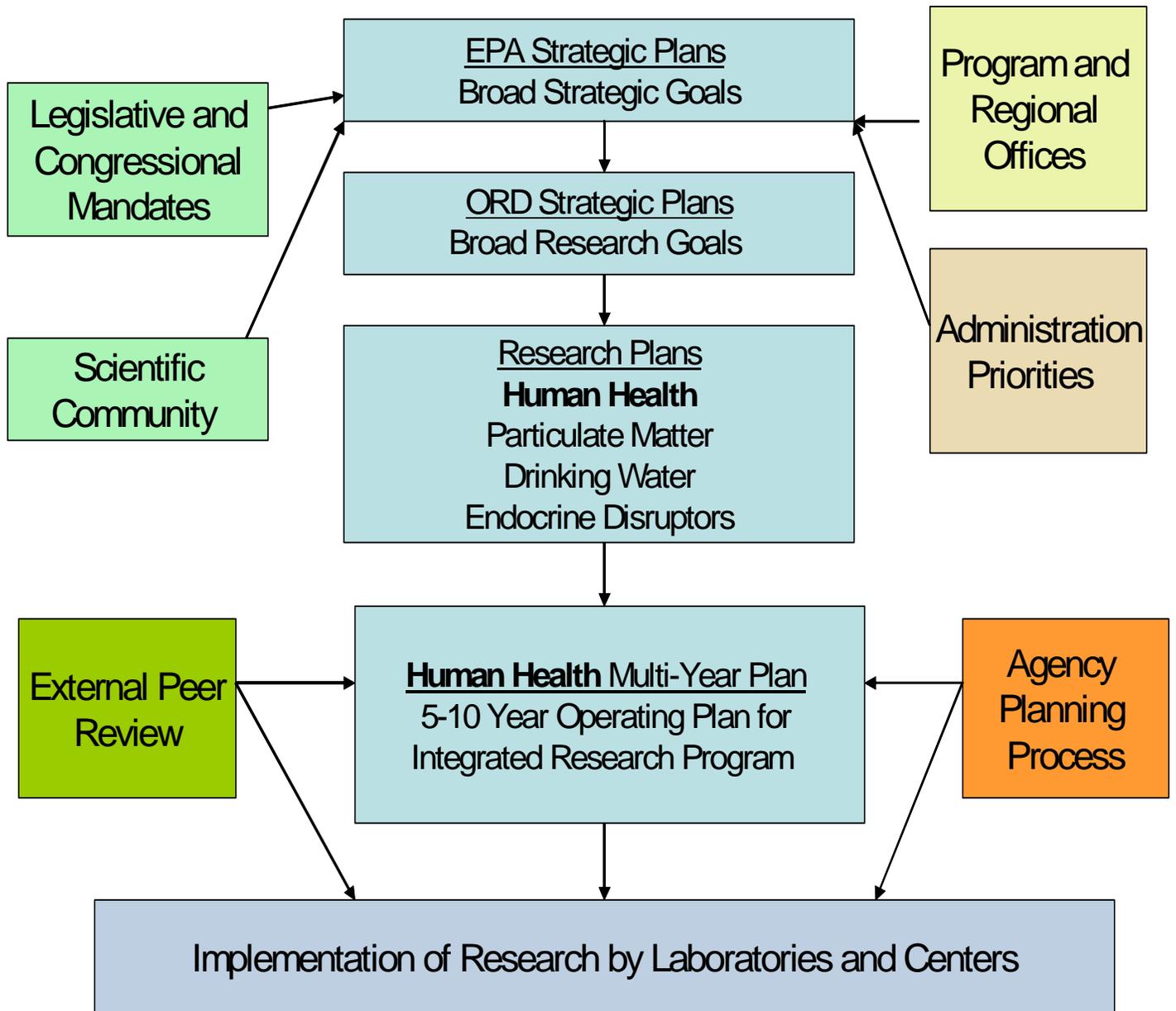
Developing Research Priorities at the EPA

The context by which research priorities are derived and how the EPA coordinates with stakeholders is illustrated in Figure 2. At a global level, EPA responds to environmental and regulatory issues raised by a variety of sources external and internal to the Agency, including legislative and congressional mandates, the scientific community, input from Program and Regional offices, and priorities from the Administration. In response to those concerns, the EPA develops Strategic Plans, which contain broad strategic goals for helping the EPA protect human health and safeguard the natural environment. The current EPA *Strategic Plan* (US EPA, 2003a), for example, consists of five goals, including Clear Air and Global Climate Change, Clean and Safe Water, Land Preservation and Restoration, Healthy Communities and Ecosystems and Compliance and Environmental Stewardship. Research related to human health is described under the goal for Healthy Communities and Ecosystems. The Office of Research and Development (ORD) also develops Strategic Plans that lay the foundation of the development of a research program addressing broad goals articulated in EPA's Strategic Plans (US EPA, 2001a).

To provide the basis for developing a program of research to address the broad strategic and research goals described in the EPA and ORD Strategic Plans, the Agency develops Plans for specific research themes, such as human health, particulate matter, drinking water or endocrine disruptors. The EPA *Human Health Research Strategy* (US 2003b), for example, was written to identify and prioritize research needs to improve the scientific foundation for human health risk assessments. This document provides a conceptual framework for future human health research by ORD for a 5-10 year period and provides the basis for the development of a *Human Health Multi-Year Plan*, which outlines specific research goals and annual measures to be accomplished during that time. The *Human Health Research Strategy* was reviewed by the Agency's Science Advisory Board (SAB) in 2002, while the *Human Health Research Multi-Year Plan* was reviewed by ORD's Executive Council in April 2003. Based on the Multi-Year Plan, each Laboratory and Center develops an implementation plan consistent with their contribution to the ORD Multi-Year Plan. For example, NHEERL developed an implementation plan for program projects following a workshop in 2002, which involved stakeholders from Program and Regional Offices, as well as scientists from other ORD Laboratories and Centers. The resulting plan (US EPA, 2003e) was peer-reviewed by governmental, academic and industrial scientists prior to its implementation.

The following narrative describes in greater detail the major steps illustrated in Figure 2.

Figure 2 Context for Research Priorities at the EPA



Legislative and Congressional Mandates for Human Health Research

There have been numerous legislative and congressional mandates for human health research over the past 25 years. The table below indicates that for major environmental

Legislative and Congressional Mandates	
Legislation or Mandate	Mandate
Resource Conservation and Recovery Act (1976)	Conduct Research Related to Adverse Health Effects
Toxic Substances Control Act (1976)	Develop Screening Techniques for Adverse Health Effects
Clean Air Act (1970)	Conduct Research Related to Cause of Health Effects
Superfund Amendments and Liability Act of the Comprehensive Environmental Response, Compensation and Liability Act (1986)	Conduct Research Related to the Causes of Effects
Congressional Mandate (1993)	Establish Research Program to Better Understand Underlying Basis Underlying Exposure and Effects- Conduct Research to understand Basic Biological Mechanisms , Extrapolation From Animals to Humans
Food Quality Protection Act (1996)	Determine Food Consumption Patterns of Infants and Children Protect Children from Aggregate Risk Determine Mechanisms Associated with Greater Risk in Subpopulations such as Infants and Children
Federal Insecticide, Fungicide and Rodenticide Act (1996)	Determine Food Consumption Patterns of Infants and Children
Safe Water Drinking Act (1996)	Research to Identify Sensitive Groups in General Population at Risk Conduct Research on Mechanisms of Effects New Approaches to Study Mixtures
Children's Health Act (2000)	Authorizes consortium of Federal agencies to conduct research on children's health

legislation between 1976 and 1984, the Agency was broadly instructed to conduct research on the adverse health effects of environmental agents. In response to a congressional mandate in the late 1980s, EPA launched a program to improve the ability of the agency to assess health risks by providing a better understanding of underlying biological, chemical and physical processes that determine exposures and effects (OTA, 1993). The resulting research program was designed to provide critical data on the relationship between exposure, dose, target tissue levels and subsequent health effects. Research to improve understanding of basic biological mechanisms, especially as they relate to extrapolation of high-to-low dose and animals-to-humans was also emphasized.

The accompanying table shows that legislation from 1996 and thereafter identified a number of knowledge gaps, including the need for research on **biological mechanisms** of health effects, the relationship between **exposure** and dose, **aggregate risk**, and susceptible subpopulations, particularly **infants and children**.

Regional and Program Offices

Regional and Program Offices have also provided input into the direction of human health research at the EPA. In 1990, ORD published a report documenting the role of health research in support of EPA’s regulatory programs (US EPA, 1990a). This report noted that the major regulatory programs all had requirements based on health research information, including regulations guiding activities related to air quality, drinking water, water quality, pesticides, toxic substances, hazardous and non-hazardous waste, and superfund. Although health research information was sometimes sufficient, it was often weak to non-existent. Review and discussion of each program’s regulatory mandate and scientific requirements identified several research gaps, including better **predictive tests** based on emerging new technologies, better **extrapolation models, exposure models** and models to predict the effects of **chemical mixtures** (see accompanying table). These priorities were reiterated at an EPA-wide meeting of Program and Regional Offices/ORD scientists and managers at a meeting in 1998 and are consistent with those recently identified by Program and Regional offices in the FY05 Planning Cycle (see table below).

Recommendations from Regional and Program Offices	
ORD Report on Role of Human Health in Support of Regulatory Programs at EPA (US 1990a).	Predictive Tests of Human Toxicity Based on Emerging Technologies Better Extrapolation Models Better Exposure Models Predictive Models of Chemical Mixtures
Office of Prevention, Pesticides and Toxic Substances (OPPTS)	Scientific Basis for Use of Mechanistic Data in Risk Assessment
Office of Children’s Health Protection (OCHP)	Tools and Data for Cumulative Risk Research on Children and Susceptible Subpopulations Collect Data on Indicators of Public Health Outcomes
Office of Air and Radiation (OAR)	Research on Asthma in Children Methods and Models for Cumulative Risk
Office of Environmental Information (OEI)	Research on Use of Mechanistic Data in Risk Assessment; Aggregate Risk ; Research on Children ; Approaches to Evaluate Public Health Outcomes

Office of Water (OW)	Use of Mechanistic Data in Risk Assessment, Aggregate and Cumulative Risk ; Research on Children and Susceptible Subpopulations
Regional Offices	Emerging Technologies for Harmonized Risk Assessment ; Data bases for Exposure ; Research on Susceptible Subpopulations

Administration Priorities

In a 2003 memorandum from John H. Marburger of the Office of Science and Technology Policy and Mitchell E. Daniels of the (OMB) Management and Budget to Heads of Executive Departments and Agencies, the Administration described its priorities for investments in Federal Research and Development programs. The Administration indicated that it will favor investments in programs that, among others, focus on long-term, potentially high-payoff activities that require a Federal presence to attain national goals, including homeland security, environmental quality, economic prosperity, **human health** and well being, and **fundamental discovery**. The memo also indicates that programs that utilize competitive, peer-reviewed processes; promote collaborations among agencies, industry and academia; and strengthen international partnerships that foster advancement of scientific frontiers will be favored. The Human Health Research Program at EPA is consistent with these priorities, as described in the following sections.

The Marburger memo also indicated that the President’s R&D agenda for the FY05 budget will include existing priorities that require significant levels of interagency coordination and planning, especially in the areas of combating terrorism, nanotechnology, networking and information technology, environment and energy, and molecular-level understanding of life processes. With regard to the latter category, EPA’s Human Health Program emphasizes research to provide a fundamental understanding of the key biological, chemical and physical processes that underlie environmental systems that are applicable to a broad range of environmental questions. As discussed later in this Overview, researchers in the Human Health Program interact significantly with scientists from other Federal research laboratories in conducting research on human health issues. Although there is no Interagency Working Group (IWGs) that provides oversight through the National Science and Technology Council, human health research is a cross-cutting issue for the Endocrine Disruptors IWG.

Recommendations from the Scientific Community

Several groups representative of the scientific community have had a significant impact on the direction of human health research at the EPA, including the SAB, an Expert Panel to Advise the Administrator, the National Research Council (NRC), and the Presidential Commission on Risk Assessment and Risk Management (see table on next page for summary).

Recommendations from the Scientific Community	
Group	Recommendation
Science Advisory Board	Agency Must Have Strong Science Base to Reduce Uncertainty in Risk Assessment (US EPA, 1988, 1990b)
Expert Panel on the Role of Science at EPA	Need for Coherent Research Program (US EPA, 1992)
Science Advisory Board	Need to Consider Aggregate Exposures (US EPA, 1995)
National Research Council	Need to Develop Better Data to Understand Potentially Harmful Effects of Pesticides on Infants and Children ; Improved Methods for Estimating Exposures (NRC, 1993)
National Research Council	Need to Improve Risk Assessment Process, including Better Exposure Models , Dosimetry Models, Use of Biological Data in Risk Assessment , Research to Resolve Uncertainties in Risk Assessment (NRC, 1994)
National Research Council	Recommended a Balance between Core and Problem-Driven Research and EPA should Conduct Research to Understand Underlying Biological and Environmental Processes (NRC, 1997)
Presidential Commission on Risk Assessment and Risk Management	Need for Harmonization of Risk Assessment Approaches for Cancer and Non-Cancer Risk Assessments (PRCARM, 1997)

Initially, the SAB was concerned with improving the quality of science used to make regulatory decisions (US EPA, 1988, 1990b). In response to those concerns, the EPA Administrator convened an Expert Panel to evaluate how the Agency can meet the goal of using sound science as the foundation of decision making. Their report (US EPA, 1992) observed that, among other things, the Agency did not have a coherent science agenda and there was a need to develop an operational plan to guide scientific efforts. In 1995, EPA's ORD requested that the NRC advise the Agency on research opportunities and priorities that could help EPA address current and future environmental problems. Their report (NRC, 1997) recommended a balance between **core and problem-driven research**. The NRC also indicated that core research should focus on understanding underlying environmental processes, including biological systems. This recommendation is the basis for supporting a core research program at the EPA and is central to the justification, planning and implementation of the Human Health Research Program (see narrative on Core and Problem-Driven Research in Section VI preceding this Overview and in the discussion on the **Relevance of Core Research** later in this Section).

In the 1990's, four other reports were published from leaders in the scientific community that have helped drive research priorities at EPA. In 1993, the NRC noted the need for better data on exposures of children to pesticides and an understanding of the biological basis for differential sensitivity of infants and children to the health effects of pesticides. In 1994, the NRC indicated that the Agency should conduct research to improve the risk assessment process, including obtaining better exposure data, determining the relationships between external and internal dose, developing biologically based dose-response models and conducting research to reduce uncertainties in risk assessment. The need to consider aggregate exposures was emphasized in the SAB report *Human Exposure Assessment: A Guide to Risk Ranking, Risk Reduction and Research Planning* (US EPA, 1995). The 1997 report by the Presidential Commission on Risk Assessment and Risk Management indicated the need to develop common approaches to assessing risks associated with cancer and non-cancer producing environmental stressors (PCRARM, 1997).

Therefore, recommendations from the scientific community concerning high priority research themes are consistent with those from EPA's Regional and Program Offices, i.e., the use of **mechanistic data** in risk assessment, understanding **basic biological processes**, the need for better **exposure models**, understanding **aggregate risk**, and research to protect **susceptible subpopulations**, especially **children**.

EPA and ORD Strategic Plans

Human health research was specifically mentioned in the 1997 version of EPA's Strategic Plan (US EPA, 1997a), which states that there is a need for research to improve the scientific basis to identify, characterize, assess, and manage environmental exposures that pose the greatest risks to the American public by developing models and methodologies to integrate information about exposures and effects from aggregate exposures.

The 2000 version of the EPA Strategic Plan (US EPA, 2000a) indicates the EPA will develop the knowledge needed to advance environmental and human health protection, from assessing risks and developing regulatory standards to investigating new technologies that make it possible to prevent or significantly reduce pollution. The 2000 Strategic Plan also noted the need to improve the scientific basis to identify, characterize, assess, and manage environmental hazards and exposures that pose the greatest health risks to the American public and methodologies to integrate information about exposures and effects from **aggregate pathways**, especially as it relates to **susceptible subpopulations, such as children and the elderly**.

The 2003 EPA Strategic Plan (US EPA, 2003a) indicated that scientists across the Agency will use the measurement-derived databases, models and protocols developed through the Human Health Research Program to strengthen the scientific foundation for human health risk assessment. In this plan, the focus of the Human Health Research Program will be on a unified risk assessment approach that incorporates **biological models** of toxicity, **aggregate and cumulative** exposures, **susceptible subpopulations**, and evaluations of **public health outcomes** resulting from risk management decisions.

In response to the Expert Panel recommendation (US EPA, 1992) that the EPA needed to develop a systematic approach to planning its research program, ORD developed a Strategic Plan (US EPA 1996a) to institute a more effective, risk-based research program at EPA. The plan was based on input from internal stakeholders (EPA's Regional and Program Offices), as well as the external scientific community. Six high-priority research areas were identified, including drinking water disinfection, particulate matter, endocrine disruptors, research to improve ecosystem risk assessment, pollution prevention and new technologies, and **research to improve human risk assessment**. High priority areas related to human health research included mechanistic and toxicokinetic research to improve exposure and dose-response steps in the risk assessment process and determining the basis for individual variability.

The priorities indicated in the 1996 ORD Strategy were reiterated in an update to ORD's Strategic Plan (US EPA, 1997b). In 2001, ORD revised its Strategic Plan and identified several high priority research areas (US EPA, 2001a) and included recommendations for the use of **mechanistic information to understanding toxicities and susceptibilities**; determining the biological basis for adverse effects in **children**, especially **asthma**; developing predictive, models for interactive effects of **chemical mixtures**; improved **exposure models** to assess **aggregate and cumulative toxicity**; approaches to **harmonize cancer and non-cancer risk assessments**; and research to **evaluate consequences of environmental risk management decisions**.

Human Health Research Strategy

In 1998, EPA sponsored a meeting of risk assessors, scientists, and managers from Regional and Program Offices with ORD scientists and managers to identify cross-cutting issues of high priority that would form the basis of the Human Health Research Program at EPA. Based on input from that meeting, as well as legislative mandates and recommendations from the scientific community, it was decided that the future ORD human health research would focus on two strategic directions:

- Research to Improve the Scientific Foundation of Human Health Risk Assessment and
- Research to Enable Evaluation of Public Health Outcomes.

It was also decided that Research to Improve Human Health Risk Assessment would emphasize three themes:

- Harmonizing Approaches to Cancer and Non-Cancer Risk Assessment
- Assessing Aggregate and Cumulative Risk
- Evaluating Risks for Susceptible and Highly-Exposed Subpopulations.

ORD subsequently developed the *Human Health Research Strategy* to provide a conceptual framework for future human health research by ORD (US EPA, 2003b). The themes indicated above are consistent with priorities identified by various legislative and congressional mandates, recommendations from the scientific community, administrative priorities and input

from the Regional and Program Offices.

As mentioned previously, the *Human Health Research Strategy* provides a conceptual framework for future human health research by ORD and focuses on developing a multi-disciplinary, integrated program to improve linkages between exposure, dose, effect and risk assessment methods. This document provides the scientific basis for a research program on 1) **harmonizing risk assessment approaches**, 2) predicting **aggregate and cumulative risk**, 3) protecting **susceptible subpopulations**, and 4) research to **evaluate public health outcomes from risk management decisions**. These themes provide the basis for the Long-Term Goals developed for ORD's *Human Health Research Multi-Year Plan*. A SAB panel provided an external review of the *Human Health Research Strategy* in 2002.

Human Health Multi-Year Plan

Based on the strategic direction provided by the *Human Health Research Strategy* (2003b), ORD developed the *Human Health Research Multi-Year Plan* (US EPA, 2003c). As discussed in the Section VI preceding this Overview, the purpose of multi-year plans is to specify Long-Term Goals and provide Annual Performance Goals (APGs) and Annual Performance Measures (APMs) for a planning window of approximately 5-10 years. Multi-Year Plans are intended to be living documents and are to be updated as needed to reflect the current state of the science, resource availability and EPA priorities. There are plans to revise the *Human Health Multi-Year Plan* following the review of the Human Health Research Program by the Board of Scientific Counselors (see the Section on **Performance** for additional discussion of the Multi-Year Plan).

The Agency Planning Process

Programmatic priorities for research are determined through the annual planning process and the Research Coordination Teams (RCTs). RCTs are composed of representatives from ORD's Laboratories and Centers and EPA's Program and Regional Offices. Each year, these teams prioritize research to be accomplished intramurally in ORD laboratories and extramurally through the extramural program (Science to Achieve Results, STAR). The subsequent research plan is based on priorities identified in the EPA and ORD strategic plans, as well as specific program needs identified at the meeting of the RCTs. A number of criteria related to relevance, quality, and past performance are used by the RCTs to determine priorities for future research. Of particular importance is the ability of each component of the program to meet annual performance goals and measures articulated in the Multi-Year Plans and the on-going research needs of the Program and Regional Offices. During the last five years, the Agency has identified a number of research initiatives through the planning process that serve as drivers for the current research program on human health. These initiatives include the need for research on Children's Health Issues, which has led to EPA's participation in the National Children's Study; research on Asthma; the National Agenda on Aging; research on Cumulative Risk; and the Accountability Initiative. The latter initiative is linked to the need to evaluate the public health consequences of risk management decision.

Relevance of Core Research

EPA's Human Health Research Program emphasizes research to increase an understanding of the fundamental processes that underlie environmentally related health problems; the development of broadly applicable research and risk assessment tools and approaches; and the design, implementation and maintenance of appropriate measures of environmental exposure (NRC, 1997)(see discussion on Core versus Problem-Driven research in the Section VI preceding this Overview). The methods, models and data generated in the Human Health Research Program are used to inform scientific uncertainties in several problem-driven areas, which have their own Multi-Year Plans. The linkage between the four Long-Term Goals in the Human Health Research Program to Long-Term Goals in Multi-Year Plans for Particulate Matter, Air Toxics, Drinking Water, Safe Products/Safe Pesticides, and Endocrine Disruptors is illustrated in Figure 3.

For example, mechanistic research has provided significant information concerning the biological plausibility for epidemiological data on air pollutants such as Particulate Matter (PM) and is playing an important role in the reassessment of the human health risk of arsenic. The Food Quality Protection Act specified that the EPA shall consider the risk associated with cumulative exposures of chemicals based on their mode of action. In order to develop predictive models of chemical interaction, fundamental research has to be conducted to identify the biological mode or mechanism of action to be used in the cumulative risk assessment of organophosphate pesticides. A component of EPA's human health research program also provides mechanistic information to identify the appropriate dose-response models for risk assessment of pesticides and for the development of predictive models for prioritizing pesticides and toxic substances based on mechanistic information. Mechanistic information is also used to provide the basis for interpreting studies suggesting the possibility of novel or newly discovered hazards, the biological basis for methods to screen endocrine disrupting chemicals, and providing the scientific basis for interpreting effects of endocrine disruptors on human health. Mechanistic research also informs research conducted within the Human Health Program. Mechanistic data on pesticides and other chemicals, for example, is necessary for the development of methods and models to characterize aggregate and cumulative risk and for understanding life-stage appropriate responses in research to identify susceptible subpopulations.

Research on aggregate/cumulative research provides the basis for developing predictive

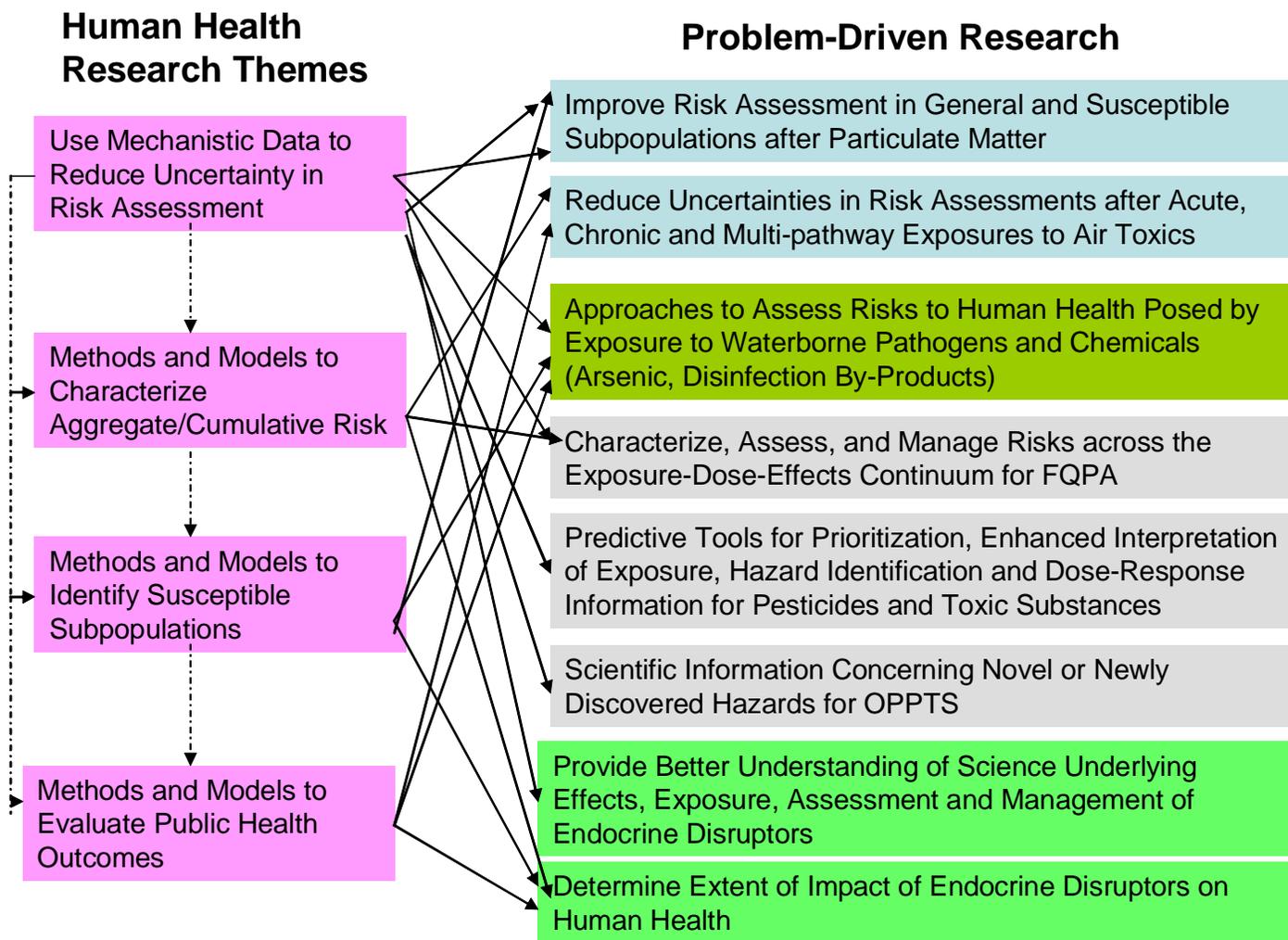


Figure 3 Relationship between Human Health and Problem-Driven Research

models of aggregate and cumulative toxicity of acute and chronic effects of air pollutants, approaches for the assessment of aggregate toxicity of pesticides as required by the Food Quality Protection Act, and the assessment of the aggregate or cumulative effects of endocrine-disrupting chemicals. Research on methods and models to identify susceptible subpopulations is important to determine the basis for the differential sensitivity of subpopulations to air pollutants and waterborne pathogens and chemicals, as well as determining if there are uniquely vulnerable populations of people sensitive to the effects of endocrine disruptors. Research on methods and models to evaluate public health outcomes will provide outcome-based indicators to assess improvement in environmental quality (e.g., air, water) and impact of regulatory decisions concerning endocrine disruptors.

Although not shown in Figure 3, there are also significant interactions between the Human Health Research Program and the newly emerging Computational Toxicology program.

Mechanistic studies have direct implications for the development of computational approaches for the prioritization of chemicals such as pesticides for screening and testing. Fundamental knowledge of the key biological events associated with the ultimate expression of toxicity provides the basis for developing biologically based models and systems biological approaches that can be studied using computational methods.

Coordination with Other Stakeholders

EPA's human health risk assessment research program is unique among Federal agencies with research programs in that it sustains an intramural multi-disciplinary workforce with expertise in all the elements of health risk assessment and risk management, in addition to a complementary extramural grants research program. EPA's research program also includes a balance of core and problem-driven research efforts. Many Federal research organizations such as the National Institutes of Health focus primarily on core or basic research questions. ORD scientists and engineers conduct research to: (1) answer questions about the link between sources, exposures, dose, response, and risk; (2) develop and disseminate measurement data, models, and protocols to reduce scientific uncertainty in health risk assessment; and (3) provide data and tools for specific exposure and risk assessment needs that arise from the Agency's Regions and Program Offices.

Because of its unique position as a research organization, the EPA Human Health Research Program can capitalize on many opportunities for collaboration with other research organizations and disciplines. For example, the National Institute of Environmental Health Sciences (NIEHS) achieves its mission through multi-disciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. The Agency has collaborated with NIEHS in establishing Centers for Children's Environmental Health and Disease Prevention to define the environmental influences on asthma and other respiratory diseases, childhood learning, and growth and development. NIEHS and the National Institute of Allergy and Infectious Diseases (NIAID) have collaborated with the Agency in conducting the Inner-City Asthma Study. This is a prevention trial to develop an intervention strategy to reduce asthma morbidity in inner-city children and adolescents. The National Allergen Study, being conducted by NIEHS in collaboration with the Department of Housing and Urban Development (HUD), examines the relationship between allergens and lead and how allergen exposures differ as a function of geographic region, socioeconomic status, housing type, and ethnicity. NIEHS and the National Toxicology Program (NTP) develop new technologies for high-throughput toxicity testing, and these agencies are responsible for one-third of all toxicity testing performed worldwide. Long term collaborative efforts with NTP, particularly in the areas of carcinogenesis, reproductive/developmental toxicity, and neurotoxicity, are well established. EPA and the NTP have also developed an Inter-Agency Agreement in which NTP generates two-year bioassay data on high priority chemicals and EPA utilizes animals and tissues for mechanistic studies. NIEHS has also established the National Center for Toxicogenomics (NCT) aims to coordinate an international research effort to develop the field of toxicogenomics. The NCT will provide a unified strategy

and a public database and develop the informatics infrastructure to promote the development of the field of toxicogenomics. NIEHS will pay special attention to toxicogenomics as applied to the prevention of environmentally-related diseases. Steps have been taken to link data collected by EPA's Computational Toxicology Program to NCT at NIEHS.

The Centers for Disease Control and Prevention (CDC), through the National Center for Environmental Health (NCEH), studies health problems associated with human exposure to lead, radiation, air pollution, and other toxicants, as well as to hazards resulting from technologic or natural disasters. These are mainly surveillance and epidemiology studies. NCEH is particularly interested in studies that benefit children, the elderly, and persons with disabilities. ORD collaborates with CDC in many of its large-scale epidemiological and exposure research programs, which include National Human Exposure Assessment Survey (NHEXAS) and studies along the US/Mexico Border under the North American Free Trade Agreement (NAFTA). The National Center for Health Statistics (NCHS) of CDC is conducting the National Health and Nutrition Examination Survey (NHANES), which is a national population-based survey and includes data on potentially sensitive subpopulations such as children and the elderly. The Agency is participating in this survey with NCHS to collect information on children's exposure to pesticides and other environmental contaminants. In 2001, CDC published the *National Report on Human Exposure to Environmental Chemicals*, which provided an ongoing assessment of the US population's exposure to environmental chemicals using biomonitoring. This report contains blood and urinary values on 27 environmental chemicals. CDC recently released a second report in January 2003, which presents biomonitoring exposure data for 116 environmental chemicals for the US population divided into age, gender, and race/ethnicity groups. There is also close relationship of our research EPA's research on public health outcomes with CDC's National Public Health Tracking Program.

The National Institute of Child Health and Human Development (NICHD) supports laboratory, clinical, and epidemiological research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children and adults. ORD is collaborating with NICHD, CDC, and other Federal agencies in the design and implementation of a National Children's Study of 100,000 children, who will be enrolled during the mother's pregnancy and followed throughout childhood and adolescence. This study was mandated in the Children's Health Act of 2000, to study environmental influences on children's health and development.

The National Center for Toxicological Research (NCTR) supports fundamental research on the effects of chemicals regulated by the Food and Drug Administration. Although some of the models used by NCTR may be similar to those used by the Agency, the chemicals and regulatory context vary significantly. Historically, NCTR has been a leader in developing models and principles for risk assessment, which has led to collaborations between the Human Health Researchers at the Agency and NCTR scientists.

The Agency for Toxic Substances and Disease Registry (ATSDR) has the mission to serve the public by using the best science, taking responsive public health actions, and providing trusted

health information to prevent harmful exposures and diseases related to toxic substances. ATSDR's applied research programs provide the scientific basis for taking appropriate actions and provide new information on toxic substances and health effects. With this new information, ATSDR can help communities determine if they have been or are exposed, if the exposure will cause them any harm, and if they can do anything to minimize their exposures and health risks. EPA researchers interact with scientists from ATSDR to identify high priority research needs.

At least two non-governmental organizations conduct collaborative research with ORD. The American Chemistry Council (ACC) supports research examining risks associated with exposures to pesticides. The Health Effects Institute (HEI) supports research programs designed to evaluate exposures to particulate matter (PM) and developing strategies for assessing public health outcomes. There are also numerous scientist-to-scientist collaborations with various academic (e.g., University of North Carolina; Duke University Medical School, North Carolina State University; North Carolina Central University), industrial or commercial (e.g., Affymetrix, US Trizole Task Force, Genelogic, CIIT), and military (US Army; US Air Force) laboratories.

QUALITY

This section on quality focuses on how outputs and outcomes from the Program are externally reviewed for scientific merit. It also attempts to illustrate how resources, including FTEs, are allocated to high priority themes that have undergone peer-review and prioritized through the Agency planning process. How extramural resources are allocated on the basis of a competitively based process is also addressed.

Peer-Review

Outputs from the Human Health Research Program are evaluated for quality by a peer-review process. Specifically, ORD follows the Agency's guidelines for conducting peer review of research products, as outlined in, *EPA Science Policy Council Handbook on Peer Review, 2nd Edition* (US EPA, 2000d). The Handbook reflects the peer review policy statement issued by the Administrator in 1994: "Major scientifically and technically based work products related to Agency decisions normally should be peer reviewed. Agency managers within Headquarters, Regions, laboratories, and field components determine and are accountable for the decision whether to employ peer review in particular instances and, if so, its character, scope, and timing." Additionally, ORD tracks peer review activities for the Agency through the EPA Science Inventory Database, and it is required to file an annual report to the Science Policy Council on the state of peer review activities around the Agency and compliance with peer review policy.

Research Divisions in ORD Laboratories and Centers (e.g., NHEERL Divisions- Human Studies, Reproductive Toxicology, Neurotoxicology, Environmental Carcinogenesis and Experimental Toxicology) are reviewed by an external review panel approximately every 3-4

Human Health Research 1999 – 2005

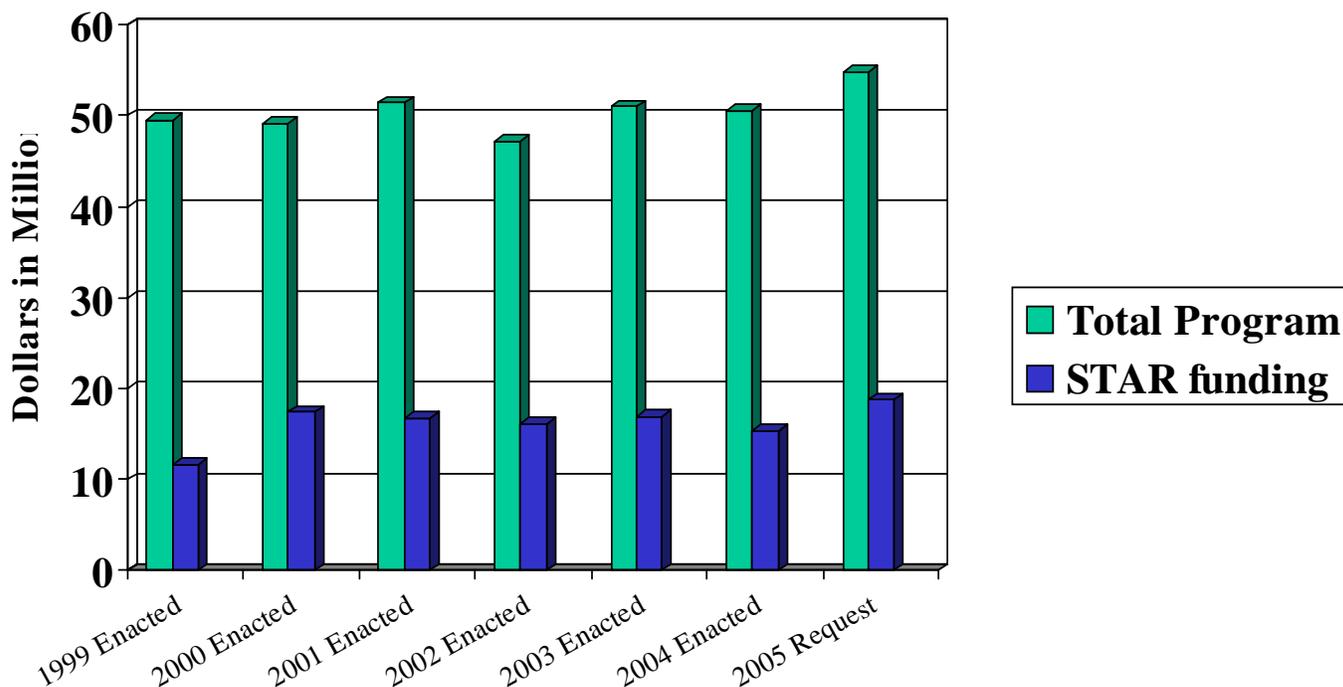
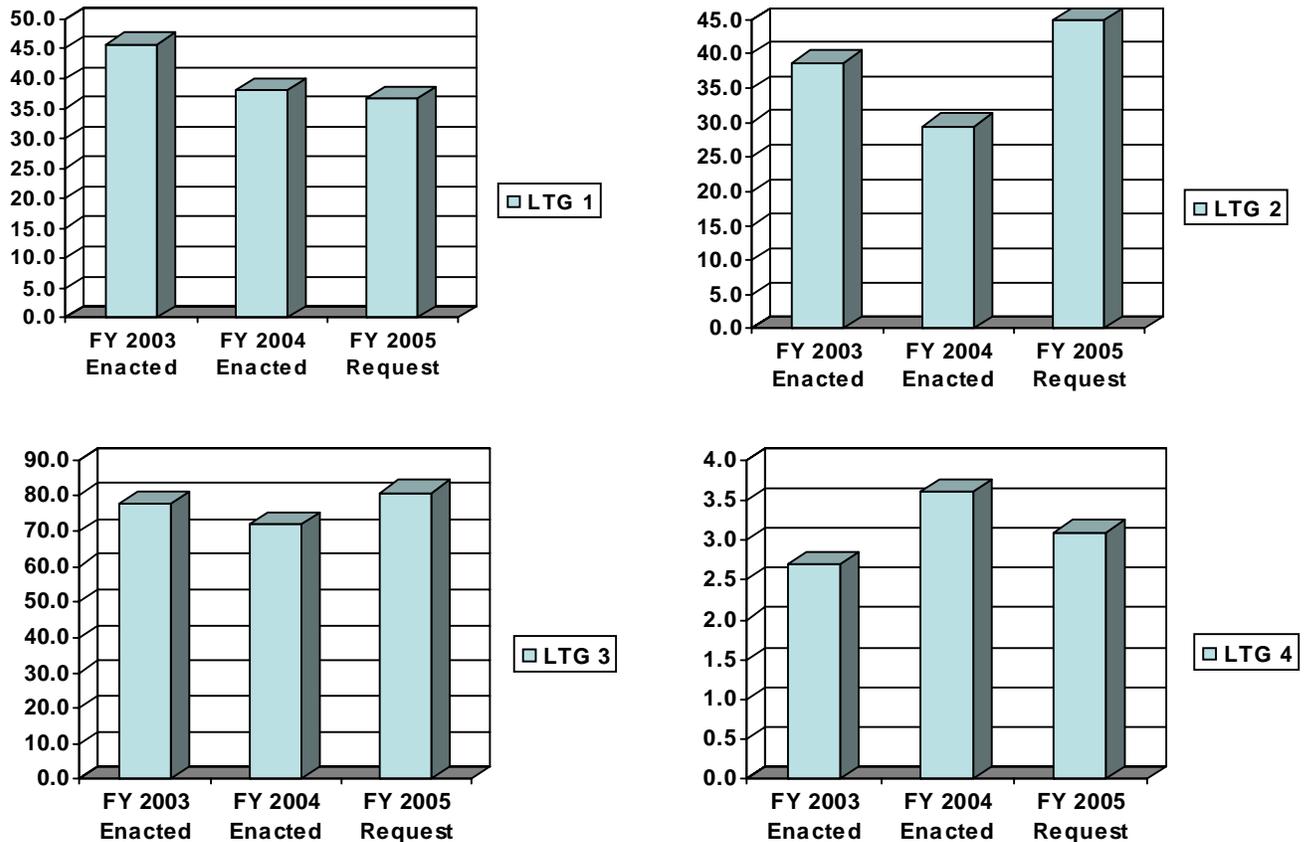


Figure 4. Funding levels reflect total program including payroll, travel, and operating expenses. STAR: Science to Achieve Results extramural grants

years. Reports from these reviews are provided to the Assistant Administrator for Research and are used by Laboratory management to determine the relevance and quality of the research program. Peer review of research in other Laboratories occurs at the Program level (i.e., Human Exposure Research Program, NERL). As discussed previously, some Laboratories within EPA/ORD have also developed externally peer-reviewed implementation plans (US EPA 2003e) documenting how they will develop the strategic goal in the *Human Health Research Strategy* at the project level.

All human health data used from regulatory purposes undergo external review, while methods, models and data prepared for publication in journals are externally reviewed. The quality of many ORD publications has been recognized by various scientific societies and through

Figure 5 Allocation of FTEs by LTG



the Science and Technology Award program sponsored by the Agency's SAB (see Table 5).

Research Strategies such as the *Human Health Research Strategy* undergo external peer review prior to implementation. EPA has recently implemented a policy to peer-review major research programs by the Board of Scientific Counselors. Research Programs are also evaluated by the OMB using their Performance Assessment Rating Tool (PART). Plans have been made by OMB to review the Human Health Program in April, 2005.

Allocation of Resources

Each year, Congress provides a budget for EPA, from which it develops a business plan for ORD. Each Laboratory and Center within ORD subsequently receives a budget from ORD.

Human Health Research

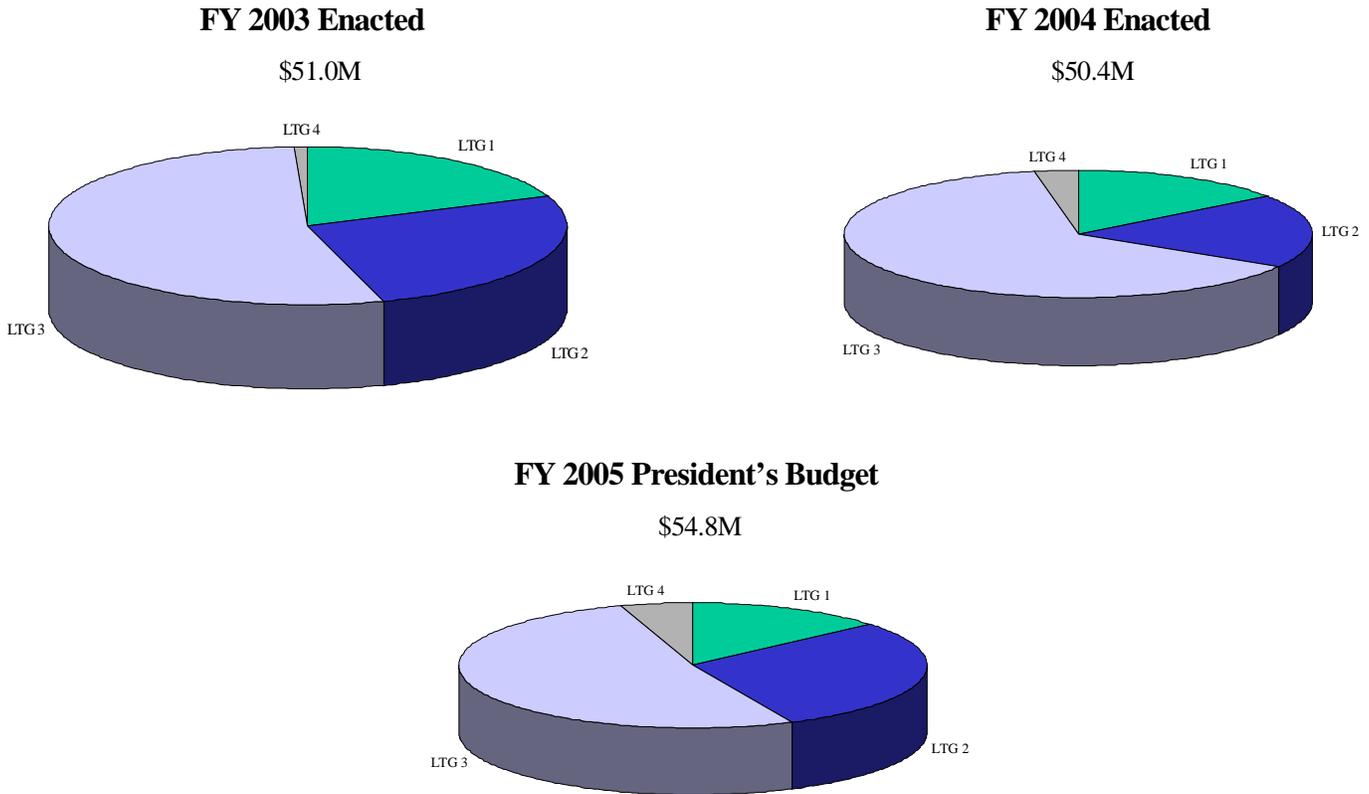


Figure 6 Allocation of Resources by Long-Term Goal

When approved by the President and Congress, the enacted budget serves as the blueprint for all EPA activities. Figure 4 summarizes the total resources allocated for ORD’s research program on human health for the last five years. Resources allocated to the extramural grants program (STAR) represent a proportion of the total in Figure 4. As can be seen, ORD’s resources for human health research have generally remained relatively fixed over the last five years. The apparent increase in resources in the FY05 budget request represent a realignment of approximately 8 FTEs from the Safe Pesticides/Safe Products Program starting in FY05. Figure 5 summarizes the total number of scientific and administrative FTEs allocated to human health by Long-Term Goal for the last 3 years, while Figure 6 shows the total resources allocated to each Long-Term Goal for the last 3 years. These figures indicate that FTEs and resources were allocated to the high priority research areas identified through the Agency’s planning process

[i.e., use of mechanistic data in risk assessment (LTG1), aggregate/cumulative risk (LTG2), susceptible subpopulations (LTG3), and evaluation of public health outcomes (LTG4)].

Some research in ORD is conducted in collaboration with Federal and other research laboratories. Additional resources to support research obtained through Interagency Agreements and Cooperative Research and Development Agreements (CRADAS) are documented in Table 1. Although the research conducted by collaborators is not evaluated through the Agency planning process, it is a policy that such extramural research projects must be linked to work that has received a high priority by the Agency's planning process. Products from collaborative research undergo external peer-review prior to publication and are subject to periodic external review of research programs at the Divisional level.

With regard to the extramural research program, the National Center for Environmental Research (NCER) manages a competitive, rigorously peer-reviewed program of research grants. Proposals are solicited from scientists at universities and non-profit institutions in response to targeted Requests for Applications (RFAs) issued by NCER. Examples of RFAs relevant to human health that have been sponsored by NCER include Children's Exposure to Pesticides (1996), Exploratory Research-Human Health (1996, 1998), Human Health Risk Assessment (1997), Center's for Children's Environmental Health (1998, 2001), Inter-individual Variation in Human Susceptibility (1998), Children's Vulnerability to Toxic Substances (1999, 2001), and Mechanistic Based Cancer Risk Assessment Methods (1999). Grants support both individual investigator research and multi-disciplinary research grants and centers. From 1999 to 2002, approximately 12-18 applications were funded annually (Table 2). Table 3 summarizes the extramural resources allocated by year and Long-Term Goal. Approximately 60% of the extramural grant funds for human health has been allocated to the Children's Centers.

Topics for grant solicitations are based on interactions between NCER staff and Research Coordination Teams during the annual planning process. Research topics selected for extramural support are intended to complement on-going intramural research and the regulatory needs of the Agency. A series of criteria are used to decide whether research would be best accomplished internally at ORD or externally through grants, cooperative agreements, or contracts. These criteria include the intramural capabilities to conduct research in a given area, the urgency of the research output, the complementary nature of the proposed extramural effort relative to on-going intramural research, and the potential interest and capabilities of scientists from academic and other research organizations.

Other criteria for consideration of RFA themes involve programmatic questions such as whether the research addresses a priority scientific needs of the EPA by improving its ability to assess or manage environmental risk. Another consideration is the possibility that there are other Federal partners interested in collaborating in similar areas. If EPA and other Federal Agencies have overlapping interests, a joint solicitation may be planned. It is expected that partnering with other Agencies will allow the Agency to leverage its own resources significantly.

The foundation of the STAR program is the peer-review process. Because all grant applications are subjected to a rigorous, independent peer review, only the most scientifically meritorious research is funded by the program. Methods, models and data generated by STAR grantees are reviewed for quality by the scientific community by peer-reviewed journals.

PERFORMANCE

Performance refers to how well the Program is making progress in answering priority research questions, informing environmental decisions, and demonstrating short-term outcomes. This section attempts to illustrate how the research in the Program is designed to address key research questions. How outputs are tracked using a multi-year plan having annual performance measures and milestones is also addressed. Finally, the section contains information concerning progress towards meeting the Long-Term Goals by providing outputs that are used by stakeholders in support of the mission of the Agency to protect human health and the environment.

The Human Health Research Multi-Year Plan

The primary mechanism used by EPA to measure performance in response to the Government Performance and Results Act is the Multi-Year Plan. Multi-Year Plans allow the Agency to plan the direction of the program, provide information to aid in and support decisions during budget formulation, focus on key research questions and scientific results, and demonstrate how ORD's research programs contribute to Agency outcomes and strategic goals. Multi-Year Plans consist of Long-Term Goals, which describe the broad strategic outcome research aggregated over several years. The Long-Term Goals for human health research are linked to the strategic goals articulated in the *Human Health Research Strategy* (US EPA, 2003b). Annual Performance Goals describe major milestones occurring over a time frame necessary to achieve the Long-Term Goals. Annual Performance Goals usually aggregate information from research from more than one Laboratory or Center. Annual Performance Measures track products or deliverables in support of the Annual Performance Goals and are generally outputs from individual Laboratories or Centers.

The *Human Health Research Multi-Year Plan* was reviewed by the ORD Executive Council in 2003. At that time, it included 4 Long-Term Goals, 37 Annual Performance Goals and 136 Annual Performance Measures. The Multi-Year Plan has been revised yearly to reflect new directions and new Annual Performance Measures, especially in the out-years, FY05-08. Currently, ORD's Integrated Resource Management System that tracks performance measures indicates that there are 29 Annual Performance Goals and 250 Annual Performance Measures on record for FY00 through FY08. Of the 110 Annual Performance Measures listed for the FY00 to FY04 reporting period, only 5 were not met. The primary reason for not meeting these measures was that key personnel left the Agency for another position.

As mentioned previously, Multi-Year Plans are intended to be living documents and the

next revision of the *Human Health Multi-Year Plan* will reflect completion of work and inclusion of new priorities. Recommendations stemming from the programmatic review by the Board of Scientific Counselors will play a significant role in the next revision of the *Human Health Multi-Year Plan*.

In preparing for the review of the Human Health Research Program, ORD held a number of meetings to develop definitions of the Long-Term Goals to make them more outcome-oriented (see Figure 1 Conceptual Framework for Human Health Research for explanation of outputs and outcomes). In addition, Key Research Questions were also formulated as a means of providing a scientific framework for on-going and future research, as well as developing performance measures for future program evaluation by OMB. EPA is requesting that the BOSCO determine if the Human Health Research Program is making progress toward meeting the Long-Term Goals by addressing the Key Research Questions (see below). The wiring diagrams used to illustrate Annual Performance Goals contained in the 2003 *Human Health Multi-Year Plan* are still relevant tracking devices and will be retained in the next revision of the Multi-Year Plan.

Revised working definitions of the Human Health Research Program Long-Term Goals and Key Research Questions are as follows:

Long-Term Goal 1 is Use of Mechanistic Information in Risk Assessment (formerly described in the *Human Health Multi-Year Plan* as research to improve harmonization of cancer and non-cancer risk assessments). The Goal of this research is that risk assessors and risk managers use ORD's methods and models to decrease uncertainty in risk assessment, which in turn reduces risk of humans exposed to environmental stress. The Key Research Questions for Long-Term Goal 1 are:

- What modes/mechanisms of action (MOA) are important for understanding the impact of environmental stressors on human health?
- What are the attributes (e.g., shape of the dose-response, species specificity) of the MOA that impact risk assessment?
- How do we measure, model and/or predict the key attributes of the MOA that could impact risk assessment?
- How do we incorporate mechanistic tools into risk assessment?

Long-Term Goal 2 is Aggregate/Cumulative Risk Assessment. The Goal of this research is that risk assessors and risk managers use ORD's methods and models to characterize aggregate and cumulative risk, which in turn reduces risks resulting from human exposure to multiple environmental stressors. The Key Research Questions for Long-Term Goal 2 are:

- What are people's real world aggregate exposures?
- What contributes to aggregate exposures?
- How do we predict cumulative risk from aggregate exposures?
- How do we mitigate aggregate/cumulative risk?

Long-Term Goal 3 is Protect Susceptible Subpopulations. The Goal of this Long-Term Goal is that risk assessors and risk managers use ORD's methods and models to identify susceptible subpopulations, which in turn reduces risk of susceptible human exposed to environmental stressors. The Key Research Questions for Long-Term Goal 3 are:

- Which subpopulations have differential risk to environmental stressors?
- What is the basis for differential risk?
- What is the risk to each subpopulation?
- How can differential risk be mitigated?

Long-Term Goal 4 is Evaluate Public Health Outcomes. The Goal of this research is that risk assessors and risk managers use ORD's methods and models to evaluate public health outcomes, which in turn determines the effectiveness of agency regulatory and risk management decisions. The Key Research Questions for Long-Term Goal 4 are:

- What public health outcomes need to be examined to evaluate Agency regulatory decisions?
- What approaches/tools are needed to evaluate (and attribute) changes in public health outcomes to Agency actions?
- Did Agency actions have an impact on public health outcomes?

Progress To Meet the Long-Term Goals

Progress toward the Long-Term Goals is determined by how much risk assessors and risk managers use ORD's methods and models to reduce uncertainty in risk assessment, characterize aggregate and cumulative risk, and identify susceptible subpopulations for risk assessment. assessors and risk managers can use ORD's products in two ways (see text box). First, the methods, models or data generated by ORD can be used directly to support a risk assessment or risk management decision. Second, clients use the technical and scientific expertise of ORD researchers to help them support the mission of the Agency to protect human health and the environment. Specific examples of contributions of ORD scientists to risk assessors and decision-makers are summarized in Table 4. The following narrative contains examples of several major contributions of the Human Health Research Program over the last 5 years.

Methods, Models and Data Used to Support Risk Assessment

Arsenic. The Arsenic in Drinking Water Rule is currently being implemented in the Office of Water. The rule lowered the Maximum Contaminant Level (MCL) for inorganic arsenic from 50 ppb 10 ppb. This level was established following the recommendations of the a report from the National Academy (NRC, 1999) which suggested using a linear approach due lack of sufficient data to support any other approach. A subsequent NAS report (NRC 2001) recommended a linear modeling approach that is more stringent than earlier report and may result in a greater estimated risk. Implementation of the Arsenic Rule is scheduled to be completed by January 2006. In addition, the Office of Pesticide Programs (OPP) completed a cancellation

action for residential use of chromated copper arsenate (CCA)-treated wood effective December 2003, and issued a preliminary risk assessment. Since that time, OPP has been working with a cross-Agency technical workgroup which includes human health scientists to resolve outstanding issues revolving about the implementation of the 2001 ruling.

PROGRESS TO MEET THE LONG-TERM GOALS

Methods, Models or Data Used to Support Risk Assessment

Expertise to Support Mission of the Agency

- Guidance and Risk Assessment Documents
- Intra- and Interagency Technical Panels
- Consultation on Scientific Matters
- Training
- Grant Reviews

ORD scientists have been instrumental in contributing to the discussions on arsenic as it relates to establishing a scientifically defensible risk assessment. The body of ORD research and resulting expertise on arsenic metabolism, pharmacokinetics, mechanism of action, and dose-response modeling been utilized by the Program Offices involved in the risk assessment of arsenic. ORD's own research and the interpretation of their data by others has resulted in the approach to treat organic forms of arsenic differently, using human epidemiological data for inorganic arsenic to support both the drinking water and CCA analyses, and animal data as the model for dimethyl arsenate potency estimation via a non-linear mechanism. ORD scientists are currently contributing to the discussion concerning the most appropriate approach for estimating potency for organic arsenic is to focus on elucidating the mode of action, define the key event, and the appropriate approach for estimating potency.

Asthma Research. Data obtained from the asthma research program have had an impact on a number of key regulatory programs. Data from the ORD asthma research program, for example, have been included in Air Quality Criteria Documents for ozone and PM and the health assessment for diesel emissions. In research focusing on environmental factors associated with children's susceptibility to the development of asthma, increased allergic sensitization to cockroaches and mice was observed in asthmatic children from inner city environments. The results of this research are being used by a variety of community partners, including advocacy groups, local health departments, and housing authorities to extend the scope of intervention projects and decision-makers at the local and state levels. For example, a cockroach-control program called "Integrated Pest Management" was designed and successfully implemented in East Harlem, New York. In addition, the Children's Environmental Health Research Centers have developed and implemented effective intervention projects of molds and cockroaches.

The effects of airborne biological particles or bioaerosols, originating from mold, bacteria, dust-mites and cockroach contaminants can impact the onset and exacerbation of asthma. These bioaerosols have been investigated by a team of ORD researchers who have shown that reducing

bioaerosol exposure by risk management alternatives can improve the respiratory health of sensitive subpopulations such as asthmatics. Identification of a potential biomarker indicator of exposure has also been developed. Based on ORD research, General Services Administration now include ultraviolet air treatment in controlling bioaerosols in Federal buildings. OPPTS is also using recommendations provided by ORD in registration of new anti-microbial agents. The Indoor Environments Division of OAR has also worked with ORD to develop a number of guidance documents on mold, while the Department of Housing and Urban Development (HUD) has developed specifications for cost-effective home remediation. A number of companies have also developed mold identification technology for identification of specific mold allergens.

ORD researchers have also collaborated with scientists and managers from OAR/Office of Air Quality Planning Standards (OAQPS) in developing public health material concerning ambient air pollution. Human health researchers have also provided information and collaborated with OAR in developing materials for outreach campaigns concerning air pollution.

The Human Health Research Program has responded to needs expressed by OPPTS, the Office of Radiation and Indoor Air (ORIA) and Regional Offices to implement the Agency's Buy Clean Initiative, which is an effort to promote purchase and use of materials and supplies that are environmentally safe for indoor usage. In response to this initiative, research was done to identify hazardous air pollutants emanating from hard-surface cleaners frequently used in class rooms and office work sites. ORD scientists then developed a model to predict chemical emissions from various water-based cleaners in the presence of surfactants. Such information could be used in a screening context to reduce exposures to hazardous indoor chemicals. This research is particularly relevant to local decision-makers in considering the potential risk to children's health since volatile organic chemicals emitted from hard-surface cleaners appear to be involved in eliciting asthma in some children.

Atrazine. Research from ORD was instrumental in assessing the cancer risk of atrazine by showing that atrazine had an endocrine mode of action responsible for the production of mammary gland tumors. This observation was critical to OPPTS's atrazine risk assessment document and the SAB review of atrazine. Mode of action studies were instrumental in identifying other potentially adverse reproductive effects, especially in the developing animal. Research from ORD played a role in applying a 3X Safety Factor to protect children's health, setting the point of departure, and establishing the acute LOAEL for atrazine. Data from other research on related chloroatrazines and common metabolites are being incorporated into the cumulative risk assessment for atrazine.

Dioxin. Human health researchers examined a series of dose metrics for use in species extrapolation for 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds. Based on this research, it was proposed that steady-state body burdens be used as the metric for cross-species extrapolation for dioxin and related compounds. The use of body burden as a dose metric reduces or replaces the uncertainty factor of 10 for animal-to-human extrapolation. EPA and other public health agencies, including the World Health Organization, Ministry of the Environment of Japan and the FAO/WHO Expert Committee on Food Additives and Contaminants, have applied body

burden as their cross-species dose metric for dioxins. It is likely that this approach will be extended to the risk assessment of other persistent bioaccumulative toxicants. ORD research also helped develop the use of toxic equivalency factor methodology for cumulative risk assessment of dioxin and related compounds and the use of linear extrapolation models for both cancer and non-cancer endpoints.

Chromated Copper Arsenate (CCA). In 2002, EPA announced a voluntary decision by industry to move away from using CCA to treat wood used in residential settings. Related to this decision was the release of the probabilistic risk assessment on CCA that evaluates potential exposure and risk to children from CCA-treated wood. The probabilistic assessment analyzes a wide range of data and provides a more scientifically robust analysis. This was the first time that EPA had used a probabilistic approach for a non-food use assessment. Among the new approaches included in the risk assessment was the probabilistic Stochastic Human Exposure and Dose Simulation (SHEDS) Model for Wood which simulated exposures to children from contact with wood preservative-treated playsets and decks. Application of the SHEDS-Wood model was reviewed by a FIFRA Scientific Advisory Panel Meeting in August 2002.

Chlorpyrifos. ORD researchers were instrumental in developing a number of methods and generating laboratory data that had an impact on the risk assessment of chlorpyrifos by OPP. Research conducted by ORD contributed to the characterization of life-stage specific susceptibility issues, including the characterization of age-related sensitivity to cholinesterase inhibition and the assessment of children's exposure to chlorpyrifos. ORD studies provided confirmation of enhanced susceptibility of the young, support for decisions regarding the adverse consequences of observed effects, a basis for extrapolation from animals to humans, methods to assess exposure to children, and information critical in identifying the point of departure for risk assessments conducted by OPP and OW. Results from the NHEXAS, Minnesota Children's Pesticide Exposure Study were used by OPP in the chlorpyrifos risk assessment to show the extent of children's exposure to this pesticides.

Developmental Neurotoxicity. Human Health research at EPA has characterized the differential response of younger animals to the neurotoxic effects of cholinesterase-inhibiting pesticides. Research indicated that when younger animals are more sensitive to these chemicals, they are less efficient in detoxifying the pesticides. This information has been used by OPP to limit the use of selected pesticides and helped form the basis for a Data Call-In to collect comparative sensitivity data for all registered organophosphate pesticides.

Cumulative Risk Assessments. The Food Quality Protection Act requires EPA to reassess by all pesticide tolerances and exemptions established before August 1996. The statute requires EPA to evaluate the cumulative and aggregate risks of all food-use pesticides having a common mechanism of action, emphasizing the protection of infants and children in determining the safety of a pesticide tolerance (i.e., the maximum level of pesticide residue allowed in or on food).

The first class of compounds to be evaluated was the oOrganophosphates (Ops), which is a group of pesticides that act to inhibit acetylcholinesterase enzyme, which results in dysfunction in

the nervous system.

The Cumulative Risk Assessment for OPs presents a major contribution to risk assessment at the Agency in providing a case study of how to estimate exposure and risk from a variety of pathways to a single chemical (aggregate risk) and from a variety of different chemicals with a common mechanism of toxicity (cumulative risk). EPA, with the aid of the FIFRA Scientific Advisory Panel, resolved a variety of groundbreaking policy and scientific issues in conducting the OP cumulative risk assessment. To protect the health of children, ORD strongly recommended that OPP change its approach to require a developmental neurotoxicity study for pesticide registration, and that in the absence of this study, OPP should consider applying the traditional uncertainty factor. This was accepted by OPP.

Exposure factors used in the cumulative risk assessment of the OPs, such as breathing rates and durations of time spent indoors or outdoors, were based in part on EPA's Consolidated Human Activity Database (CHAD) and EPA's *Exposure Factors Handbook* (1996b). ORD scientists also developed the OP CumRisk Program to facilitate the data analysis for the OP dose-response assessment, specifically to determine relative potency estimates and points of departure for the index chemical used in the OP cumulative risk assessment. Other EPA scientists are refining the current aggregate SHEDS-Pesticides exposure model to estimate exposures and absorbed dose to environmental contaminants by children and adults. Data that focus on aggregate exposure and risk from multiple chemicals through multiple pathways, particularly for children, are being analyzed. Other studies are focusing on pesticide exposure to residents following application in their homes and residential areas. The results of those studies will become available in the near future. ORD's exposure research program contributed to the Relative Cumulative Risk Assessment of the Organophosphate Compounds (US EPA, 2002c) and has provided a scientifically defensible approach for similar pesticide evaluations involving relative potency factors based on a common mode of action (i.e., thiocarbamate, dithiocarbamate, N-methyl carbamates, chloroacetanilides).

ORD researchers have also been involved in developing a PBPK/PD mode for N-methyl carbamate, a pesticide which also inhibits acetylcholinesterase enzyme in the nervous system. For the purpose of risk assessment, three processes have been identified that could lead to interactions between chemicals having a comparable mechanism, including metabolism, distribution and interaction at the molecular target site. The model developed by ORD is being considered in ongoing discussions with OPP concerning the risk assessment of N-methyl-carbamate. In a parallel effort, a series of theoretical PBPK/PD models similar to the N-methyl carbamate model is being developed to generate dose-response curves for high priority chemicals. The effect of exposure to multiple chemicals on probable target sites is being explored in order to determine if and how interactions between chemicals might lead to deviations from dose-additivity. In order to address issues of model structure and parameter uncertainty, molecular modeling approaches are being used to study the interaction between acetylcholine and pesticides. Predictive models based on molecular modeling has significant potential to assist OPPTS and other Program Offices in addressing their need to develop approaches to help prioritize and rank chemicals for screening and testing and prediction of chemicals in mixtures

Other research in ORD is focusing on cumulative risk assessment of disinfection by-

products in drinking water. A new risk assessment methods-the Cumulative Relative Potency Factors Approach- was developed by ORD to integrate the principles of dose-addition and response-addition to produce multi-route, chemical mixture risk assessments using internal doses. This approach evaluates human health risks using total internal doses and dose-response data based on knowledge or assumptions regarding toxic modes of action. This approach will play a significant role in the risk assessment of disinfection by-products in drinking water.

Databases. Providing full and open public access to tools and analyses is critical element of the regulatory development process. The *Technology Transfer Network* (TTN) developed in part by ORD researchers is a collection of technical Web sites containing information about many areas of air pollution science, technology, regulation, measurement, and prevention. In addition, the TTN serves as a public forum for the exchange of technical information and ideas among participants and EPA staff. The Fate, Exposure and Risk Analysis (FERA) website <http://www.epa.gov/ttn/fera/> provides tools which include EPA's Total Risk Integrated Methodology, assists Agency's efforts to evaluate the health risks and environmental effects associated with exposure to common air pollutants including ozone and particles and toxic air pollutants.

ORD has been an active participant in the design and development of several of the exposure models generated by OAQPS, most notably, the Air Pollutants Exposure Model (APEX). APEX serves as the human inhalation exposure model within the Total Risk Integrated Methodology model framework. APEX is intended to be applied at the local, urban, or consolidated metropolitan area scale and currently only addresses inhalation exposures. The model simulates the movement of individuals through time and space and their exposure to the given pollutant in various microenvironments (e.g., outdoors, indoors residence, in-vehicle). The user may choose the number and types of microenvironments to be included, select the time period of interest, use either monitored ambient air quality data or values provided from dispersion or other modeling runs, and use either a mass balance approach or an empirical ratio-based (factor) approach to estimate indoor and/or in-vehicle concentrations.

ORD Laboratories maintain the Consolidated Human Activity Database (CHAD), which is recognized as integral to modeling tools and links. OAQPS also provides specific guidance for stakeholders, interested parties and regulatory staff on modeling in their Air Toxics Reference Library (http://www.epa.gov/ttn/fera/risk_atra_main.html), which also refer to these databases in guidance of how to estimate inhalation exposure. CHAD contains data obtained from pre-existing human activity studies collected at city, state, and national levels. CHAD is intended to be an input file for exposure/intake dose modeling and/or statistical analysis. CHAD is both available on the OAQPS website to support modeling efforts, but is also integrated into APEX.

ORD also maintains a Human Exposure Database System (HEDS), which is an integrated database system that contains chemical measurements, questionnaire responses, documents, and other information related to EPA research studies of the exposure of people to environmental contaminants. A web-based data repository for human exposure studies (<http://www.epa.gov/heds/aboutheds.htm>), the mission of HEDS is to provide data sets,

documents, and metadata for human exposure studies that can be easily accessed and understood by a diverse set of users. HEDS operates in conjunction with the Environmental Information Management System (EIMS), ORD's metadata repository. HEDS provides data and accompanying documentation from research studies and allows for download of documents for review or data sets for analysis. Included in HEDS are data from NHEXAS studies conducted in the 1990s. These include three population-based survey and sampling programs conducted in three diverse geographical areas of the US. HEDS and NHEXAS databases are accessed routinely by several academic, industrial and governmental scientists.

Other research in ORD has focused on developing a database of pharmacokinetic information in human and animal across various life stages. Discussions are underway with OPP to develop pharmacokinetic models that provide interspecies comparisons across life stages for risk assessment. The ultimate goal is to develop PBPK models for one- and two-generation toxicological studies since they often serve as the basis for risk assessments based on developmental or reproductive toxicity. Validation of PBPK models is being accomplished using chemicals with known effects on absorption, distribution, metabolism and excretion.

The National Center for Environmental Assessment in ORD is the lead organization for maintenance of the *Integrated Risk Information System* (IRIS), which is used by Agency Regional and Program Office risk assessors and by scientists at organizations outside the Agency (states, tribes and other governmental groups). IRIS contains documentation of risk assessments performed on high priority environmental stressors and involves the development of and peer-review of scientific information to support such risk assessments.

Methods for Measurement and Exposure Studies. Analytical methods have been developed in collaboration with the HUD as part of the American Health Homes Survey. These methods better assess bioavailability of contaminants such as perfluorinated compounds in environmental media. Such methods are being used to provide population-based assessment of perfluorinated compounds for the Children's Total Exposure to Pesticides and Persistent Pollutants (CTEPP) program and to support programmatic needs of the OPPTS.

Other human health research has focused on the development of tools and methods to characterize children's pesticide exposures, including methods for collecting urine samples, non-invasive saliva biomonitoring methods, procedures for collecting and analyzing dust samples, a method to evaluate exposure from pets, techniques to characterize child activity patterns, methods to estimate dermal exposure and environmental sampling. This research has resulted in a Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways, which has been used by EPA Program Offices, other Federal Agencies, and researchers in academia and industry to estimate children's exposure to pesticides.

ORD human health research has determined pesticide exposures and health outcomes for a wide range of children's ages for a variety of exposure scenarios and demographic categories. These studies have found that EPA restrictions on the use of certain OP pesticides in the home have reduced the exposure of both mothers and infants to these pesticides, and that since

insecticide exposure levels have been reduced significantly, this population is no longer considered by Agency risk assessors to be at high risk of developmental toxicity.

In collaboration with scientists supported by the STAR program, epidemiological studies have called into question the assumption that established RfD and RfC values represent negligible risk due to increased risk in susceptible subpopulations. Major sources of exposure for children in an agriculture setting can be attributed to farm worker parents bringing pesticide residues into the home. These results have led to better hygienic requirements in the field and the development of education programs for workers. Other studies have confirmed that aerosol application of pesticides in housing is a significant sources of exposure in children.

Research at ORD has also focused on exposure of uniquely vulnerable populations. For example, the Border XXI research program was designed to test the hypothesis that pesticide levels in young children living in the border regions between the US and Mexico vary as a function of proximity of their home and/or school to agricultural fields. Although this hypothesis was not strongly supported by initial findings, the program has facilitated communication on children's environmental health issues at the Federal, State and local levels, as well as foster cross-border dialogue.

EPA researchers and collaborators helped coordinate health effects and exposure studies designed to assess health risks of workers and residents of lower Manhattan following the collapse of the World Trade Center. Data were released to the public in 2002 in conjunction with Region 2 and Office of Environmental Information (OEI). These data have provided a context for discussion of a wide range of public health officials concerning the potential long-term health effects of that disaster.

Particulate Matter (PM). Mechanistic research at EPA has focused on putative mechanisms or modes of action of air pollutants such as PM. EPA's air quality criteria document for PM discusses formation of reactive oxygen species as a putative mode of action underlying many of the adverse health effects of PM. Some of the most reliable extrapolations of toxicity from acute-to-chronic exposure scenarios and from animals-to-humans involve are based on oxidative stress as a MOA. ORD researchers are pursuing the possibility that oxidative stress may serve as a common and measurable mode of action for the effects of many different types of air pollutants.

Perfluorooctanoic Acid (PFOA) and its Salts. ORD scientists have played a critical role in OPPTS's effort to better better understand the human health exposure and risk concerns from exposure to PFOA and its salts in the wake of unexpected toxicological and bioaccumulation discoveries. This family of chemicals is of concern from both a exposure and health effects perspective. Organic fluorochemicals increasingly are being used for a variety of household and industrial applications. These include the surfactant coatings for fabrics and paper products, fire-fighting foams, electronic etching baths and insecticides. Recent evidence of extensive distribution and persistence in both humans and wildlife of perfluorooctanesulfonate (PFOS) led to the withdrawal of this chemical from the market by the 3M company. PFOS is the primary

degradation product of a widely-used class of sulfonyl-based fluorochemicals primarily manufactured by 3M. There is some recent information, mostly derived from rodent and monkey studies, concerning the potential developmental, reproductive and systemic toxicity of PFOS. ORD has also helped develop two test protocols for determining whether PFOA can be formed as a result of thermal degradation and UV irradiation of fluoropolymers. The former protocol has been accepted by industry.

ORD scientists have been actively involved in researching the health effects of PFOA and its salts, attempting to identify critical effects, mechanisms of action and develop pharmacokinetic models. ORD human health researchers participated in a joint effort with OPPTS in presenting to the SAB the draft Risk Assessment of the Potential Health Effects Associated with Exposure to PFOA and its salts. Human health researchers advised OPPTS on the approach to use serum concentrations of PFOA in rats, monkeys and humans for the calculation of a margin of exposure type analysis for risk assessment. The approach was a major focus of the SAB review along with issues related to the mode of action for carcinogenicity and evaluation of other toxicological and epidemiological endpoints.

Physiologically Based Pharmacokinetic Models (PBPK). ORD human health scientists have developed the Exposure-Related Dose-Estimating Model (ERDEM), which is a physiologically based pharmacokinetic model to simulate the human organism and its ability to absorb, store, metabolize and eliminate chemicals. ERDEM has been used by Agency risk assessors to simulate the reaction of multiple (cumulative) pesticides and their metabolites with cholinesterase enzymes in the nervous system. Discussion are now in progress concerning how the model can be interfaced with a probabilistic human exposure and dose simulation model to provide enhanced dose estimates. Model development to improve organ representations and model applications to other chemicals are of regulatory interest to the Agency's Program and Regional Offices. Such an approach has been applied to malathion and selected volatile organic compounds in the air and water.

Expertise to Support the Mission of the Agency

Chemical Risk Assessments

Delisting of Ethylene Glycol Monobutyl Ether. The American Chemistry Council (formerly the Chemical Manufacturers Association (CMA)) has petitioned the EPA Administrator to delist ethylene glycol monobutyl ether (EGBE) from the list of hazardous air pollutants. The decision on whether the petition meets the requirements hinged on the determination that EGBE is likely to be a nonlinear acting carcinogen (though a linear relationship cannot be fully dismissed). This is an illustration of the importance of research on mechanistic information to reduce uncertainty in risk assessment. Based on scientific and technical advice from ORD researchers, EPA concluded that EGBE is not genotoxic and that two distinctly different nonlinear modes of action are principally responsible for the increased forestomach and liver tumors reported in an National Toxicology Program assay.

ORD played a major role in preparing an Interim Final position paper “An Evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl Ether”, which described the modes of action in detail to support the Agency’s decision. The synthesis of the available information and additional research supported by the petitioner, indicate a non-linear mode of action for the male mouse liver tumors and female fore-stomach tumors observed following EGBE exposure.

Delisting of Methanol as a Hazardous Air Pollutant. ORD scientists co-authored the technical information used in the denial of the petition to delist methanol as a hazardous air pollutant to OAQPS.

Perchlorate. ORD scientists played a significant role in coordinating an integrated assessment approach to risk characterization based on the mode of action. Each Laboratory and Center in ORD, the Program and Regional Offices, and scientists from other Federal agencies (i.e., NIEHS, NIOSH) were involved. The approach applied state of the science research in human health effects, ecotoxicological risk, analytical methods, biotransport and fate and technology transfer and communication.

Computational Toxicology Implementation Steering Committee (CTISC). This ORD-wide steering committee was formed with the specific charge of implementing the recently developed *Framework for Computational Toxicology Research Program* (US EPA, 2004). The committee, which includes a number of human health researchers, was responsible for developing a RFA for projects to supported by the recent Computational Toxicology Initiative. The committee also developed criteria for the evaluation of internally supported proposals and provided the Director of the National Center for Computational Toxicology with recommendations concerning priorities for funding of proposals.

Exposure Factors Handbook. ORD scientists played a critical role in developing the *Exposure Factors Handbook* (1996b), which provides a summary of the available statistical data on various factors used in assessing human exposure. The document includes an introduction and discussion of uncertainty factors, including skin area and soil adherence factors. Also addressed are data for consumption of fruits and vegetables, fish, meat and dairy products, homegrown foods, and breast milk, as well as data for human activity factors, consumer product use, and reference residence. Basic equations using the parameters to calculate exposure levels are provided as are the recommended values for various segments of the population who may have characteristics different from the general population. This document is widely used by Program and Regional Office risk assessors to estimate human exposure to chemicals. An Agency-wide advisory group has been established to assist ORD in identifying data gaps and set priorities for exposure factors research.

Genomics Task Force. In early 2002, the Science Policy Council charged an Agency Action Plan Workgroup to develop an interim Genomics Policy and an action plan to address technical and policy challenges for appropriate use of genomics technologies and data in EPA. Human health researchers played a significant role in developing an interim policy in which EPA encourages and supports continued genomics research as a tool for understanding the

molecular basis of toxicity and developing biomarkers of exposure, effects and susceptibility. The interim policy also indicates that genomics data alone are currently insufficient as a basis for risk assessment and management decisions. Geonomics data may be useful in a weight-of-evidence approach for human health and ecological risk assessments. The resulting action plan called for a research program on computational toxicology, standardization of methods and databases for use in computational toxicology, and addressed several ethical, social and legal implications to ensure privacy and fairness in the use and interpretation of genetic information. The action plan also called for a study of approaches for the ultimate incorporation of genomic information into Agency risk assessments, developing a coordinated genomics education program, and communicating genomic science and policy decisions internally and externally. Human health researchers were also asked to serve on a Genomics Short-Term Implementation Workgroup.

Guidance Documents. EPA human health scientists have contributed significantly to guidance documents addressing a wide variety of risk assessment issues for a range of adverse effects (Table 4). For example, Human Health researchers played a major role in the development of *Revised Guidelines for Carcinogen Risk Assessment*, which are currently being used by the Agency (US EPA 2003f).

ORD researchers worked with scientists from Program Offices to write a review of the reference dose (RfD) and reference concentration (RfC) process (US EPA, 2002e) used across the Agency. This document has had a significant influence on risk assessment in the Agency by providing appropriate definitions and identifying various risk assessment practices across the Agency (US EPA, 2002e). EPA human health scientists also played a major role in the development of Benchmark Dose Software and Draft Technical Guidance (US EPA, 2004). These products are widely used throughout Program and Regional Offices of the EPA, as well as by many state and international agencies. EPA scientists played a major role in the development of guidance documents for the use of RfD/RfC approaches in risk assessment and risk assessment of neurotoxicity and metals .

Human health researchers have been particularly active in shaping the Agency's approach to cumulative risk assessment. Workshops sponsored by ORD range from training sessions on assessment methods to discussion of case studies from Regional and Program Offices. ORD scientists have been involved in preparing guidance documents including the 2000 *Supplementary Guidance for Mixture Risk* (US EPA, 2001b) and the *Framework for Conducting Cumulative Risk Assessment* (US EPA 2004).

ORD Human Health Scientists have made significant contributions to a number of guidance documents related children's health, including the writing of the *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens* (US EPA 2003g) and the *Strategy for Research on Environmental Risks to Children* (US EPA, 2000b). ORD made a significant contribution to writing of the *Child-Specific Exposure Factors Handbook* (2002d) and draft *Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants*. These documents will strengthen the overall risk assessment process across the Agency.

National Agenda for the Environment and the Aging. In recognition of the changing demographics of the American population, the Agency is participating in the development of an Administrator-initiated National Agenda for the Environment and Aging. ORD has a history of conducting research on environmental hazards that affect the health of susceptible subpopulations, including the effects of environmental hazards on older persons. Because of their expertise in this area, ORD human health researchers have been actively involved in developing a comprehensive national approach to the problem of the environment and older populations. The Agenda is being developed through a public participatory process which includes on-going work in the Agency; input from public listening sessions held across the country; proceedings from a National Academy of Sciences report (NRC, 2004); collaboration with Federal, state and local government groups; and interactions with academic laboratories, as well as environmental and public health organizations.

ORD scientists have collaborated with the Office of Children's Health Protection (OCHP) to develop an inventory of projects on the environmental health of older adults. ORD scientists have also compiled reports on baseline changes in physiology across organ systems and on the PK and PD handling of therapeutic drugs in older individuals. This information will be useful to risk assessors considering the possible risk of older persons to specific classes of environmental stressors. ORD scientists are working with OPPTS and extramural investigators to develop a PK model of prototype environmental stressors to identify the factors that most affect tissue dosimetry as a function of life-stage.

National Children's Study (NCS). Human health researchers have been intimately involved in the formation of the NCS. ORD scientists are working closely with scientists from other lead Federal agencies in the planning and design of the study, and in developing and testing methods for data collection for the NCS. ORD is leading an Inter-Agency effort to initiate an early cohort in North Carolina to answer research questions of interest to the NCS Steering Committee. ORD scientists are also working with the larger scientific community to develop and test methods for data collection, biological markers and other tools, such as questionnaires and characterization of environmental information for the NCS. Research from ORD has led to the development of methods to use non-invasive samples that reflect in utero exposures and the usefulness of fingernail DNA for assessment metabolic and detoxification genetic polymorphisms. Exposure-related work has focused on potential use of validation of sub-samples to provide adequate statistical power to detect effects attributable to environmental and personal exposures.

ORD human health scientists have provided leadership through collaborations with other Federal and non-Federal scientists and through serving on the NCS's Working Groups. For example, ORD researchers developed a position paper and manuscripts on potential exposure assessment approaches and worked to integrate exposure measures into the NCS Study Plan. Collaborations with the National Center for Health Scientists were established to implement the sampling strategy to be used in the NCS.

Report on the Environment. ORD scientists played a significant role in drafting the Draft Report on the Environment (US EPA, 2003h). The report outlines the key to using outcome-based indicators to understand the sequence of events that link changes in environmental conditions to human health. In the Health Chapter of the report, a number of data gaps were identified relating to the need for improved indicators of the actual public health impact associated with Agency decisions and actions. Another report on the environment is due in 2006.

Research Strategy Documents. Human health researchers have played a significant role in the drafting of several research strategy documents, including the *Research Plan for Arsenic in Drinking Water* (US EPA, 1998a), *Research Plan for Endocrine Disruptors* (US EPA, 1998b), *Strategy for Research on Environmental Risks to Children* (US EPA, 2000b), *Mercury Research Plan* (US EPA, 2000c), *Asthma Research Strategy* (US EPA, 2002a), *Air Toxics Research Strategy* (US, 2002b) and *A Framework for a Computational Toxicology Research Program* (US EPA, 2003d). These documents lay the foundation for future research in a number of high priority areas that include human health as a cross-cutting issue.

Training and Technical Assistance. Human health researchers have also contributed to Program Offices by providing training workshop and seminars, developing methods for hazard identification, interpreting submitted data, and serving on data review panels and workgroups. ORD scientists also provided technical assistance to the regional offices, agency risk assessors and the STAR program. Human health researchers participate in many intra- and inter-agency workgroups and technical panels (see Table 4 for examples).

Recognition of Contributions of Efforts to Mission of Agency. That the efforts of ORD scientists have made have had an impact on EPA's mission to protect human health and the environment is evidenced by approximately 20 Honor Awards and over 30 Gold/Silver/Bronze Medals for Exceptional Service awarded since 1999 (Table 5).

SCIENTIFIC LEADERSHIP

The last evaluation criterion is Scientific Leadership, which can be defined as contributing to advancing the state-of-knowledge in those scientific disciplines related to the priority research questions (see text box). EPA scientists provide vital leadership in the environmental research arena, and its scientists are active in the scientific community at many levels.

Table 6 summarizes the number of peer-reviewed outputs (methods, models and data) published in peer-review journal or as peer-reviewed documents since 1999. ORD scientists have published over 1,100 papers in approximately 170 different journals. The rate of publication has been relatively constant for the last 5 years. Table 5 indicates that many papers published by human health researchers have been recognized externally by being named as "best paper" at society meetings or in prestigious journals. A number of papers from ORD human health research were recognized by the SAB with a Science and Technology Achievement Award (STAA).

ORD scientists are frequently invited to present their findings at seminars, symposia,

workshops and other scientific gatherings. Nearly 700 presentations were given by ORD scientists at the local (e.g., university departmental seminars, local scientific societies), regional/national (e.g., Society of Toxicology, Society for Risk Analysis), and international meetings (e.g., World Health Organization/International Programme on Chemical Safety, International Dioxin Conferences) during the period 1999 to 2004.

Human Health researchers have also demonstrated scientific leadership by participating in advisory boards, national or international steering groups, and technical workgroups. Table 7 shows that ORD scientists served on peer panel and scientific advisory boards of approximately 70 different organizations, including private companies, national/international scientific societies, foundations, other federal agencies, universities, states and municipalities. In some cases, several ORD scientists were asked to contribute their expertise to

prestigious organizations such as the International Life Sciences Institute (ILSI) and the International Programme on Chemical Safety. Table 7 also shows that ORD human health researchers played an active role in the planning and organization of over 50 national or international symposia or conferences during the last 5 years. ORD researchers played a particularly significant role in symposia sponsored by the Society of Toxicology. ORD

human health researchers served as elected officers in over 20 national or international societies, including specialty sections of the Society of Toxicology. ORD researchers held adjunct appointments in departments in at least 20 universities and were particularly active in various outreach efforts as evidenced by designing and presenting training workshops for over 20 academic departments, scientific societies, and targeted conferences or symposia. In addition, ORD scientists were invited to participate in the review of grant applications for nearly 20 different industrial, academic and governmental groups, including study sections for the National Institutes of Health and served as associate editors or as members of the editorial board of more than 30 peer-reviewed journals. Table 8 shows that ORD human health researchers have been actively involved in the training of several pre- and postdoctoral students.

INDICATORS OF LEADERSHIP

Peer-Reviewed Outputs (Methods, Models, Data)
Recognition by Scientific Community
Invited Presentations at National and International Meetings
Serving in Advisory Capacity (Advisory Boards)
Organizing Major Conferences or Symposia
Elected officers in National or International Scientific Societies
Adjunct Appointment at Colleges or Universities
Training Courses for Universities or Scientific Societies
Training Students and Postdoctoral Students
Serving on Grant Review Committees
Serving on Editorial Boards of Peer-Reviewed Journals

SUMMARY

The Human Health Research Program in ORD focuses on addressing the highest priority research needs identified in the *Human Health Research Strategy* (US EPA, 2003b), i.e., Use of

Mechanistic Data in Risk Assessment, Aggregate/Cumulative Risk, Susceptible Subpopulations, and Research to Evaluate Public Outcomes of Risk Management Decisions. ORD's Human Health Research Program provides fundamental understanding of the key biological, chemical, and physical processes that underlie biological and environmental systems and the output from this Program have been applied to a wide range of environmental problems. The Human Health Research Program utilizes a multi-disciplinary, multi-dimensional approach, which integrates the efforts of experimental biologists, modelers, engineers, statisticians, risk assessors and risk managers. The scientific and technical expertise of ORD human health scientists is widely sought after within the Agency and by organizations external to the EPA. ORD human health scientists are actively engaged in the scientific community and are viewed as leaders in their respective disciplines.

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