

HUMAN HEALTH
MULTI-YEAR PLAN

April , 2003

The Office of Research and Development's (ORD) multi-year plans (MYPs) present ORD's proposed research (assuming constant funding) in a variety of areas over the next 5-8 years. The MYPs serve three principal purposes: to describe where our research programs are going, to present the significant outputs of the research, and to communicate our research plans within ORD and with others. Multi-year planning permits ORD to consider the strategic directions of the Agency and how research can evolve to best contribute to the Agency's mission of protecting human health and the environment.

MYPs are considered to be "living documents." ORD intends to update the MYPs on a regular basis to reflect the current state of the science, resource availability, and Agency priorities. ORD will update or modify future performance information contained within this planning document as needed. These documents will also be submitted for external peer review.

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INTRODUCTION

This Multi-Year Plan (MYP) sets forth ORD's plans for conducting research in support of the Government Performance and Results Act (GPRA) Goal 8.2 – Human Health research. As a MYP, this document exists to bridge the gap between the *Human Health Research Strategy* (USEPA 2003) and the implementation plans established by the individual labs and centers. The MYP provides a more detailed description of how the research will achieve its goals than does the research strategy, but it provides less technical detail than would be expected in an implementation plan.

ORD's effort to produce MYPs is consistent with ORD's Strategic Plan (SP). The MYPs are a critical component of the SP goal to ensure that the efforts are integrated across the labs and centers. A major objective of the MYP formulation process is to ensure that our efforts are more than an accumulation of high-quality, but disparate, research tasks – that the work across labs and centers comes together to constitute a sound research program that will have a major impact in helping EPA in its mission of “protecting human health.” After all, supporting the Agency's mission is the first goal set forth in ORD's Strategic Plan.

The research set forth in this Goal 8.2 MYP does not, indeed, can not, stand alone! This MYP largely describes ORD's core “Sound Science” research, but it builds upon and provides tools to the problem-driven research areas. Even a quick review of the research sections in this MYP will reveal numerous linkages to ORD's research in support of the Clean Air Act, the Safe Drinking Water Act, the Food Quality Protection Act, the Toxic Substances Control Act, etc. MYPs in other GPRA areas with strong legislative mandates and deadlines and well-defined client needs can more easily lay out a time-line and research program to address those needs. The core Human Health research program is driven not by one of these legislative mandates, but by all of them! The core Human Health research program benefits all of these problem-driven areas, and, in turn, our fundamental understanding of human health risk is enhanced as we learn from our efforts to address the specific problems in those other areas.

The *Human Health Research Strategy* describes ORD's core Human Health research as an iterative process, where: the state of our knowledge is applied to address a real-world environmental problem (in one of the problem-driven GPRA areas); we learn from that

experience and identify research gaps; we conduct research to overcome the short-comings and incorporate the new insights into our tools – our methods, models, measurements / data; we use the improved technical tools to address the next real-world problem (in the same or a different GPRA area). Such an approach clearly envisions research efforts that bridge GPRA goals, where the various other problem-driven GPRA Goals represent the opportunity to address real-world environmental problems, while the Goal 8.2 core Human Health research effort serves to provide sound scientific insights that will benefit several problem-driven areas, and to assemble and integrate the insights gained from the problem-driven programs, in order to share and distribute that knowledge to address other environmental problems.

To that end, ORD's GPRA Goal 8.2 Human Health research focuses on three major areas of research:

Harmonization of cancer and non-cancer risk assessments;

Aggregate & cumulative exposure and risk; and

Characterizing risk to susceptible human populations, especially children, the elderly, and individuals with pre-existing health conditions.

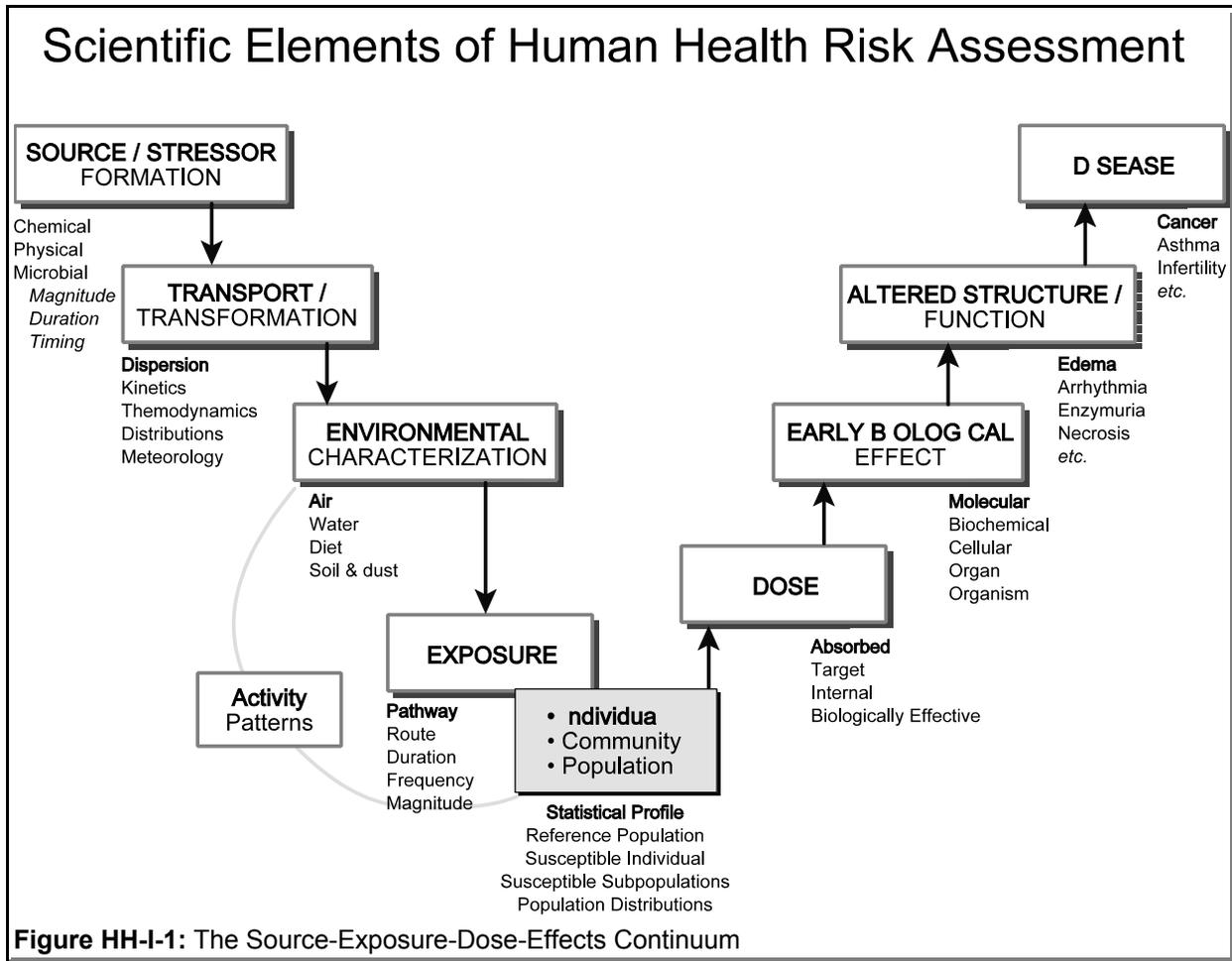
In addition, we are concerned with issues of accountability and ensuring that our research products produce desirable public health outcomes – therefore, we have included a section on public health outcomes in this MYP, even though we do not have an extensive research program on this topic. We consider these four areas as appropriate for our core research because these topics are so broadly applicable: harmonization research provides fundamental knowledge on the mode of action of pollutants, so that EPA may to assess the complete health impacts of environmental pollutants, especially the effects of mixtures of pollutants – an issue in all media and GPRA areas; since all of the problem-driven program areas need to assess the impact on individuals of pollution that can come via many pathways and can integrate over time, our research on aggregate & cumulative risk is broadly applicable to many GPRA areas; and whether we are discussing the impacts of air pollutants, pesticides in food, or contaminants in water, we need to be especially vigilant to protect the health of susceptible subpopulations in our midst.

In our efforts to develop a core research program that is integrated across all labs and centers, the writing team members relied upon the source-exposure-dose-effects continuum and paradigm set forth in the *Human Health Research Strategy* (see Figure HH-I-1). It illustrates the areas of knowledge and expertise that must be considered in conducting a risk assessment.

Some level of understanding of each component in the continuum is necessary to determine if the risk from an environmental hazard is large enough or wide-spread enough to warrant action by the Agency to protect human health. If regulatory action is warranted, then the same areas must be considered in selecting the most appropriate risk management options. Finally, the continuum is considered in evaluating the environmental health outcomes of our policies. This focus on the source-exposure-dose-effects continuum – and its repeated use in risk assessment, risk management, and evaluation – emphasizes the need for, and the value of, a research program that integrates and involves the talents of all of ORD’s labs and centers.

ORD’s human health risk assessment program is based on the assumption that major uncertainties in risk assessment can be reduced by understanding the fundamental principles of how, at what level, and how often humans are exposed to pollutants; of how much of the toxic moiety arrives at the target site; and understanding the basic biological changes that lead to a toxic or adverse health effect. Research questions related to harmonizing risk assessment, assessing aggregate and cumulative risk, and evaluating risk to susceptible and highly exposed subpopulations will be framed to address knowledge gaps and interrelationships of events along a continuum from source through exposure and dose to effect (Figure HH-I-1). The overall objective of ORD’s human health research program is to link exposure, dose, and effect approaches along this continuum to provide an integrated information base for scientifically defensible risk assessment and risk management decisions.

So, the research set forth in the HH MYP addresses the components of the continuum in the following ways. The Aggregate and Cumulative research efforts are focused principally on the continuum components of source through dose (see Figure HH-I-1). This core research is directed at understanding and describing the many ways that a pollutant, or multiple pollutants, move through the environment to come into contact with people. The work continues with efforts to characterize the probability, sequence and timing of exposures and to understand how these exposures over time contribute to a pollutant dose that may harm people’s health. The Harmonization research is focused on identifying those pathways of biological response induced



by pollutant exposures, that such pollutant exposures-dose induce, leading to a cascade of events resulting in altered function(s) and disease in humans. As such, the harmonization research focuses on the right side of the continuum – from exposure-dose through the manifestation of disease. ORD’s core research on Susceptible Subpopulations involves all aspects of the continuum, and allows ORD to test its understanding of these critical elements, especially as they apply to children, the elderly, and those with pre-existing diseases or genetic susceptibility. The susceptible subpopulation research describes the routes and pathways by which these sensitive populations are exposed, together with the special biological responses that their lifestage or their condition may bring about. Finally, the HH MYP includes core research to evaluate the effectiveness of Agency actions on protecting human health. Agency actions to regulate sources or to limit exposures of pollutants should manifest themselves by changes in disease, as illustrated by the continuum. The Public Health Outcomes research in the MYP

represents our initial efforts to relate those regulatory actions to measurable changes in disease. The research is working to identify indicators of public health status, be they indicators of disease or altered function, and to attribute any observable changes to changes in exposures or source strengths due to Agency actions.

The four research areas included in this MYP are linked by the contributions that each makes to understanding the elements of the continuum. Two areas (Harmonization and Aggregate-Cumulative) focus on major portions of the continuum, while the Susceptible Subpopulations and the Public Health Outcome areas involve the continuum as a whole.

This is the third iteration of this Human Health MYP. This version includes the use of Logic Diagrams as a tool to help design the research programs. By focusing on the outcomes that our research is to achieve, we can more appropriately design a research program that brings to bear all of the talents and skills of the various ORD's labs and centers to accomplish those outcomes.

This MYP begins with this introduction, and is followed with a discussion of the resources (FTE and extramural dollars) dedicated to this core Human Health research effort. Each of the four major topic areas – Harmonization, Aggregate & Cumulative Exposure and Risk, Susceptible Subpopulations, and Public Health Outcomes – is then discussed in turn. Each of those sections contains one or more flow diagrams illustrating how the Annual Performance Goals (APGs) come together to achieve the topic area's Long-Term Goal(s). Tables listing the Annual Performance Measures associated with each of the APGs are included at the end of each section. The Appendix identifies additional science needs and expected results from investing additional resources in each area.

RESOURCES

The FY04 resources in the President's budget directed at achieving the Human Health Long Term Goals total \$30,085.4 K in extramural funds and 116.2 FTE. About half of the funds in these areas are directed toward grants to support fundamental research, especially research on children. Resources directed specifically toward each of the four major research areas are:

Harmonization: \$3,003.9K and 32.0 FTE

Aggregate & Cumulative: \$8,265.1K and 23.5 FTE

Susceptible Subpopulations: \$16,966.6K and 56.8 FTE

Public Health Outcomes: \$1,849.8K and 3.9 FTE

In developing the MYP, the writing teams assumed that the total funding would remain constant for the next several years. To meet the intertwined goals of the four research activity areas, it may be necessary to shift resources between the research areas.

HARMONIZATION OF CANCER AND NON-CANCER RISK ASSESSMENT

Introduction

The purpose of the Multi-Year Plan on Harmonization of Cancer and Non-Cancer Risk Assessments is to serve as a tool to plan the direction of research and to communicate the program both within ORD and with others, especially risk assessors in the Agency's Regional and Program Offices. It is intended that this MYP will permit consideration of future strategic direction of harmonization research in the Agency and determine where scientific discovery can contribute. This MYP is intended to ensure the relevance, quality, and performance of the harmonization research program in ORD over the next 8-10 years.

The research on harmonization of cancer and non-cancer risk assessment described in this MYP is consistent with the strategic principles formulated in ORD's *Human Health Research Strategy*, and supports mechanistic research needs identified by the Food Quality Protection Act of 1996, the 1996 Amendments to the Safe Drinking Water Act, and the Office of Pesticide Programs 2001 *Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Action*.

Approximately two thirds of the harmonization research effort is executed through grants as part of EPA's STAR program. Resources for this effort are expected to remain relatively stable over the next few years, but the focus of the program will adjust over time as progress is made. We expect the level of effort within themes in the plan will change over time:

- Identification of Common Modes of Action: initially stable, then decline
- Study of Toxicity Pathways: flat, then increase to stable level beginning in FY 04
- Pharmacokinetic Modeling and Scaling: Stable, then decline
- Modeling of Mechanistic Data: flat for a few years, then increase to stable level

Background

The assessment of health risk from exposures to environmental agents has traditionally depended on whether the effect is cancer or a non-cancer health effect. However, the 1997 report "Risk Management in Regulatory Decision Making" from the Commission on Risk Assessment and Risk Management concluded that a simple dichotomy between cancer and non-cancer risk assessment is not fully supportable by current scientific evidence. Current approaches

result in expressions of risk that are not directly comparable and these expressions differ significantly in defining maximal exposures considered to have negligible risk. In addition, the National Research Council's report on Science and Judgment in Risk Assessment (NRC, 1994) noted the importance of a risk assessment approach that is less fragmented, more consistent in application of similar concepts, and more holistic than endpoint-specific guidelines. The Agency's Risk Assessment Forum has been actively involved in reexamining approaches to cancer and non-cancer risk assessment by sponsoring internal colloquia to encourage input and discussion between scientists and risk assessors. One conclusion from these discussions is that there is a need to develop a consistent, flexible set of principles and guidelines for using and drawing inferences from scientific information across all types of effects in risk assessment. This need is further articulated in ORD's *Human Health Research Strategy*.

Use of Mechanistic Information in Risk Assessment

One issue related to the disparity in approaches to cancer and non-cancer risk assessments is the limited understanding of the mode or mechanism of action of compounds. This lack of knowledge can limit the relevance and accuracy of experimental designs, methods, human information, and animal models that have been used to support hazard identification and dose-response phases of human health risk assessments. **Understanding an agent's mode or mechanism of action is considered a key aspect in developing relevant as well as more accurate prediction and characterization of hazard and risk, and is the basis for developing harmonized risk assessment approaches for all health endpoints.**

At present, risk assessment guidelines for cancer and non-cancer endpoints differ with respect to the use of mode or mechanism of action information. For non-cancer risk assessments such as Reproductive Toxicity, Developmental Toxicity, and Neurotoxicity, information on mechanisms is largely used in a weight-of-evidence framework to strengthen the evidence that a human hazard could exist. For example, mechanistic data could be used to support findings from an epidemiological study or explain results from animal toxicity studies and relate them to results from human studies. Mechanistic data could also be used on a case-by-case basis to reduce the magnitude of uncertainty factors used to calculate the Reference Dose, Reference Concentration, or Benchmark Dose. For example, if the same mode or mechanism of toxicity

could be demonstrated to occur in humans and animals, then the uncertainty factor for animal-to-human extrapolation might be reduced in the risk assessment.

The use of mode or mechanistic information is spelled out in great detail in the draft Guidelines for Carcinogen Risk Assessment (US EPA, 2002). As in the case of non-cancer endpoints, mode of action data can be used in a weight-of-evidence framework to support the evidence for carcinogenic hazard potential based on epidemiological or animal toxicity studies. However, the draft Cancer Guidelines also note that mode of action information is key to addressing various default options in the risk assessment. Biologically-based dose response models using mechanistic information can be used to relate dose and response on an agent-specific basis and to extrapolate to lower dose levels, if needed. Mode of action data can be crucial for establishing causal inferences of precursor effects that may then be used as a point of departure for risk assessment, the linearity or non-linearity of the dose response relationship, and the biological plausibility of a response. Mode of action data are also important for determining key events that may be of increased concern to susceptible subpopulations, such as children, and extrapolation from animals to humans. Mode or mechanistic information play a central role in determining appropriate dose measures to estimate dose in target tissues and help define relative sensitivity of various tissues to toxicants. Unlike risk assessment guidelines for non-cancer endpoints, the draft Cancer Risk Assessment Guidelines contains a framework for the analysis of carcinogenic mode(s) of action information, including steps necessary to define the postulated mode of action, identification of key events, and assessment of experimental evidence supporting the postulated mode of action.

There is a clear need to develop a common approach for the use of mode or mechanistic data in risk assessment. Specific questions addressed by ORD's research on harmonization include the following:

- Can a similar framework be defined for using mode and mechanism of action for cancer and non-cancer endpoints?
- What are the PK and pharmacodynamic (PD) factors underlying the expression of cancer and non-cancer effects, especially as they relate to differences in responsiveness between species?
- Are there potential common modes or mechanisms of action underlying cancer and non-cancer effects?
- What are the most appropriate methods to study mode or mechanism of action for cancer and non-cancer effects?

Harmonization as it Relates to the Human Health Multi-Year Plan

In the context of this Multi-Year Plan, harmonization refers to developing a consistent, flexible set of principles for using and drawing inferences from available information on mode or mechanism of action to support risk assessment. Such a framework should be responsive to differences that exist among various modes or mechanisms of toxicity and the amount of relevant toxicity data available. For the purposes of the Human Health Multi-Year Plan, the term “**mode of action**” is defined as a series of **key events** starting with interaction of an agent with a cellular or molecular target site and proceeding through functional and morphological changes to result in an adverse effect. “**Mechanism of action**” implies a more detailed understanding and description of the key events, often at the molecular level. “**Key events**” are defined as empirically derived precursor steps consistent with the mode or mechanism of action. The sequence of biological changes leading to an adverse effect at a given internal dose is also known as the “**toxicity pathway**”. Toxicities arise from a range of factors that may be specific to the chemical or chemical class, the physiology, biochemistry or anatomy of the organism, or the pathological process. A framework for harmonization of risk assessment approaches must facilitate incorporation of data that accounts for these factors.

The Logic Model on the following page attempts to link specific environmental problems, strategic goals and objectives, and clients addressed with the research required to strengthen decision-making in human health risk assessment.

Progress to Date / Changes from the Previous Version

Over the last year, harmonization research has contributed to the following areas:

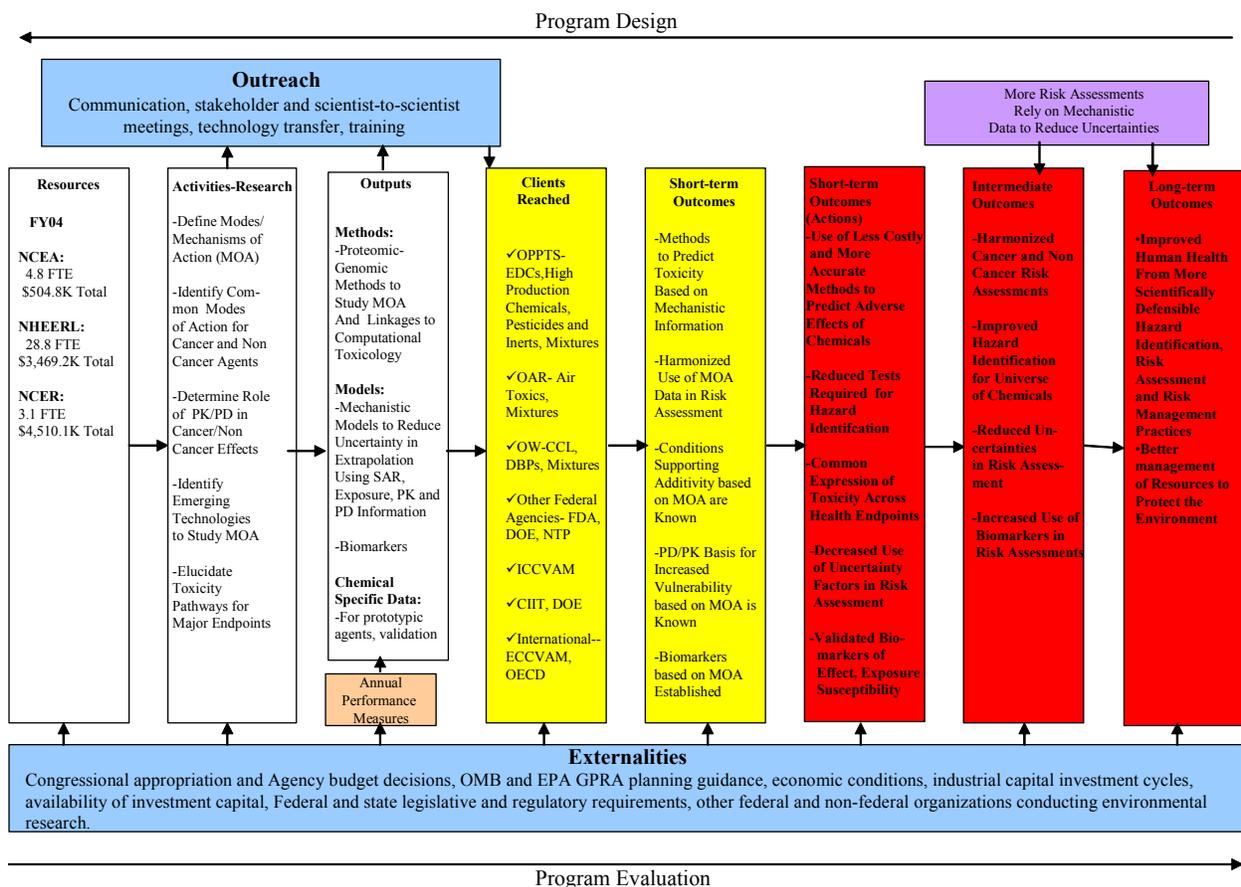
- Fundamental biological studies to support mechanistic research on endocrine disruptors
- Fundamental research on the mechanism of arsenic
- Research to determine the mechanism of species differences underlying metabolism of arsenic
- Fundamental biological studies on relationship between thyroid dysfunction and adverse health effects
- Developed a biologically based dose-response model for developmental toxicity of prototypic compound
- Development of molecular profiling approaches to assess the effects of chemicals at various life stages
- Held a workshop on harmonization of risk assessment

Based on comments from the Executive Council review of the Human Health MYP, this version of the MYP for harmonization research:

- Includes a section on integration and communication
- Shows more explicit linkages with other MYPs, as well as with other components of the Human Health MYP (i.e., Susceptible Subpopulations, Aggregate/Cumulative Risk)
- Updates ORD’s unique role and other organization’s research
- Ties mechanistic research to emerging computational toxicology initiative
- Incorporates application of genomics and other new technologies
- Includes integrated exposure and effects research project
- Includes two synthesis documents

Finally, the time of completion of the Long-Term Goal and two crucial Annual Performance Goals (APGs) has been extended from FY08 in the previous version of the MYP to FY12 in this revision. The reason for this change is that research on harmonization has become more focused on elucidating specific toxicity pathways to generate principles for the use of

Harmonization of Risk Assessment



mechanistic data in risk assessment. This approach will require the use of genomic and proteomic techniques and bioinformatic approaches which are only just becoming applicable to toxicological investigations. In addition, crucial new research to develop models describing the source-dose-effect relationship was initiated in FY02 and it will take time to include this information in developing a common approach for the use of mechanistic data in risk assessments, especially as it applies to questions of extrapolating between species and defining the parameters of intraspecies variability.

Overview of the Long-Term Goal

The Long-Term Goal of ORD's research program on harmonization of risk assessment approaches is to: ***“Develop a commonly accepted approach for estimating the risk to human health posed by exposure to toxic chemicals in the environment that incorporates information on biological modes or mechanisms governing their toxicity”.***

An integrated research program between ORD's Laboratories and Centers will be necessary to meet the Long-Term Goal. In general, NCEA will be responsible for conducting workshops to identify conceptual issues related to the use of mechanism or mode of action information in harmonized risk assessments and helping to derive principles that can be used by Program Offices to formulate guidance. NHEERL will conduct laboratory research to identify toxicity pathways and generate chemical-specific information, while NHEERL, NCEA and NERL will collaborate to develop exposure-dose-effect models. NCER will sponsor mechanistic research through the Strategic Research to Achieve Results (STAR) grants program. A flow diagram of how the APGs will be combined to achieve the Long-Term Goal is shown in Figure HH-H-1 on the next page. Table HH-H1 located at the end of this narrative describes the APMs that contribute to each of the APGs.

Description of the Flow Diagram

Develop a Framework for Defining Mode and Mechanism of Action

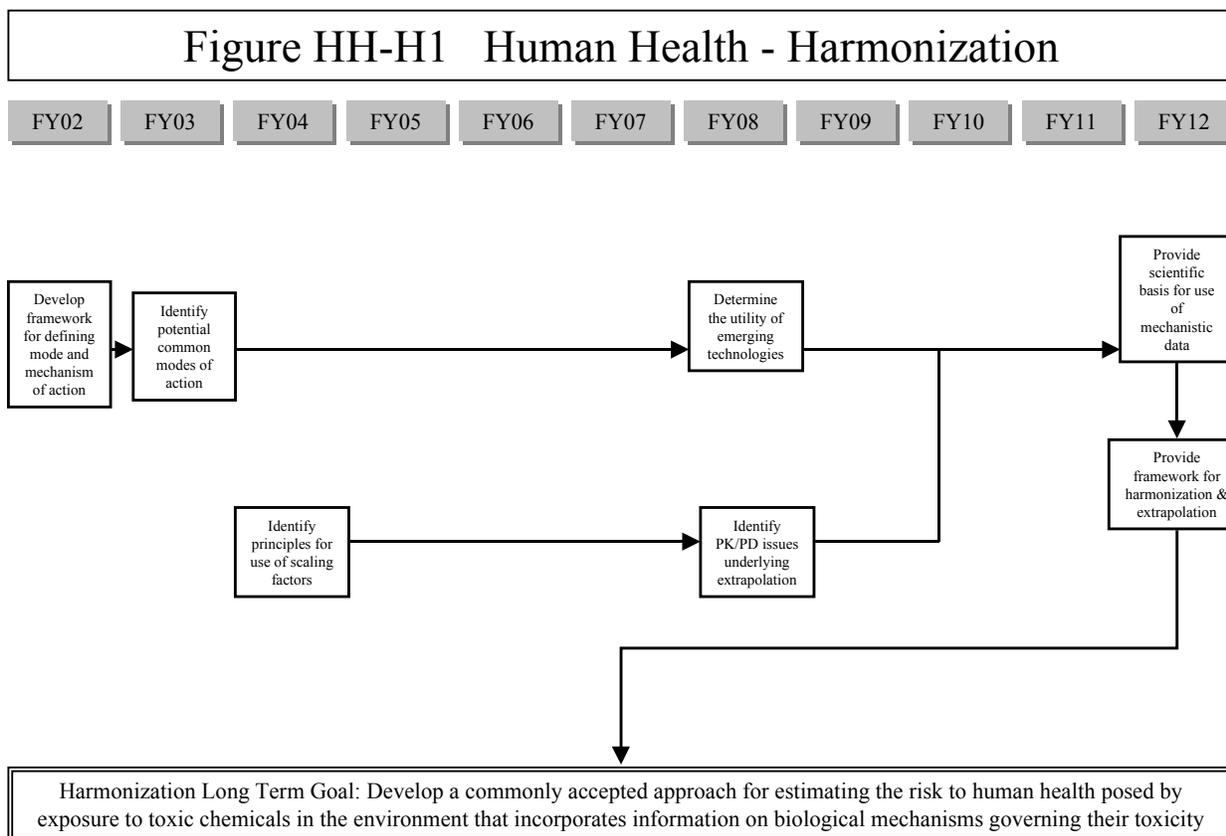
In order to achieve a more harmonized approach for risk assessment based on mechanistic information, there must first be a common framework for defining mode or

mechanism of action. The APG to “**Develop Framework for Defining Mode and Mechanism of Action**” in FY02 resulted in an APM (report) from NCEA on the results of a workshop.

The overarching theme of this workshop was to determine the level of evidence necessary to establish causality, i.e., from being associative to being causal. This information will be important for developing a common set of criteria for defining modes or mechanisms of action for cancer and non-cancer endpoints.

Common Modes of Action for Cancer and Non-Cancer Endpoints

Once a framework has been developed to define mechanism and mode of action for use in risk assessment, work will be done to identify possible common modes of action for chemicals producing cancer and non-cancer effects. The APG in FY03 to “Identify Potential Common Modes of Actions that Underlie Different Toxic Effects” will attempt to develop a clear understanding of the biological changes that occur following delivery of the active chemical moiety to target sites and the relationship of response to dose. Emphasis will be placed



on identifying possible common precursor steps (e.g., cell proliferation, receptor interaction, response to injury or stress) for prototypic chemicals that have both cancer and non-cancer effects. The overall objective of this APG is to demonstrate the feasibility of determining potential common precursor modes of action for cancer and non-cancer effects. This information will provide the basis for subsequent research to high priority toxicity pathways for several prototypic chemicals with differing modes of action. Toxicity pathways include cell signaling pathways such as MAP-Kinase, oxidative stress, hormonally (non-estrogen/androgen)-mediated effects, and interaction with various forms of P-450 and other xenobiotic metabolizing enzymes. The approach to study these toxicity pathways is based on discussions held at an ORD-wide Scientist-to-Scientist meeting sponsored by NHEERL in October, 2001. A workshop sponsored by NCEA in FY03 will summarize the state-of-the-science concerning potential common modes of cancer and non-cancer endpoints. Work covered under this APG will be crucial for future studies designed to characterize the key events or toxicity pathways necessary to produce effects mediated by putative common modes or mechanisms.

Role of Pharmacodynamic and Pharmacokinetic Factors in Risk Assessment

Over the last few years, risk assessors have used physiologically-based Pharmacokinetic (PBPK) models to help evaluate and estimate measures of toxicologically relevant doses within the body. These models are excellent tools to relate exposure to dose, and they are particularly useful for predicting the dose from measured and modeled exposure conditions. PBPK models are often used to support risk assessment decisions concerning extrapolation across species. However, the use of such models in risk assessment varies according to the type of health effect assessed. Furthermore, there has been much less research on the use of pharmacodynamic (PD) models in risk assessment of cancer and non-cancer endpoints.

One issue related to the harmonization of cancer and non-cancer risk assessments is the use of scaling factors and default assumptions for animal-to-human extrapolation. The APG “Identify Principles for Use of Scaling Factors in Risk Assessment” in FY04 will address the issue of comparable dosing of animals and humans in cancer and non-cancer risk assessments. This research addresses the rationale for interspecies defaults and the relationship to cross-species scaling factors. NHEERL will also produce research on pharmacokinetic (PK) models to be used in to reduce uncertainties in extrapolation in risk assessment, while NCEA will address

the scientific basis for using various pharmacokinetic models, particularly as they relate to animal-to-human extrapolation. Research from the STAR program will provide biomarkers of human exposure to pesticides utilizing a new PBPK model and kinetic data for pesticide metabolism in humans.

A second issue concerning harmonization of risk assessments is the use of mechanistic or mode of action data in developing PK/PD models to predict internal dose or effects in animals and humans exposed to cancer or non-cancer-causing agents. The APG to “Identify Pharmacokinetic / Pharmacodynamic Issues Underlying Extrapolation” in FY08 focuses on developing the scientific basis for using PK and PD modeling in a more coordinated and cohesive manner in cancer and non-cancer risk assessments. In FY02, NHEERL will report on key components and parameters necessary for inclusion of mechanistic data in PK/PD models for risk assessment. This research will be followed by an interim report in FY06 on the development of such models, which will be followed by a summary report in FY08 on the application of such models in risk assessment, especially as it relates to harmonized approaches for animal to human extrapolation. Information on the use of mechanistic data to develop PK/PD models for cancer and non-cancer endpoints will be critical for developing a harmonized approach for risk assessment in the future.

A key element ORD’s research program on human health is the ability to link external exposure to internal dose to adverse effect in humans. Understanding these linkages requires the development of an integrated, multi disciplinary research approach involving two or more Laboratories or Centers in ORD. For example, discussions between researchers at NHEERL and NERL have led to the development of an integrated modeling approach consisting of the ability to incorporate human exposure data with specific physiological information concerning absorption, distribution, metabolism, and excretion. Information obtained from animal experiments can also be taken into consideration since physiological modeling has the potential to account for scaling across species. This approach could facilitate the ability to link exposure and dose data, evaluate differences between species and reduce uncertainties in the risk assessment process. In addition, once an integrated model has been validated for a specific chemical, the information can be applied to chemicals having similar modes or mechanisms of action and be used to evaluate interactions between multiple chemicals.

NERL and NHEERL are working together to develop an integrated model of exposure and dose applied to selected environmental pollutants. A research program was initiated in FY02 linking selected components of a stochastic human exposure model (SHEDS) with an exposure-related, dose-estimating model (ERDEM), a physiologically-based pharmacokinetic (PBPK) model. The collaborative research project between NERL and NHEERL involves taking the output from the SHEDS model and translating it in such a way as to link it to input files that could be processed by ERDEM. The objective of this effort is to automate the conversion process for future use with environmental pollutants. The NERL-NHEERL collaboration marks the first time that exposure and dose models have been integrated to predict a complete scenario in a target population exposed to widely used environmental pollutants. This process provides an example of sustained cooperation between the exposure and effects laboratories in ORD. Program offices such as OAQPS and NCEA within ORD have expressed interest in examining the potential of these integrated models to support dosimetry assumptions during the risk assessment process.

Utility of Emerging Technologies in Harmonization of Risk Assessment

It is likely that a key element of research on the use of mechanistic data in risk assessments will be the application of emerging technologies to identify and characterize key events in toxicity pathways underlying cancer and non-cancer effects. For example, methods and approaches based on proteomics and genomics will likely prove crucial in testing hypotheses concerning toxicity pathways of chemicals that produce both cancer and non-cancer effects. The APG in FY08 to “Determine Utility of Emerging Technologies” will determine the extent to which these emerging technologies could be used to inform mechanistic questions in risk assessment. Of particular concern will be approaches to quantify changes in gene and protein expression in toxicological studies and the generation of a framework for the interpretation of such changes in a risk assessment context. Research from NHEERL will employ proteomic and genomic methods to study changes in toxicity pathways. Mechanistic research from STAR grantees will be summarized in a symposium and in papers on the applications of mechanistically based biomarkers and on the importance of receptor-mediated metabolism of chemicals to improving risk assessment.

A summary on the use of emerging technologies for risk assessment will be provided in FY08. As discussed below, this work is linked to research being projected by the Computational Toxicology Initiative in that information on toxicity pathways developed for relevant classes of compounds will be used to generate a library of databases that could be used to develop in silico approaches for the prioritization of chemicals for screening and testing. Emerging technologies will also be important for the development of biomarkers of effects, exposure and susceptibility. The APM “Summary report on the use of emerging technologies in risk assessment” by NHEERL in FY08 will serve as a synthesis document for this work.

The Use of Mechanistic Data to Provide a Framework for Harmonized Risk Assessment

Information derived from work on defining and identifying toxicity pathways, the use of mechanistic data to develop Pharmacokinetic/Pharmacodynamic (PK/PD) models, and the application of emerging technologies for risk assessment will be used to support an APG in FY12 to “Provide the Scientific Basis for the Use of Mechanistic Data in Risk Assessment”. Research from NHEERL will also provide empirical data from prototypic classes of chemicals affecting major biological pathways associated with toxicity, including:

- Cell signaling pathways
- Oxidative stress
- P450 metabolism
- Effects on luteinizing hormone

The objective of these studies is to elucidate key events in toxicity pathways for cancer and non-cancer effects using the best available molecular methods and models to identify possible precursor events and develop a framework for defining and applying mode or mechanism of action information data in risk assessments. Models linking exposure to dose and effect by NERL and NHEERL will also play a major role in developing principles for using mechanistic data in risk assessment. NCEA will sponsor a workshop in FY12 to help develop this unifying framework. The Some questions that will be addressed at this workshop include the following:

- How can mechanistic data at the low end of the dose-response curve inform decisions about the most appropriate risk assessment model?
- How can mechanistic data inform decisions about the presence or absence of a threshold?

- How can mechanistic information lead to a common way of expressing adversity across toxicities in dose-response assessment ?
- How can the use of a consistent response level (i.e., 5 or 10% change) be used to compare across various health effects?
- How can mechanistic information consistently be used to select the point of departure?

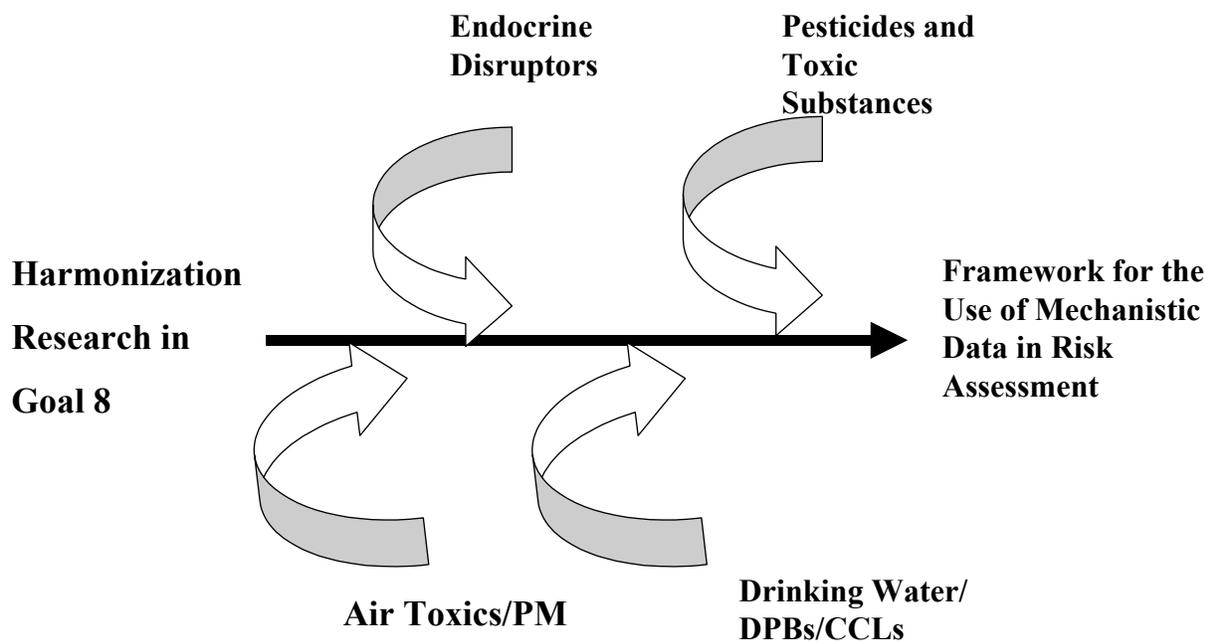
The APM “Summary of research on the use of mechanistic data in risk assessment” in FY12 by NHEERL will serve as a synthesis document for this work.

One of the major goals of the Agency is to better understand the chemicals in our environment and help prevent and reduce exposure of toxic chemicals in humans through regulations and enforcement laws. Once an individual is exposed to a chemical, there is a potential for various disease outcomes to manifest resulting from internal changes within the body. It is not enough to know the nature chemical exposure to protect humans. It can also be very important to determine the complete toxicity pathway or the chemical’s mechanism of action that leads to adverse health outcomes. The knowledge of a chemical’s mechanism of action could provide measurable data on the cellular, biochemical, or molecular level alterations in the biological media, such as human tissues, cells, or fluids. These molecular tests and assays used in the laboratories can be used as biological markers (biomarkers) or indicators to provide better understanding of the disease pathogenesis and allow earlier disease detection. For examples, simple biomarkers (of exposure), such as blood lead, could be measured in body fluids or excreta. Other biomarkers (of effect), based on mechanistic information, could be used to measure the resulting biochemical or physiological changes to target organs that result in adverse health outcomes. Finally, some biomarkers (of susceptibility) could be used to measure genetic or acquired factors that can result in certain adverse outcomes. With extensive understanding of individual chemical’s mode of mechanism, used as biomarkers, baseline information could be formulated for the general (normal) population in different age, gender, or other population groups. Based on the laboratory studies to be conducted to identify the toxicity pathway of chemicals, as discussed in this chapter, the Agency can conduct risk assessments and epidemiological studies to help the communities in US to reduce or prevent chemical exposure in our environment and thus improve the quality of life and health. By identifying critical steps in biological pathways leading to cancer or non-cancer endpoints and determining the biological basis for differential sensitivity to exposure to chemicals, it may be possible to develop sensitive biomarkers that can be used in risk assessment.

In FY03, NCER will sponsor an RFA on research to develop mechanistically based biomarkers which will lead to a subsequent workshop on advancements in biological marker development and papers on new biomarker methods in risk assessment.

Links to Other Research on Human Health and Other Multi-Year Plans

Mechanistic research described in this MYP has significant links to other research programs on human health (i.e., aggregate/cumulative toxicity, susceptible subpopulations), new research initiatives (i.e., computational toxicology), and several other research programs (i.e., endocrine disruptors, air toxics and particulate matter, drinking water, and pesticides/toxics). Information from all of these areas will contribute to the overall goal of developing a framework for the use of mechanistic data in risk assessment (see Figure on next page). The main thrust of the research program on harmonization will focus on the understanding of major toxicity pathways. This will have long-term benefits to risk assessors as information becomes available. Mechanistic problem-driven research supported by other research goals will provide short-term solutions to Regional and Program Office priorities. Taken together, information from harmonization and problem-driven research will provide the basis for generating an overall framework for the use of mechanistic data in risk assessment. Table 1 at the end of this section summarizes linkages between harmonization research and other research on human health, computational toxicology, and problem-driven research goals.



Research on Human Health

Aggregate/Cumulative Toxicity- Congress has mandated that risk assessments take into consideration the combined toxic effects of pesticides and other chemicals with similar mechanisms of action. Harmonization research to identify common modes of action and develop emerging technologies to study mode or mechanism of action is crucial to develop the tools needed to assess cumulative risks associated with exposure to multiple chemicals.

Harmonization research on common modes or mechanisms of action using prototypic chemicals will provide the scientific basis for the use of mechanistic data in risk assessment by identifying key events in specific toxicity pathways that can be used to develop the framework and protocols for assessing the health risks of cumulative exposures. In order to understand principles of how chemicals in mixtures interact, knowledge of modes or mechanisms of action will be imperative. Research on mode or mechanisms of action using prototypic chemicals will also identify key events in specific toxicity pathways that can be used to develop a framework and protocols for evaluating cumulative exposures.

Susceptible Subpopulations - Much of the research on susceptible subpopulations focuses on the biological basis for differential responsiveness to chemical exposure, i.e., life-stage, preexisting disease, genetic predisposition. A crucial determinant in these studies is to know whether the mode or mechanism of action of a chemical is the same in the susceptible

subpopulation as compared to the general population. For example, to evaluate the risks from childhood exposure, it is imperative to know if toxicokinetic factors resulted in an increased concentration of the active chemical at the target site or if key events in the toxicity pathway are of increased frequency or expressed at a higher rate in children. It is also possible that infants or children may have differential sensitivity or susceptibility because a chemical acts on a developmental process that is not present in the adult. Harmonization research on potential common modes of action and identification of key events in representative toxicity pathways from research on harmonization is important in addressing several issues related to susceptible subpopulations, including 1) determining the variation in susceptibility to environmental agents as a result of life stage, health status or genetic predisposition, 2) determining the relationship between adverse health outcomes and exposure to environmental agents in utero and during infancy and childhood, and 3) elucidating the role of environmental agents in the induction and exacerbation of asthma.

Research Initiatives

Agency Genomics Task Force- This Agency-wide task force has asked ORD to take the lead for integrating genomics information into how the Agency performs its risk assessments. ORD is focusing on the application of genomics to improve risk assessment in regulatory decisions. In meeting this challenge, ORD's research to develop emerging technologies will address the need to apply genomic approaches to characterize toxicity pathways to determine human and ecological risks.

Computational Toxicology- The goal of computational toxicology is to integrate modern computing and information technology with the technology of molecular biology to improve the Agency's prioritization of data requirements and risk assessments for toxic chemicals. Computational toxicology techniques have excellent promise for focusing research on reducing uncertainties in both ecological and human health risk assessments. However, use of key predictive toxicology tools/approaches, including PBPK and QSAR models and/or alterations in gene (or protein) expression profiles, is useful only in the context of a thorough understanding of toxicity pathways. Specifically, for these types of predictive methods to be truly useful, it is necessary to link adverse outcomes (e.g., reproductive or developmental changes, cancer) to mechanism of action, ideally through the cascade of biochemical and physiological changes that

occur as a result of the initial interaction(s) of xenobiotics with biological molecules (e.g., receptor binding, enzyme inhibition). A particularly key aspect of this is identification of the proximal (often initial) biological alteration associated with any particular toxicity pathway. For example, chemicals which bind to and activate the androgen receptor elicit a relatively predictable suite of biochemical and physiological responses that are species/class-specific, but culminate in very similar adverse reproductive and developmental effects across (vertebrate) species. Identification of common initiating events, such as receptor activation, can enable the successful use of models or gene expression assays to deal with xenobiotics as classes of compounds rather than individual chemicals. Further, through understanding the cascade of events that occur as a result of receptor activation, in conjunction with accurate dosimetry predictions (e.g., as enabled through simple PBPK models), it would become possible to predict adverse outcomes associated with exposure to, as yet, untested chemicals. For this to be feasible, an understanding of toxicity pathways based on discrete initiating events is imperative.

Definition of toxicity pathways associated with discrete mechanisms of action has a variety of direct benefits and implications germane to the risk assessment process. For example, the ability to associate endpoints with one another through a continuum of biological organization (i.e., across molecular, cellular, target organ and apical endpoints) is powerful both for prospective and diagnostic risk assessments. In the former case, it would be possible to better link responses at intermediate biological levels of organization both to mechanism of action and adverse outcome. In the case of diagnostic assessments, delineation of toxicity pathways would contribute directly to an understanding of the toxicological significance of alterations in biomarkers of exposure based on changes in gene expression. From another perspective, knowledge of key initiating events relative to alterations in endpoints at higher levels of organization could enable a direct assessment of the technical validity of using mixture models based on similar versus dissimilar mechanisms of action. In addition, identification of these events via alterations in gene expression could help in species extrapolation..

Demonstration that toxic mechanisms of action are similar across species (e.g., as indicated by alterations in expression of well-defined gene products) would reduce uncertainty associated with extrapolation across species. Knowledge of common mechanisms of action for a chemical or class of chemicals would focus the challenge of extrapolation across species on comparative dosimetry. However, species can also display unique responses to the same perturbation, and

while the proximate mechanism of action may be identical across species, responses can diverge significantly such that different genes and tissues are affected in different species.

Other Research Areas

Endocrine Disrupting Chemicals (EDCs)(Goal 8.3)- Research on EDCs focuses on estrogenic or androgenic mechanisms or effects that are mediated through the thyroid gland. Approaches to the study of mode or mechanism of action will be important to understand how to: 1) characterize the effects of exposure to multiple EDCs in various combinations such as those with similar and different mechanisms of action, 2) determine the shape of the dose-response curve in a variety of species exposed to ambient levels of EDCs, 3) determine critical biological factors during development resulting in toxicities later in life, 4) determine the degree to which effects of EDCs with defined mechanisms/modes of action can be extrapolated across classes of vertebrates, 5) determine the extent to which exposure to EDCs contribute to onset or increase in severity of diseases, 6) develop standardized protocols for screening chemicals for their potential endocrine-mediated effects to meet FQPA requirements , and 7) develop standardized protocols for testing chemicals for their potential endocrine-mediated effects. Harmonization research will also facilitate the development of emerging technologies involving the use of proteomic and genomic techniques that will be crucial for developing sensitive screens and tests for endocrine disrupting chemicals.

Drinking Water Multi-Year Plan- Harmonization research will provide a sound scientific basis for implementing the arsenic rule and the decision whether or not to propose a revised MCL . Much of the research on arsenic involves the elucidation of the mode or mechanisms of cancer and non-cancer effects and the development of PK models based on mechanistic studies. Harmonization research will lay the scientific groundwork for studies on the mechanisms of carcinogenicity of priority disinfectant by-products (DBPs) and an evaluation of the scientific basis for common modes of action of DBPs and their application to risk assessment. Research to provide a sound scientific basis for the development of the Contaminant Candidate List #3 will also rely on mechanistic data on cancer and non-cancer information generated by research on harmonization. Finally, research to improve data and tools for assessing and managing potential health risks associated with drinking water contaminants will

involve a development of a weight-of-evidence approach based on common mechanisms and toxicity for cumulative risk assessment for drinking water contaminants.

Air Toxics Multi-Year Plan- Research on modes and mechanisms of action will contribute to research in Air Toxics by developing the framework for: 1) estimating human health effects and aggregate exposures to hazardous air pollutants, 2) extrapolating animal- to-human data for selected hazardous air pollutants, 3) determining the shape at low doses of the dose response curve for selected PAHs, 4) determining and testing mode of action methods for characterizing and predicting toxicity of HAPs, 5) characterizing structural and biological factors related to genotoxicity and carcinogenicity for selected HAPs, and 6) developing and applying methods, models and modes of action information to characterize the effects of HAPs and HAP mixtures. Mechanistic data from research on Air Toxics will contribute to the data bases required to develop a framework for the use of mechanistic data in risk assessment.

Particulate Matter (PM) Multi-Year Plan- Harmonization research to develop a framework for the use of mechanistic data in risk assessment will contribute to mechanistic work on PM to describe health effects of PM and its components in normal and susceptible subpopulations and identify mechanisms of toxicity for PM constituents/sources.

Pesticides and Toxic Substances- Harmonization research on potential common modes of action and to develop a framework for use of mechanistic data in risk assessment will be enhanced by planned work on pesticides and toxic substances, including: 1) investigating the assumption of additivity in pesticides with common modes of action and 2) developing tests to assess mode of action of pesticides. Pesticides and Toxic Substances research will also examine mechanisms of developmental toxicity based on mode of action of selected chemicals, explore QSAR/SAR approaches to evaluate pesticides, and develop emerging technologies to characterize reproductive effects of pesticides and toxic substances. Thus, Pesticides and Toxics research will benefit from research to identify potential common modes of action of targeted chemicals and determine the utility of emerging technologies. Harmonization research will also provide chemical-specific information to help develop a framework for the use of mechanistic data in the risk assessment of pesticides.

Table 1. Summary of Links Between Research on Harmonization and Other Research Goals

Harmonization Research	Interconnecting Theme	Associated Research Goal
Identify Common Modes of Action	<ul style="list-style-type: none"> >Determine modes or mechanisms of chemicals to predict mixtures >Biological models of asthma >Determine if mechanism of action is same across different life stages, or predisposing factors such as genetics or disease >Modes of action of pesticides >Identify potential modes of action of chemicals affecting endocrine systems >Mechanisms of air toxics >Mechanisms of PM constituents and sources >Mechanisms of arsenic and drinking water contaminants >Differing modes across species >Identifying toxicity pathways for effects of concern to the Agency >Characterization of selected toxicity pathways 	<ul style="list-style-type: none"> 8.2 Aggregate / Cumulative Risk 8.2 Susceptible Subpopulations 8.2 Susceptible Subpopulations 8.3 EDCs 8.3 EDCs 1 Air toxics 1 Particulate Matter 2 Drinking Water 4 Pesticides and Toxics Computational Toxicology Computational Toxicology
Determine Utility of Emerging Technologies in Risk Assessment	<ul style="list-style-type: none"> >Develop methods to study complex mixtures >Develop molecular techniques to screen and test EDCs >Emerging technologies to characterize reproductive effects of pesticides >Proteomic/Genomic methods to study toxicity pathways 	<ul style="list-style-type: none"> 8.2 Aggregate / Cumulative Risk 8.3 EDCs 4 Toxics and Pesticides Computational Toxicology
Use of Mechanistic Data in Risk Assessment	<ul style="list-style-type: none"> >Principles for using mechanistic data to predict effects of EDCs in mixtures >Develop SAR information to predict chemical effects >Mechanistic data in wildlife as surrogates for effects in humans >Predicting toxicity for HAPs 	<ul style="list-style-type: none"> 8.2 Aggregate / Cumulative Risk, and 8.3 EDCs 8.3 EDCs 8.3 EDCs 1 Air Toxics

	<ul style="list-style-type: none"> >Mechanistic data used in risk assessment of PM >Mechanistic data to support risk assessments of DBPs and CCL >Mechanistic data to predict effects of pesticide mixtures > Toxicity data bases of toxicity pathways 	<ul style="list-style-type: none"> 1 Particulate Matter 2 Drinking Water 4 Pesticides and Toxics Computational Toxicology
Identify PK/PD Issues Underlying Extrapolation	<ul style="list-style-type: none"> >Toxicokinetic factors associated with life stage, genetics, or preexisting disease >Determining PK factors associated with in utero exposures to chemicals >Mechanistic basis for understanding PK interactions between chemicals in mixtures >Mechanistic information to estimate effects of aggregate exposures and interspecies extrapolation >PK pathways for metabolic models used for computational toxicology 	<ul style="list-style-type: none"> 8.2 Susceptible Subpopulations 8.2 Susceptible Subpopulations 8.2 Aggregate / Cumulative Risk 1 Air Toxics Computational Toxicology

Interaction between ORD and Other Agency Offices

Intramural Coordination:

- Individual ORD Laboratories/Center will develop plans to implement the research outlined in this section of the Human Health Multi-Year Plan. These implementation plans should be peer-reviewed by groups incorporating Program and Regional Office staff, e.g., Goal 8 RCT Working Group on Human Health.

- For intramural research, it is assumed that investigator-initiated responses will be consistent with the ORD Human Health Research Strategy, this Multi-Year Plan, and individual laboratory/center implementation plans.

- Research on harmonization will complement mechanistic work supported by the STAR program.

- Coordination within the intramural program is crucial for research that cuts across divisions and branches within ORD and will require coordination and collaboration through individual investigator-initiated collaborations, scientist-to-scientist meetings, and trans-ORD research teams.

- Annual reports of progress and updating of this Multi-Year plan by each ORD Laboratory and Center facilitate integration of research efforts and assist ORD in alignment of research to be consistent with the highest priority areas and help shape the research program to address high priority research needs raised by Program and Regional Offices.

Intramural and Extramural Coordination:

- Integration of the intramural research program with STAR-supported research is important to maintain the balance of research to address cutting-edge, high priority research

needs. This Multi-Year Plan will be coordinated with research priorities outlined in the Human Health Research Strategy and through the STAR program.

- RFAs for extramural research support should be consistent with themes outlined in the Human Health Research Strategy.

- Interactions between recipients of STAR grants and intramural investigators will be encouraged, since it is likely that such an exchange of information would help focus the program and provide opportunities for future collaborations.

Coordination with Program and Regional Offices

- Results will be transmitted to Program and Regional Offices in several ways, including annual briefings, scientist-to-scientist meetings, website information, and providing publications of peer-reviewed products

Summary of Non-Agency Research Supportive of the Long-term Goal

The use of mechanistic data in conducting environmental chemical risk assessments is a scientific challenge unique to the Agency. The challenge for the Agency is distinct from the purpose of other research programs in the US, such as the Food and Drug Administration (FDA) and the National Institute of Environmental Health Sciences (NIEHS) and internationally, such as the Organization of Economic Cooperation and Development (OECD). Through its Toxicogenomics Program, NIEHS focuses on the development of biological networks that can be used by the Agency to help understand gene-environment interactions, while the FDA is moving toward the use of pharmacogenomics to understand genetic susceptibility and response to therapeutic drugs. Principles derived from their studies will complement the Agency's program to develop an understanding of toxicity pathways of environmental chemicals, as well as tailoring emerging technologies to risk assessment questions that encompass issues of effective experimental design, data collection, and interpretation of results for the purpose of risk assessment. The development of information on toxicity pathways for use in risk assessment is a crucial component of the initiative on computational toxicology, which is dedicated to the use of computational methods with knowledge of mechanistic information to meet Agency's data requirements and help establish principles for prioritization of chemicals for screening and testing. In this regard, the Agency is positioned to work with other research groups (e.g., Department of Energy, CIIT Center for Health Research) to develop the area of genomics and proteomics in a risk assessment context.

Potential Additional Work

The Long-Term Goal for the Multi-Year Plan on Harmonization of Risk Assessment is to develop a commonly accepted approach for estimating the risk to human health posed by exposure to toxic chemicals in the environment that incorporates information on biological modes or mechanisms governing their toxicity. The focus of the multi-year plan is to develop a conceptual framework for including mechanistic data in risk assessments for all health endpoints and conduct research to derive a consistent, flexible set of principles and guidelines for using and drawing inferences from scientific information. Research will be done to identify common precursor steps for cancer and non-cancer effects and derive principles for the use of mechanistic data, particularly as it relates to interspecies extrapolation.

It should be noted that because of the resources available, other extrapolation factors (i.e., intrapopulation variability, less-than-lifetime exposures) were not included in the multi-year plan for harmonization. This omission was based on the possibility that some of these factors could be evaluated in other parts of the Human Health Multi-Year Plan or would be covered in some experiments on the use of mechanistic data in risk assessment. Issues related to intrapopulation variability, for example, are addressed to some extent in the Susceptible Subpopulation section of the Human Health Multi-Year Plan. However, none of the APGs/APMs described in the Susceptible Subpopulation component of the Human Health Multi-Year Plan address the problem of different mechanisms of action of chemicals in subpopulations that could contribute to intrapopulation variability.

If 10-20 percent more resources were made available for research on harmonization of risk assessments, results from work on intrapopulation variability could be included in the development of principles for using and drawing inferences from mechanistic data in risk assessments for all health endpoints. The new Long-Term Goal for the multi-year plan on harmonization would be to **“Derive Commonly Accepted Principles for the Use of Mechanistic Data in Risk Assessment, Including Issues Related to Animal-to-Human Extrapolation and Intrapopulation Variability”** .

To accomplish this new Long-Term Goal, it is suggested that an additional **APG** and two **APMs** be included in the multi-year plan for harmonization. The new **APG** would be due in FY10 and would be entitled **“Provide Guidance Concerning the Role of Intrapopulation Variability in Risk Assessment”**. The first **APM** for this **APG** would be a report in FY07 from

a workshop sponsored by NCEA to discuss harmonization of approaches to account for intrapopulation variability (i.e., genetics, preexisting disease) in risk assessments. A second APM in FY09 would be the results of laboratory research from on the influence of intrapopulation variability on risk assessment approaches. The information derived from this **APG** would be linked directly to the **APG** in FY12 to provide the scientific basis for the use of mechanistic data in risk assessment and the second **APG** in FY12 to provide a framework for harmonization of extrapolation factors and mechanistic data in risk assessment. The overall goal of the multi-year plan on harmonization is to develop a conceptual framework for including mechanistic data in risk assessments for all health endpoints and conduct research to derive a consistent, flexible set of principles and guidelines for using and drawing inferences from scientific information. Such a framework should be responsive to differences that exist among various modes or mechanisms of toxicities by which chemicals produce toxicity across subpopulations and the extent of relevant toxicity data available for chemicals.

TABLE HH-H-1: ANNUAL PERFORMANCE GOALS AND MEASURES

GOAL 8.2 Human Health Research (Harmonization)

LONG TERM GOAL. By 2012, develop approach for estimating the risk to human health posed by exposure to toxic chemicals in the environment that incorporates information on biological mechanisms governing their toxicity.

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
APG - Develop framework for defining mode and mechanism of action		2002	ORD
<i>APM</i>	<i>Report on mechanistic studies of the cellular metabolic and signal pathways in transition metal-induced animal airway injury and inflammation and relate to human cell findings (Goal 1 APM Particulate Matter)</i>	<i>2002</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on relationship between molecular structure and effects on the estrogen receptor (Goal 8.3 APM Endocrine Disruptors)</i>	<i>2002</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on the molecular basis for the antiandrogenic effects of some endocrine active environmental chemicals (Goal 8.3 APM Endocrine Disruptors)</i>	<i>2002</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on the molecular mechanisms underlying estrogen receptor functions in ER knockout mice (Goal 8.3 APM Endocrine Disruptors)</i>	<i>2000</i>	<i>NCER</i>
<i>APM</i>	<i>Report on toxicant-induced alterations in mammalian reproductive development to compare dose-response relationships, critical periods of exposure, in vivo tissue levels of the active toxicant and in vivo and in vitro mechanisms of action (Goal 8.3 APM Endocrine Disruptors)</i>	<i>2001</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on GABA-a receptor activation plays a role in endocrine-mediated developmental neurotoxicity (Goal 8.3 APM Endocrine Disruptors)</i>	<i>2001</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on mechanism(s) by which developmental exposure to PCBs disrupts thyroid hormones to produce ototoxicity, characterization of the effects of exposure to mixtures of PAHs and determination of whether non-AH receptor mechanisms underlie the neurotoxicity of some PAHs (Goal 8.3 APM Endocrine Disruptors)</i>	<i>2001</i>	<i>NHEERL</i>

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
APM	<i>Report on mechanisms of EDCs in thyroid carcinogenesis (Goal 8.3 APM Endocrine Disruptors)</i>	2002	NCER
APM	<i>Report on mechanisms of halogenated aromatic hydrogen hydrocarbon toxicity in birds (Goal 8.3 AMP Endocrine Disruptors)</i>	2002	NCER
APM	<i>Report on proof- of-concept for use of a biologically based, dose-response model of a specific, cellular, developmental event to predict the risk of adverse outcome (Goal 8.2 APM 22 Susceptible Subpopulations)</i>	2002	NHEERL
APM	Report from workshop that develops framework of use of mechanistic data in risk assessment	2002	NCEA
APG - Identify pharmacokinetic / pharmacodynamic issues underlying uncertainties for extrapolation		2008	ORD
APM	Report of research to identify key components and parameters for PK/PD models for interspecies extrapolation	2002	NHEERL
APM	<i>Report on metabolism and toxicokinetics of halogenated DBPs and develop biomarkers of effect (Goal 2 APM Drinking Water)</i>	2002	NCER
APM	<i>Report on animal models for mechanistic studies of arsenic carcinogenicity (Goal 2 APM Drinking Water)</i>	2004	NHEERL
APM	<i>Report on physiologically based PK model for arsenic in humans (Goal 2 APM Drinking Water)</i>	2004	NHEERL
APM	<i>Report on routes of metabolism, mode of action, genotoxicity, and carcinogenicity of chlorinated hydrocarbons (Goal 1 APM Air Toxics)</i>	2005	NHEERL
APM	<i>Report on modeling to integrate exposure and dose information from humans and animals for aggregate exposure and risk assessment (Also 8.2 Aggregate)</i>	2006	NHEERL/ NERL
APM	Interim report on PK/PD model for interspecies extrapolation in risk assessment	2006	NHEERL
APM	Summary report on PK/PD for interspecies extrapolation in risk assessment	2008	NHEERL
APG 35 - Identify potential common modes of actions that underlie different toxic effects		2003	ORD

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
APM 104	Report on the use of oxidative stress measurements as broadly applicable indicators of toxicity	2003	NHEERL
APM 105	Report on immunohistochemical methods for the detection of signal transduction activation in vivo in animals and humans exposed to pollutants	2003	NHEERL
APM 106	Report on an experimental model of vascular reactivity to study mechanisms of pollutant-induced cardiovascular effects	2003	NHEERL
APM 107	Report summarizing biological basis for common precursors for cancer and non-cancer effects by prototypic agents	2003	NHEERL
<i>APM</i>	<i>Report on mode of action and carcinogenicity of selected CCL contaminants (Goal 2 APM Drinking Water)</i>	<i>2003</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on mechanisms of carcinogenicity of priority DBPs (Goal 2 APM Drinking Water)</i>	<i>2003</i>	<i>NHEERL</i>
<i>APM</i>	<i>Report on mechanism by which PM and gaseous irritants alone and associated with PM affect pulmonary and cardiac functions and the neurogenic control of those functions</i>	<i>2003</i>	<i>NHEERL</i>
<i>APM</i>	<i>Final report on mechanistic studies of pesticide mixtures and immunotoxicity (Goal 8.2 APM 80 Susceptible Subpopulations)</i>	<i>2003</i>	<i>NCEA</i>
APM	Report from workshop on common modes of action for different toxic effects	2003	NCEA
APG45 - Identify principles for use of scaling factors in risk assessment		2004	ORD
APM 7	Summary of research on PK/PD modeling to account for interspecies extrapolation in risk assessment	2004	NHEERL
APM	Biomarkers of human exposure to pesticides utilizing a new PBPK model and kinetic data for pesticide metabolism in humans	2004	NCER
APM	Report from workshop on scaling factors and interspecies extrapolation	2004	NCEA
APG - Determine utility of emerging technologies in harmonizing risk assessment		2008	ORD

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
<i>APM</i>	<i>Report on biological model (fish) for viewing tissue and organ specific changes in gene expression caused by EDCs (Goal 8.3 APM Endocrine Disruptors)</i>	2001	NCER
<i>APM</i>	<i>Technical report on molecular biological diagnostic indicator methods for EDCs in mixtures (Goal 8.3 APM Endocrine Disruptors)</i>	2003	NERL
APM	Report from human health risk assessment research symposium: Use of mechanistic data in risk assessment	2003	NCER
<i>APM</i>	<i>Report on the sensitivity and reproducibility of estrogen sensitive cDNA macroarray: the effects of life stage and critical environmental factors on gene expression (Goal 8.3 APM 47 Endocrine Disruptors)</i>	2004	NHEERL
<i>APM</i>	<i>Report on mode of action and carcinogenicity of selected CCL contaminants (Goal 2 APM Drinking Water)</i>	2004	NHEERL
<i>APM</i>	<i>Report on molecular methods to identify androgenic and anti-androgenic effects of EDCs in multiple species (Goal 8.3 APM 31 Endocrine Disruptors)</i>	2004	NHEERL
<i>APM</i>	<i>Report on the use of genomics for monitoring expression of health status through analysis of accessible tissues and cells (Goal 8.2 APM Susceptible Subpopulations)</i>	2004	NHEERL
APM	Papers on the applications of human tissue and fluid-based biomarkers in human health risk assessment	2005	NCER
APM	Report on the development and application of emerging technologies to detect changes in signal transduction in vitro and in vivo	2005	NHEERL
<i>APM</i>	<i>Report on utility of molecular profiling in discriminating pollutant responses in animal models exposed to individual and combined atmospheres (Goal 1 APM Particulate Matter)</i>	2005	NHEERL
<i>APM</i>	<i>Report on molecular profiling approach to ascertaining cardiopulmonary effects in healthy animal models after model and ambient PM exposures (Goal 1 APM Particulate Matter)</i>	2005	NHEERL

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
<i>APM</i>	<i>Technical report on development of DNA microarray methods for diagnostic characterization of select EDCs and other model environmental stressors (Goal 8.3 APM Endocrine Disruptors)</i>	2005	NERL
<i>APM</i>	<i>Report on molecular methods to characterize endocrine disrupting effects of environmental chemicals (Goal 8.3 APM Endocrine Disruptors)</i>	2006	NHEERL
<i>APM</i>	<i>Report on gene expression changes correlated with latent adverse health effects of developmental exposures (Goal 8.2 APM Susceptible Subpopulations)</i>	2006	NHEERL
APM	Papers on the importance of receptor-mediated metabolism of chemicals to improving risk assessment	2006	NCER
APM	Report on the use of toxicogenomic and related technologies to define common modes of action of P450 modulating chemicals	2006	NHEERL
<i>APM</i>	<i>Report on potential for molecular profiling approaches for identifying and assessing susceptibility factors in animals exposed to PM (Goal 1 APM Particulate Matter)</i>	2007	NHEERL
<i>APM</i>	<i>Report on gene array data from animal and human polymorphisms and relation to disease susceptibility and underlying oxidative stress (Goal 8.2 APM Susceptible Subpopulations)</i>	2008	NHEERL
APM	Summary report on the use of emerging technologies in risk assessment	2008	NHEERL
APG133 - Provide scientific basis for use of mechanistic data in harmonized risk assessment		2012	ORD
<i>APM</i>	<i>Use of cancer mode of action data of structurally related CCL contaminants in risk assessment (Goal 2 AMP Drinking Water)</i>	2003	NCEA
APM	Report from workshop on potential use of mechanistic data can be used in risk assessment	2004	NCER
<i>APM</i>	<i>Development of a weight-of-evidence approach based on common mechanisms and toxicity for cumulative risk assessment of drinking water contaminants (Goal 2 APM Drinking Water)</i>	2004	NCEA

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
<i>APM</i>	<i>Report of studies on modeling of dose-response curves of prototypic chemicals having similar or different modes or mechanisms of action (Goal 8.2 APM 12 Aggregate/Cumulative Risk)</i>	2004	<i>NHEERL</i>
APM 8	Report on the use of mechanistic data to define common modes of action for risk assessment of P450 modulating chemicals	2004	NHEERL
<i>APM</i>	<i>Evaluation of the scientific basis for common modes of action for reproductive effects of DBPs and their application to risk assessment (Goal 2 APM Drinking Water)</i>	2005	<i>NCEA</i>
APM	Report on developmental neurotoxicity of organotins (trimethyl-, monomethyl-, or dimethyl-, or dibutyltin)	2005	NHEERL
APM	Report on potential increased risk from perchlorate exposure in a rodent model of subclinical iodine deficiency	2005	NHEERL
APM	Report on cancer mode of action of bromate	2005	NHEERL
<i>APM</i>	<i>Report on information on the mechanisms of carcinogenicity of priority DBPs (Goal 2 APM Drinking Water)</i>	2005	<i>NHEERL</i>
<i>APM</i>	<i>Report on mode of action and carcinogenicity of selected CCL contaminants (Goal 2 APM Drinking Water)</i>	2005	<i>NHEERL</i>
<i>APM</i>	<i>Report on method for studying mechanisms of effects in tissue from human subjects exposed to PM (Goal 1 APM Particulate Matter)</i>	2005	<i>NHEERL</i>
<i>APM</i>	<i>Report on generality of mode of action across VOCs and use information to categorize VOCs in terms of neurotoxicity (Goal 1 APM Air Toxics)</i>	2005	<i>NHEERL</i>
<i>APM</i>	<i>Report on structural and biological factors contributing to high POM carcinogenicity (Goal 1 APM Air Toxics)</i>	2005	<i>NHEERL</i>
APM	Technical report on approaches to harmonization of uncertainty factors for cancer and non-cancer risk assessments	2005	NCEA
APM	Report on the range of chemicals that modify regulation of luteinizing hormone	2005	NHEERL

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
APM	<i>Report on the mechanisms of carcinogenicity of priority DBPs (Goal 2 APM Drinking Water)</i>	2006	NHEERL
APM	<i>Develop chemical mechanisms for 33 air toxic compounds that can be used in EPA air quality models to predict ambient concentrations (Goal 1 Air Toxics)</i>	2006	NERL
APM	Report on the mechanisms involved in altering luteinizing hormone	2006	NHEERL
APM	Report on determining common modes of action for developmental reproductive and neural toxicities induced by P450 modulating chemicals	2006	NHEERL
APM	Report on the role of oxidative stress in toxicant specific target organ effects	2006	NHEERL
APM	Report on analyzing and characterizing point of departure for cancer and non-cancer endpoints	2007	N NCEA
APM	Report summarizing use of cell signaling data as common mode of action for harmonization	2007	NHEERL
APM	Report from workshop demonstrating how mechanistic data can be used in risk assessment	2006	NCER
APM	<i>Report on mechanisms of carcinogenicity of priority DBPs (Goal 2 APM Drinking Water)</i>	2007	NHEERL
APM	Report on use of cell signaling data for extrapolation of mode of action information from in vitro to the whole animal	2008	NHEERL
APM	Report on the integration of toxic effects, P450 modulation, structure-activity analysis, and gene expression profiling for application to risk assessment	2008	NHEERL Richard
APM	Report on characterization of cancer and non-cancer reproductive effects following modulation of luteinizing hormone secretion	2008	NHEERL
APM	Report summarizing data from prototypic compounds acting through p450 / XME modulation	2008	NHEERL

ANNUAL PERFORMANCE GOALS AND MEASURES <i>(Note: Italics indicate a linkage with another HH or GPRA area.)</i>		YEAR	LAB/ CENTER
APM	Report on evaluation of risk associated with multiple exposures to chemicals having differential effects on secretion of luteinizing hormone	2010	NHEERL
APM	Report on the use of cell signaling data for extrapolation of mode of action information for interspecies extrapolation	2010	NHEERL
APM	Report summarizing harmonized risk assessment for chemicals modifying luteinizing hormone secretion	2012	NHEERL
APM	Report summarizing risk assessment for chemicals acting by oxidative stress	2012	NHEERL
APM	Summary report on use of cell signaling data for use in harmonization of risk assessment	2012	NHEERL
APG - Provide a framework for harmonization of extrapolation factors and mechanistic data in risk assessment		2012	ORD
APM	RFA on research to develop biologically based markers of cumulative risk of toxins	2003	NCER
APM	Workshop report on advancements of biological marker development for risk assessment	2005	NCER
APM	Papers on new biomarker methods for risk assessment	2007	NCER
APM	Report from workshop to develop a framework for the use of mechanistic information in risk assessment, including extrapolation issues	2012	NCEA

AGGREGATE AND CUMULATIVE RISKS

Introduction

The interrelated fields of quantitative exposure assessment and quantitative health risk assessment are dynamic. Changes in methodologies, approaches and procedures occur in response to changes in the scientific understanding of the physical, chemical, biological and biochemical dimensions characterizing environmental exposures to contaminants, their toxicity, and their mechanism of toxic action. A central aspect of ORD's mission is to continually improve the scientific basis of the Agency's regulatory assessments, determinations and requirements. This section of the Goal 8 Multi Year Plan (MYP) reflects the spirit of this mission in that it describes a research program in the area of aggregate and cumulative risk assessment that will significantly advance the state-of-the science of risk assessment and significantly enhance EPA's efforts to protect human health and the environment.

Background

ORD's research program on aggregate and cumulative risk addresses the fact that people are not usually exposed to a single environmental contaminant by means of a single exposure pathway. Multiple contaminants are released from sources as chemical mixtures. Once released into the open environment, the environmental fate and transformation processes alter the composition and chemical characteristics of mixtures as contaminants move away from the source and through the environment. Individual chemical constituents of mixtures can degrade, transform and persist in environmental media, as well as accumulate into certain biological compartments. These factors effect the nature, pathways and extent of human exposures to environmental contaminants. Exposure by different pathways may result in differential absorption, metabolism, and toxic responses even for the same chemical. Most risk assessments for chemical mixtures rely on single component approaches; however, exposure to multiple chemicals may alter the effect in the target organ in ways not predicted or expected based on the dose-response curves of the single chemicals and assumptions with regard to additivity. There is also concern that toxicity may be seen in unexpected organs. Likewise, different components of a mixture may have different modes or mechanisms of action or multiple mechanisms. Currently, response-addition is the risk assessment default assumption for mixtures of chemicals

with diverse modes of action, thus research is needed to examine the potential for additivity of mixtures of chemicals with different modes of action. Research outlined in this section will provide the scientific support for Agency decisions concerning the potential human health risks posed by exposure to a single contaminant by multiple routes of exposure or to multiple contaminants having a similar mode of action. ORD will also develop approaches to study how people and communities are affected following exposure to multiple pollutants and other stressors that may interact with other environmental stressors.

The development of risk assessment methods during the 1970s and early 1980s closely followed the Agency's strategy for pollution control. Historically, EPA has evaluated the risks of chemicals on the basis of a single pollutant in a single exposure media. In reality, people are constantly exposed to mixtures of pollutants which may come from a variety of sources, including air, water, food, direct contact with contaminant residues on surfaces, and contact with contaminants bound to dusts, soils and sediments. Further, the composition and concentration of pollutants in the environment is constantly changing, depending on people's activities and geographical location. It is now fully understood that exposure to environmental contaminants primarily occurs via multiple exposure pathways, including: direct inhalation of contaminants present in air; ingestion of contaminants present in drinking water; consumption of wild-caught contaminated fish and game; consumption of contaminated farm-raised and store-bought foods; inadvertent ingestion of contaminated soils; and dermal absorption of contaminants upon contact with contaminated media. Research on aggregate and cumulative risk focuses on defining the multitude of ways in which people are exposed to environmental contaminants, quantifying the magnitude, frequency, and duration of these exposures, and characterizing the subsequent effects and risks.

Although aggregate and cumulative risks are difficult to assess, and methods are still under development, Congress has passed legislation requiring the Agency to evaluate risks emanating from total exposure to multiple contaminants and stressors. The Food Quality Protection Act of 1996, for example, requires the EPA to include in its assessment of pesticide safety the risk associated with the cumulative effects of chemicals that have a common mechanism of toxicity, and to consider aggregate dietary and non-occupational sources of exposure. Under the Clean Water Act, the Agency is required to assess risks from exposure to mixtures of disinfectants and their byproducts, and must balance those risks against the risks of

toxic microbes in the drinking water supply. The Air Program needs methods to assess risks from multiple pathways of exposure to mixtures of criteria air pollutants and hazardous and toxic air pollutants. The Waste Program must assess the risks that may be associated with exposures to mixtures of many different chemical classes found together in the soil, water, and air of waste sites and their surroundings. In addition, the EPA's Program and Regional Offices undertake evaluations of communities and subpopulations that may be more highly exposed than average and subject to a variety of other stressors such as poverty, lack of access to medical care, inadequate nutrition, and stresses associated with living near landfills, incinerators, and/or heavy industry.

For purposes of this multi-year plan, aggregate exposure and cumulative risk are defined broadly, in accordance with the working definitions developed by the EPA's Science Policy Council.

- Aggregate exposure is the combined exposure of an individual or defined population to a single agent or stressor via all relevant routes, pathways, and sources.

- Aggregate risk is the risk resulting from aggregate exposure to a single agent or stressor.

- Cumulative Exposure: When exposures accumulate over time, pathways, sources or routes for a number of agents or stressors.

- Cumulative risk is the combined risks resulting from cumulative exposures to multiple agents or stressors.

Basically, there are two general types of risk assessments, those that are chemical-focused and those that are population-based. Chemical-focused assessments start with a source and evaluate how the chemical gets from the source to various populations. Population-based assessments start with the human receptor, and determine what chemicals, stressors, or other risk factors adversely affect the individuals within a well-defined population. Historically, EPA has focused its assessments and regulatory decisions on a chemical-focused approach often looking at a single chemical being released from one source into a single environmental compartment. However, individual and community health status are reflective of all stressors accumulated over time and by all routes of exposure. Thus from a public health perspective, aggregate exposures, cumulative exposures, and cumulative risks are better evaluated using population-based assessments. Several recent reports have underscored the importance of cumulative risk assessments, aggregate exposure assessments, and research on chemical mixtures (NRC 1993,

1994, NAPA, 1995, PCRARM, 1997, USEPA, 2000). Cumulative risk issues raised by the Environmental Justice movement were the basis of Executive Order 12898, 1994.

On July 3, 1997, the Administrator issued a memorandum stating that all major risks assessments should embrace a cumulative approach, taking into account risks that may be associated with total human exposures to multiple chemicals. The Administrator's memorandum included other important risk factors, particularly the social, economic, behavioral or psychological factors that also may contribute to adverse health effects. The memorandum pointed out that assessment of these factors is often hampered by a lack of data to establish plausible cause-and-effect relationships, difficulties in measuring exposure, incidence and susceptibilities related to these risks, and lack of methods for assessing or managing these risks. The Administrator called for Agency guidance on cumulative risk, and the EPA's Risk Assessment Forum started a program to develop such guidance. On September 23, 2002 the Risk Assessment Forum issued a draft *Framework for Cumulative Risk Assessment* (EPA/630/P-02/001A). The research outlined in this multi-year plan supports the Agency's goal of extending the state-of-the-science of human health risk assessment to be inclusive of aggregate and cumulative exposures to mixtures of chemicals that may be present in the environment. To achieve this end and to support EPA's mission, ORD is highlighting important research in this MYP that leads to the near term and future development of methods, guidance, and ultimately EPA guidelines for conducting aggregate and cumulative risk assessments.

Progress has been made over the past two decades toward developing a population-based methodologies, assessments and databases for aggregate and cumulative exposure and risk assessment. Aggregate and cumulative exposure and risk assessment research has been directed at addressing a number of key scientific questions (see text box on the next page) that span across the risk paradigm from source-to-exposure-to-dose-to-effects. All of ORD's aggregate and cumulative exposure and risk assessment research can be identified with one or more of these research questions or themes. The aggregate and cumulative risk assessment research efforts overlap and are not mutually exclusive.

Key Scientific Questions in Aggregate and Cumulative Research

1. What is the nature of the mixtures of contaminants in ambient and microenvironments to which people are exposed?
2. How do we describe the environmental fate and movement of contaminants and mixtures from their sources to the places where people come into contact with them?
3. What are the important factors that determine the extent of human exposure, including people's behaviors and activity patterns, pollutant transfer rates, contact rates, ingestion rates, etc.?
4. How do we best measure and then describe the human behaviors, activity patterns and other exposure factors that are responsible for variability in human exposures?
5. How can we best describe the spatial distribution of contaminants and populations in estimating their exposures, including the use of Geographical Information Systems (GIS) technologies?
6. How can we best measure aggregate and cumulative exposures of individual and multiple chemicals via multiple exposure pathways (ingestion, dermal contact, inhalation)?
7. How can we accurately and realistically model aggregate and cumulative exposures and dose?
8. What data and databases describing the sources, exposure factors, exposures, and body burdens are available to support the accurate exposure assessment for mixtures of compounds?
9. How do we address, and reduce, the uncertainties implicit in extrapolating observed effects in animals to likely effects in humans, and in reducing the overall scientific uncertainties inherent in cumulative risk assessment?
10. What is the most appropriate way to provide the framework and guidance for undertaking cumulative risk assessment?

The following examples highlight some of the progress to date in addressing the important questions / themes in aggregate and cumulative exposure and risk assessment research:

•NERL's Children's Human Exposure Measurements Program is an example of research conducted within themes 3, 4, and 6. Preliminary modeling work was conducted to identify critical data gaps that represented the greatest uncertainty and the greatest potential exposure and risk. Pilot scale field and laboratory studies have been conducted to determine the factors that influence exposures by each route and pathway, with a emphasis on dermal and nondietary exposure routes. Approaches for collecting and mathematically combining data on activity patterns, transfer factors and environmental concentrations to estimate aggregate exposure have been developed and published. Ongoing pilot-scale measurement studies are providing critical information on the exposure factors, exposure pathways, and activities of children in their homes and daycare centers. Beginning in FY '03, NERL is initiating a large-scale study to produce a core set of high quality exposure data for children. This field measurement study will develop distributional data on exposures and exposure factors for children of different ages groups. Results will also be used evaluate age and developmentally-related differences in exposure and to assess the activity patterns that lead to exposure. These data will reduce the reliance on default assumptions for exposure assessments and provide input data to both develop and evaluate exposure models. All data from these studies will be made publically available as part of NERL's Human Exposure Database. NERL will work with NCEA to publish results in the Exposure Factors Handbook.

•The National Human Exposure Assessment Survey (NHEXAS) provides an additional example of research conducted by ORD (NERL, NCEA, NCER) under themes 3, 4, and 6. NHEXAS was designed to provide critical information about multipathway, multimedia (aggregate) population exposure distributions to chemical classes (cumulative exposure). It was a population-based pilot study of the exposure of over 500 people in three areas of the U.S. to metals, pesticides, volatile organic compounds, and other toxic chemicals. Measurements were made of the air people breathed, the foods and beverages they consumed, and the soil and dust in/near their home. Chemicals in their blood and urine were measured. The participants also completed questionnaires to help identify possible sources of exposures and to characterize activities that might contribute to exposure. NHEXAS is the largest multimedia, multipathway, multichemical study of its kind. Key goals included documenting the population distribution of exposure to the chemicals examined, understanding the factors that contribute to high exposures, and improving the accuracy of exposure models. All of the NHEXAS data are available as part of NERL's

Human Exposure Database. Exposure factors generated as part of NHEXAS will be included in the next update of NCEA's Exposure Factor Handbook. Data analysis is being conducted to generate descriptive statistics, evaluate predictors of exposure, examine spatial and temporal variability of exposure, estimate aggregate and cumulative exposure, and evaluate/refine exposure models. Analysis is being conducted by NERL, NCER, and NCEA following the framework developed as part of the NHEXAS Data Analysis Plan.

- Stochastic Human Exposure and Dose Simulation (SHEDS) model and Exposure Related Dose Estimating Model (ERDEM) are examples of research conducted under theme 7 by NERL. The goal of this research is to develop a physically-based probabilistic computer model designed to estimate human exposure, absorbed dose, and eliminated dose. Models also describe the uncertainty and variability associated with the estimates. The SHEDS model provides estimates of aggregate exposures to multiple chemicals through four routes of exposure: inhalation, dermal absorption, dietary ingestion, and non-dietary ingestion. Input data for this model come from a variety of data sets that contain information on human activity patterns, food intakes, and concentrations of pesticides in environmental media. Based on these input databases, the SHEDS model provides time profiles of external exposure by each route. ERDEM, is used to assess internal or absorbed dose based on exposure route and time profile of exposure. This is essentially a pharmacokinetic model that can predict measures of internal dose based on exposure estimates. The level of sophistication of this model varies with the knowledge and data base available for a particular chemical. In its simplest form, it is a classical pharmacokinetic model. In its more sophisticated form, measures of internal dose are estimated using physiologically-based pharmacokinetic models. The ERDEM model has been used to simulate cholinesterase inhibition after exposure to organophosphorus pesticides.

- The LandScanUSA is an example of a GIS-based assessment tool under development within NCEA under research theme 5. NCEA and the Office of Civil Rights (OCR) are collaborating with the Department of Energy's Oak Ridge National Laboratory (ORNL) to develop LandScan USA, a high resolution population distribution database for the continental USA. ORNL has already developed a similar global database called LandScan1998 (updated in 2000) that is unique and innovative. LandScan, the best available global population distribution database, is the first of its kind to use satellite imagery in population distribution modeling to produce population distribution data at a much finer resolution than previously available. LandScan 1998

and 2000 have a grid cell size of 30 seconds (<1 kilometer) and use census data in combination with many other geospatial data, such as land use/cover, topography, slope, roads and nighttime lights, in order to improve the estimation and prediction of the spatial distribution of residential populations. ORNL is developing LandScan USA using similar data layers as in LandScan 1998 and 2000 but with a much smaller grid cell size of 3 seconds (<100 meters). This smaller grid cell size is much more appropriate for the types of risk assessment and exposure modeling work conducted by EPA. Currently, ORNL is conducting a pilot study in a 29 county area in southeast Texas (around Houston and Port Neches) in order to develop the necessary algorithms and identify and resolve issues surrounding development of LandScan USA. Based on this pilot, ORNL plans to complete LandScan USA, which should become a very valuable data resource for EPA and other agencies that need more detailed information on the spatial distribution of the US population.

- The Inventory of Sources and Environmental Releases of Dioxin-Like Compounds of NCEA-directed research under research theme 1. This inventory provides an accurate assessment of environmental releases of dioxins, furans and coplanar PCBs for all known anthropogenic source activities operating in the United States. This Inventory provides a quantitative basis for evaluating population-based exposures to chemical mixtures.
- The National Dioxin Air Monitoring Network (NDAMN) is an example of NCEA-directed research under theme 6. Comprised of 34 monitoring stations geographically distributed throughout the U.S., NDAMN is an attempt to provide seasonal and annual measurements of mixtures of dioxin-like compounds present in rural and background air. The overall purpose of NDAMN is to quantitatively link sources with human exposures.
- The Dioxin Exposure Initiative is a research project of NCEA falling within research theme 6. In September of 1994, NCEA released its first public review draft of the Dioxin Reassessment (DR). This review draft was scrutinized by the public and the Science Advisory Board. At that time, NCEA also announced that it would initiate a Dioxin Exposure Initiative (DEI) to fill critical data gaps regarding the sources of dioxin that contribute to human exposure. The fundamental goal of the Initiative is to quantitatively link dioxin sources to general population exposure. This is being accomplished by pursuing two simultaneous lines of inquiry. One approach is to focus on identifying sources of dioxin-like compounds and work forward along their pathways of transport and deposition. The second is to start with human body burdens and

work backwards through the process of bioaccumulation and uptake. As these two lines of inquiry merge, they should provide an adequate understanding to enable EPA to target future exposure reductions efforts to those sources and pathways that most significantly contribute to human risk. Several projects have been completed, and several are ongoing. The DEI is jointly funded and managed by EPA's Office of Prevention, Pesticides, and Toxic Substances (OPPTS), and ORD. ORD's participants include both NCEA and NRMRL.

- Guidance on Cumulative Risk Assessment is an example of research within theme 10 that is under development within NCEA's Risk Assessment Forum. This is a synthesis of all cumulative risk assessment research in terms of providing guidance on quantitatively and qualitatively evaluating cumulative risks to multiple chemicals/stressors via multiple exposure pathways.

- The Exposure Factors Handbook is an example of research being conducted by NCEA under research theme 6. The Exposure Factors Handbook provides a summary of the available statistical data on various factors used in assessing human exposure. This Handbook is addressed to exposure assessors inside the Agency as well as outside, who need to obtain data on standard factors to calculate human exposure to toxic chemicals. These factors include: drinking water consumption, soil ingestion, inhalation rates, dermal factors including skin area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, homegrown foods, breast milk intake, human activity factors, consumer product use, and residential characteristics. Recommended values are for the general population and also for various segments of the population who may have characteristics different from the general population. NCEA has strived to include full discussions of the issues that assessors should consider in deciding how to use these data and recommendations.

- The Body Burden Database (BBD) is NCEA based research under research theme 8. The BBD is an on-line database which includes data on the concentration of contaminants of concern (pesticides, persistent and bioaccumulative toxics, and others) in body matrices (blood, urine, etc.). All of this data originates from completed studies of high quality, often EPA-sponsored studies and studies conducted by other government Agencies such as CDC, state government institutions, and other institutions such as Universities. Users can view or download the data into Excel files for further perusal. While the BBD contains the measurement data and additional key information on the studies themselves, an important feature of the BBD is that users can

learn more about the studies and obtain further downloads of data from concurrent entries on all BBD studies in EPA's Environmental Information Management System (EIMS). This information database has been developed and is sponsored by ORD, and is also an important component of other on-line information systems such as the Human Exposure Database System (HEDS).

- Human Exposure Database System (HEDS) is NERL directed research under research themes 6 and 8. HEDS 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.
- Consolidated Human Activities Database (CHAD) is an example of NERL directed research under theme 8. CHAD contains data obtained from pre-existing human activity studies that were 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 a master database providing access to other human activity databases using a consistent format. This facilitates access and retrieval of activity/and questionnaire information from those databases that EPA currently has access to-and-uses-in its various regulatory analyses undertaken by program offices.
- The Source-to-Microenvironmental concentration model under development by NRMRL falls under research theme 2. This is a module that will input to overall source-to-receptor-to-effect modeling needed for the cumulative risk assessment of indoor sources of contaminant exposures.
- Research identifying key components and parameters for PK/PD models for interspecies extrapolations from animal to humans. This research is being conducted by NERL and NHEERL under research themes 7 and 9.
- Research to determine the overall health effects of exposures to chemical mixtures is being conducted by NHEERL under research theme 9. This will provide a quantitative basis for the cumulative risk assessment of human exposures to chemical mixtures.

Long-Term Goals

The goal of ORD's research program on aggregate and cumulative risk is to provide methods, models, data and guidance for assessing human health risk so that the EPA can protect the health of the public and environment more effectively. These tools are intended to address issues which arise through public concerns about a specific location or as a result of risk management issues and to enlighten policy decisions about the best ways to minimize exposures and to protect human health. This research area, more than many others, highlights the spectrum of ORD's expertise – utilizing NRMRL's expertise in source characterization, NERL's expertise in exposure, NHEERL's expertise in estimating effects, and NCEA's expertise in putting all of the information together in developing guidance and conducting selective risk assessments.

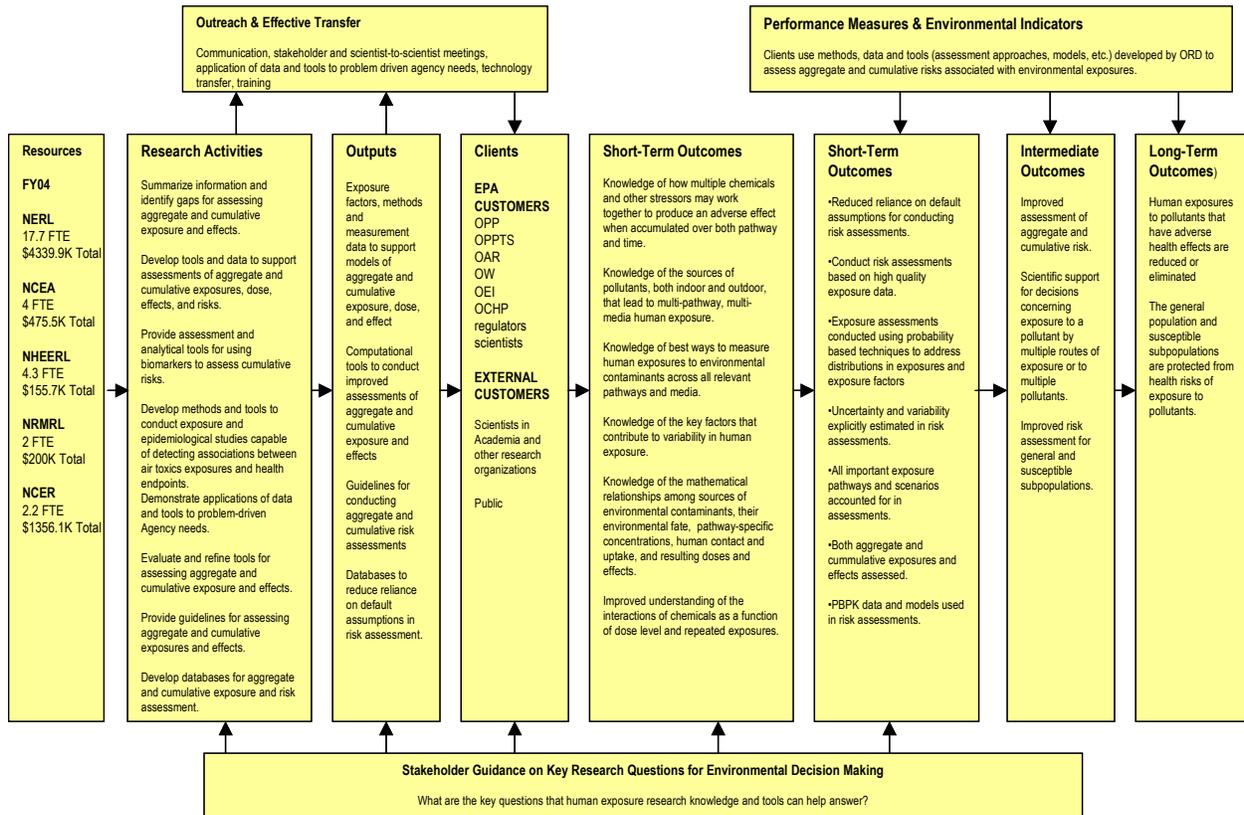
While the goal of this effort is to develop method, data, models, and guidance that can be used in many Agency programs, not all of the research needed is conducted within this program area. Measurements, methods, and model applications are often developed in other program areas to address specific Agency problems (e.g., particulate matter research under Goal 1; children's exposure to pesticides under Goal 3). The developed tools are then incorporated into the products of this core research effort, so that they may find application again in other problem-driven areas. Sound science research for susceptibles and harmonization also contribute to this area.

Two long-term goals have been developed in Goal 8.201 to guide the overall achievement and coordination of aggregate and cumulative risk assessment research.

- 1. By 2008, provide regulatory decision makers with data-based models, risk assessment approached, and guidance that will be used for conducting assessments for aggregate exposure and risks to pollutants that pose the greatest health risks to the American public.**
- 2. By 2012, provide regulatory decision makers with data-based models, risk assessment approached, and guidance will be used for conducting assessments for cumulative exposure and risks to pollutants that pose the greatest health risks to the American public.**

Logic Diagram

Aggregate and Cumulative Risk Assessment



In order to achieve these two long-term goals for aggregate / cumulative risk research – and to ensure that the research products are useful in protecting human health, a number of intermediate outcomes and outputs will need to be attained. The diagram shown below highlights ORD’s partners in this effort, the intermediate outcomes that are desired and the short-term outputs that will help EPA achieve the end result. The relationship between our research program and the achievement of the long-term goals is further explained in the next section.

Annual Performance Goals and Measures

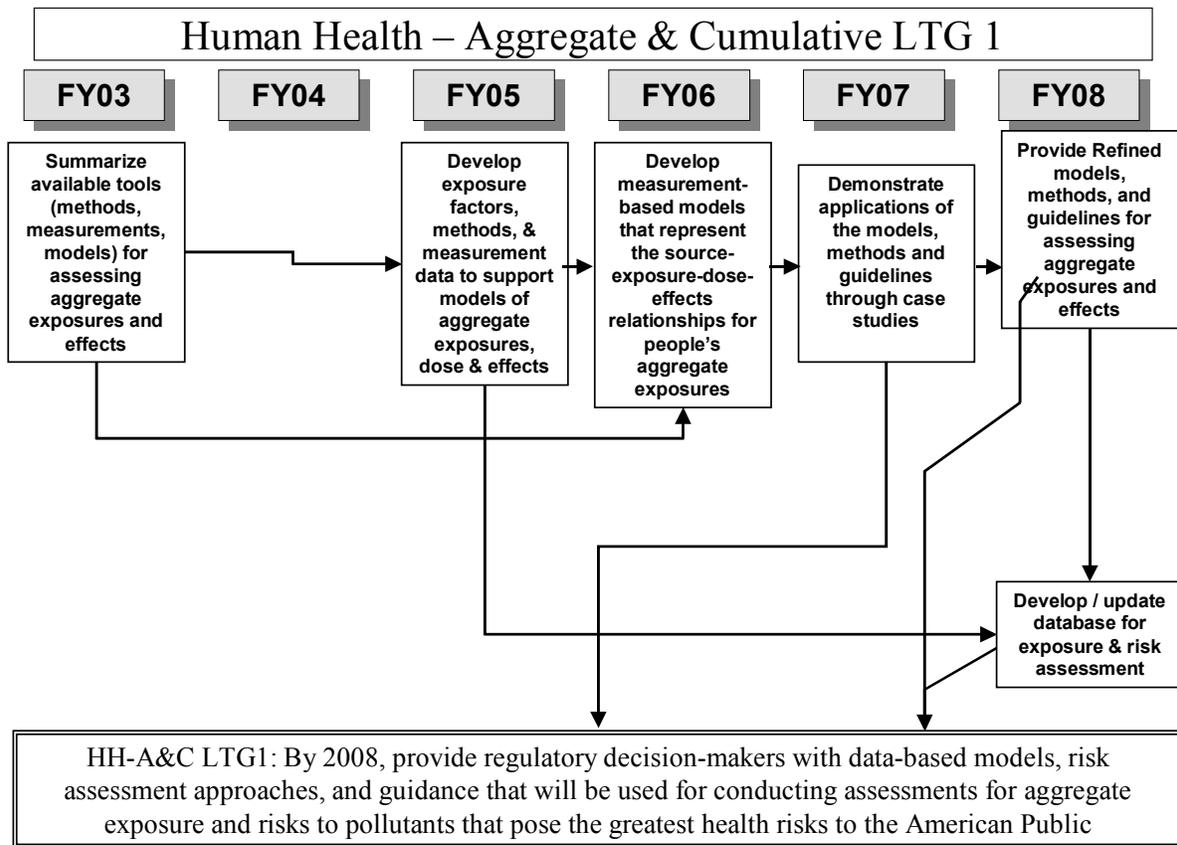
The ultimate goal of ORD’s research in the area of aggregate/cumulative risks is to provide the Agency and the public with reliable methods, tools, and guidance for quantitatively estimating distributions of total cumulative human exposure and risk for both impacted individuals /communities and for the population at large. Because resources are insufficient to carry out all the research needed to reach this goal, ORD’s research is progressive in its development – beginning with simpler issues and expanding to include more complex concepts.

Much of the effort in this area starts by addressing aggregate exposures and risks to single chemicals (especially the development of exposure and dose models and the generation and reporting of data on exposure and exposure factors). The research then expands to consider multiple stressors (both chemical and non-chemical in nature) and the multiple or combined effects of exposure to mixtures of pollutants, *i.e.* cumulative exposure and risk. The research is intended to result in a comprehensive exposure and risk approach to describe how multiple chemicals or other stressors may work together to produce an adverse effect when accumulated over both pathway and time. The research under Long Term Goal 2 will support the effort to develop EPA guidelines for cumulative risk assessment through the Risk Assessment Forum under GPRA Goal 7.

Flow diagrams of the research program to achieve the Long-Term Goals are shown in Figures HH-A&C-1 (for aggregate risk) and HH-A&C-2 (for cumulative risk). Tables describing the Annual Performance Goals and Measures are found at the end of this section.

The Aggregate/Cumulative APGs and APMs reflect a logical step-wise approach. Specific goals and measures start with increasing our knowledge of aggregate (multi-pathway) exposures and risks to single chemicals, and then progressing toward enhanced understanding of multiple chemicals and combined effects (cumulative). The modeling goals ensure that we can integrate that increased understanding into a workable and practical tool for addressing Agency needs in human health. For both the aggregate and cumulative long term goals, the sequence of research with the APGs and APMs is the same.

- a. Assemble available tools and identify major uncertainties,

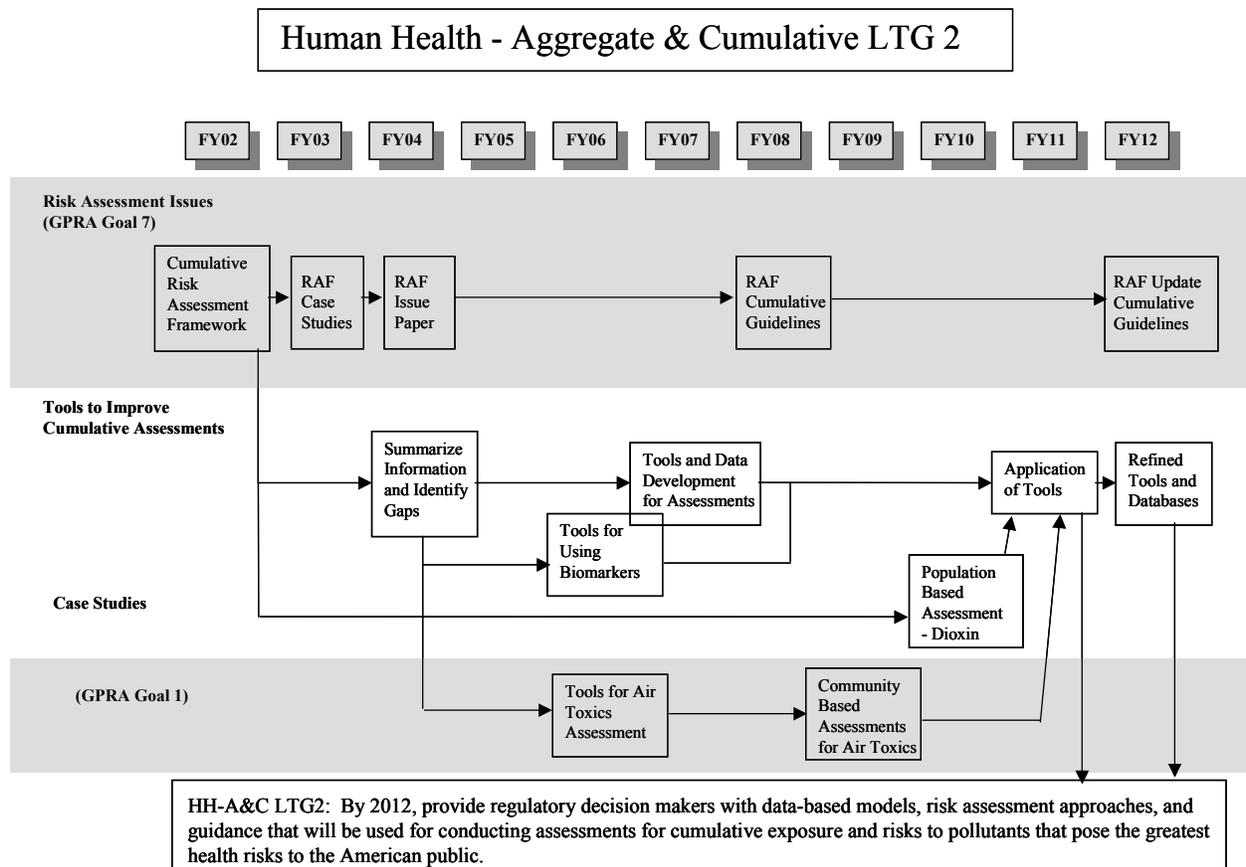


- b. Develop methods and measurement data to support models,
- c. Develop measurement-based models,
- d. Provide Guidance Documents for assessing risks,
- e. Provide a framework for linking models that address different portions of the source-concentration-exposure-dose-effect paradigm
- f. Demonstrate application of the models, framework, and Guidance documents through case studies
- g. Develop/Update Databases for use in Exposure Models

For some of the research in this area (*e.g.*, much of the human exposure research), the distinction between aggregate and cumulative is less significant, since the research is intrinsically multi-chemical to begin with. However, even here, the development is progressive. The human exposure research progresses through an iterative combination of human exposure modeling and human exposure measurements: that is, the model is assembled and used to

identify the areas of greatest risk and uncertainty; measurement studies are undertaken to address the research needs; and the model is refined and applied once again to address Agency problems. The aggregate/cumulative modeling goals are twofold. First, specific models or modules are developed to estimate environmental concentrations, exposures for given concentrations and human activities, or dose from given exposures. Second, frameworks are to link individual models/modules together will be evaluated, refined, and/or developed. A necessary component of a framework is to ensure that different models or modules are compatible with one another so that where needed the output from one module can serve as input to the next. Frameworks are also intended to provide user-friendly tools for combining and modeling across different components of the risk paradigm from source-to-exposure-to-dose-to-effects. In this context, aggregate and cumulative risk assessment research is viewed here as being a totally integrated program that is complimentary and inclusive of research across ORD Laboratories and Centers. Additionally, emphasis is given to close collaboration between and among Laboratories and Centers.

For 2008, ORD has established an initial long term goal of developing models, modeling



frameworks, and the necessary data, methodologies and guidelines needed to describe aggregate human exposures and risks for important classes of pollutants, describing the pollutants fate from source through exposure to dose; and assembling our understanding of aggregate exposures into useful Guidance Documents for conducting assessments of aggregate exposures. By 2012, we intend to extend these tools – our models, our frameworks, our methodologies and guidelines, and our available data – to include cumulative exposure and effects. We also propose to publish additional Guidance Documents for cumulative risk assessments, including the effects of mixtures of chemicals. It is important, however, to note that research on developing cumulative exposure and dose models will be initiated and some of it will be accomplished much earlier than this date. For example, aggregate exposure and dose models being developed by NERL for certain classes of pesticides or metals can be used in some of the near-term Agency exposure or risk assessments requiring estimates for cumulative exposures to these compounds. We expect that the tools developed for aggregate and cumulative exposures will be used as soon as they become available to address important Agency problems (under this or other GPRA Goals). It is intended that the results of these applications will provide case studies to document and refine the modeling frameworks and Guidance Documents to be published in 2007 for Aggregate Assessments and 2011 for Cumulative Assessments.

For cumulative research under Long Term Goal 2, three research tracks are shown. The first track addresses the development of the Guidelines for Cumulative Risk Assessment Guidelines. This work will be performed by the Risk Assessment Forum under Goal 7. The second track describes research for developing and refining the tools and data for individual steps in the risk assessment process. Research in this track follows the sequence of steps described above. The third track includes case studies for conducting cumulative risk assessments across the entire paradigm for source-to-health outcomes. Work in this track will be conducted on dioxins by NCEA. A second set of case studies is proposed through an initiative this is under development for Goal 1 specifically to understand community-based risks to air toxics and other environmental stressors. All of the research conducted under this Long Term Goal is intended to provide the scientific foundation for developing and updating the Cumulative Risk Assessment Guidelines that will be developed by the Risk Assessment Forum under Goal 7.

A look at the tables of APGs and APMs for the Aggregate/Cumulative effort will show how the expertise of the various labs and centers fits together to contribute to the long term

goals. NRMRL's APMs focus on describing the sources of pollutants, both indoor and outdoor, that lead to multi-pathway, multi-media human exposures. They are contributing significantly to the Source component of the Source-to-Dose / Effects modeling framework, and their efforts should contribute substantially in helping to enlighten any regulatory decisions about how to reduce exposure and risks. NERL's APMs focus on producing the modeling framework and the critical exposure data and models. NERL's iterative approach of human exposure modeling and measurements ensures that the models are well grounded in reality and tested against real-world data. The modeling framework, with its associated data base, provides an integrating function, taking advantage of advances made under other GPRA goals and outside EPA. A major goal of the research at NHEERL is to examine those circumstances under which dose-additivity is a reasonable assumption. Included in this effort is the development of efficient experimental designs and statistical methods for mixtures more complex than 2-3 chemicals. NHEERL research focuses on determining the appropriateness and predictive value of response-addition versus dose-addition for various mixtures. An extremely important issue for either component-based or whole mixture approaches is whether the quality, *e.g.*, nature (greater than-, less than-, or additive) or magnitude, of the interactions of chemicals change as the dose level changes or as a function of repeated exposure. NHEERL research focuses on describing the dependence of interaction magnitude on mixing ratio, total mixture dose and on component fractions. Historically, most mixtures research has focused on short-term exposure to higher portions of the dose-response curve where such situations as saturation kinetics might be influencing the interactive outcome. In contrast to this historical situation, NHEERL research will include a targeted focus on the low end of the dose-response range and on repeated exposures. NHEERL research also addresses the problem of determining a threshold response for the endpoint(s) of interest. Included in the dose-response analysis will be dose levels below the apparent threshold of response. These may include doses at or below the No-Observed-Effect-Level or No-Observed-Adverse-Effect-Level of the single chemicals and doses representing either levels found in the environment or at or near the RfD. *In vitro* work will make assumptions regarding the extrapolation of experimental doses to the target site concentration *in vivo*. The work described under the Harmonization section of this MYP also feeds into the cumulative risk assessment research effort: the long term goal under the Harmonization section of developing an accepted set of principles defining how mode or mechanism of action information can be used in

risk assessments will be critically important to the Agency in laying the scientific basis for addressing cumulative risks.

NCEA's APMs focus assembling data and research results from many sources; analyzing and interpreting the data; and developing guidance and methods for conducting and interpreting aggregate and cumulative risk assessments. NCEA's work builds upon itself and draws from many EPA and external contributions. NCER's APMs focus mainly on advancing the science related to the critical, but very difficult, issue of the effects of mixtures. Their grants to external researchers will undoubtedly provide critical information to the cumulative risk assessments. Together, the labs and centers are working to produce useful tools for the Agency and the public in quantitatively assessing cumulative human exposures and risks. These tools – the modeling framework, the guidance documents, and the supporting data – will enable EPA to better protect human health and to make better, more scientifically-sound, regulatory decisions.

Summary of Non-EPA Research

A variety of federal agencies are conducting research related to aggregate and cumulative risks. For example, the Centers for Disease Control has published, and will continue to update, a “National Report on Human Exposure to Environmental Chemicals.” This report, associated with CDC's National Health and Nutrition Examination Survey (NHANES), measures the presence of a number chemicals or their metabolites in the blood or urine of the participants. Unfortunately, such measures simply define the level of a chemical in biological fluids: they do not describe how or why the chemical came to be present, whether they will cause a health impact, nor do they illuminate approaches to mitigate the resultant risks. To address this shortcoming, an initiative funded for FY03 will develop methods, models and data that will allow us to predict exposure and exposure sources for the biomarker data developed by CDC. As part of the research proposed under Susceptibles, EPA is working with NICDH, NIEHS, and other federal agencies to develop method and conduct the National Children's Study. This study is a longitudinal epidemiological study that will evaluate the health outcomes for children resulting from cumulative exposures to chemicals and other stressors. Additional collaborative research is being conducted with ORD and nongovernmental organizations. Research partnerships have been developed with the American Chemistry Council to conduct analysis of

NHEXAS data to further elucidate the important determinates of aggregate and cumulative exposures and to collect additional data on children's exposure to chemical contaminants.

Goal 8.2 – Aggregate / Cumulative Risk

LTG 1: By 2008, provide regulatory decision makers with data-based models, risk assessment approaches, and guidance across the risk paradigm that will be used for conducting assessments for aggregate exposure and risks to pollutants that pose the greatest health risks to the American public.

APG 33- Summarize available tools (methods, measurements, models) for assessing aggregate exposures and effects.		2003	ORD
APM 29	Publish data and results from the National Human Exposure Analysis Survey (NHEXAS) that will help characterize exposures to key pollutants and summarize exposure factors that can be used by the Agency to improve exposure and risk assessments	2003	NERL
APM 28	Test, evaluate and refine modeling Framework that integrates modules from Source through Exposure to Dose so that EPA can produce improved assessments of aggregate exposure and risks.	2003	NERL
APM 27	Launch the HEDS (Human Exposure Database System) web site and provide access to human exposure data via the world wide web Program Offices, Regions, States, exposure modelers and other stakeholders for conducting aggregate and cumulative risk assessments	2003	NERL
APM	Evaluate novel statistical and other analytical methods for assessing exposure using existing exposure related behavioral and environmental data.	2003	NCER
APG -Develop exposure factors, methods and measurement data to support models of aggregate exposures, dose, and effects.		2005	ORD
APM 30	Complete field monitoring portion of the “Children’s Total Exposure to Pesticides and Persistent Organic Pollutants (including EDCs) Study” which will provide the Agency with critical data to substantially improve aggregate exposure assessments for young children.	2003	NERL
APM 141	<i>Evaluation of validity of route-to-route extrapolation for selected air toxics with a HAP group (Goal 1, Air Toxics)</i>	2004	NHEERL

APM 218	<i>Conduct analysis of the “Children’s Total Exposure to Pesticides and Persistent Organic Pollutants (including EDCs) Study” to estimate aggregate exposure and identify critical exposure factors that can be used by the Agency to improve exposure and risk assessments (Also Goal 3); Note, the APM is listed under Susceptible Subpopulations, APG 44.</i>	2004	NERL
APM	Conduct analysis of existing data for assessing aggregate human exposure to environmental toxins for exposure assessors and modelers in EPA, industry and state and local governments	2004	NCER
APM	Develop exposure factors for use in aggregate assessments	2004	NCEA
APM	Compile exposure factors, methods, and measurement data to be used by EPA exposure modelers and risk assessors to substantially improve aggregate exposure assessments.	2005	NERL
<i>APM 107</i>	<i>External review draft of an updated Exposure Factors Handbook for Children, incorporating new data from ORD-supported studies. Note: APM is formally listed under Susceptible Subpopulations, APG 44, as APM 107.</i>	2005	NCEA
APM	Papers on novel analyses of existing human exposure data for assessing potential risks from exposure to environmental toxins for risk assessors in EPA, state and local governments and industry	2007	NCER
APG – Develop measurement-based models and modules that represent the source-exposure-dose-effect relationships for aggregate exposures.		2006	ORD
APM	Develop model components to estimate exposure and dose to environmental contaminants for EPA to use in conducting assessments of aggregate exposure and risk.	2005	<i>NERL</i>
APM	Development and demonstrate a method for assessing exposure to particle-borne contaminants in indoor air due to resuspension from flooring surfaces	2005	NRMRL

APM	Evaluate prototype version of Source Modules for aggregate exposure modeling of indoor sources / source types, using available models / data. Include non-indoor sources as possible.	2005	NRMRL
APM	<i>Report on modeling to integrate exposure and dose information from humans and animals for aggregate exposure and risk assessment (Also 8.2 Harmonization)</i>	2006	NHEERL/ NERL
APG - Demonstrate applications of the models, methods, and guidelines through case studies and chemical assessments.		2007	ORD
APM	Demonstrate use of exposure factors.	2005	NCEA
APM	Report on aggregate pollutant exposure potential to humans from weathered cumulative toxic chemical residues in soil.	2006	NCEA
APM	Apply human exposure and dose model components in priority areas identified by Program Offices and regions to evaluate models and provide aggregate exposure assessments for environmental decision making (usually applied in other areas / headings, like Goal 1, Goal 3, or Goal 8.2-Susceptibles).	2007	NERL
APM	Demonstrate use of dermal assessment methods.	2007	NCEA
APG- Provide Refined models, methods, and guidelines for assessing aggregate exposures and effects			
APM	Refine Source Module for aggregate exposures, based on analyses of targeted source emissions measurement characterization / model development programs.	2007	NRMRL
APM	Provide evaluated exposure and dose modeling tools to conduct aggregate exposure assessments to be used by the Program Offices as part of the environmental decision-making process.	2008	NERL
APM	Link Source Module with exposure modules for use by Program Offices and public to conduct aggregate assessments	2008	NRMRL
APG -Develop/Update database for exposure and risk assessment		2008	ORD

APM	Launch the HEDS (Human Exposure Database System) web site and provide access to human exposure data to Program Offices, Regions, States, exposure modelers and other stakeholders for conducting aggregate risk assessments. (APM 27 Under APG-33)	2003	NERL
APM	Make the Body Burden Database (BBD) available to the public as a live, on-line searchable database on the body burden measurements of pesticides, PBTs, and other contaminants of concern.	2006	NCEA
APM	Incorporate NERL's human exposure measurement data into a comprehensive data base so that Program Offices, Regions, States, exposure modelers and other stakeholders have access to high quality, high quantity data for aggregate risk assessments	2008	NERL
<i>APM</i>	<i>Publish updated Exposure Factors Handbook (includes efforts under Human Health–Susceptibles).</i>	<i>2008</i>	<i>NCEA</i>

Goal 8.2 – Aggregate / Cumulative Risk

LTG 2: By 2012, provide regulatory decision makers with data-based models, risk assessment approaches and guidance across the risk paradigm that will be used for conducting assessments for cumulative exposure and risks to pollutants that pose the greatest health risks to the American public.

<i>Risk Assessment Issues -</i>			
<i>Goal 7</i>	<i>Risk Assess Forum Case Studies for assessing Framework for Cumulative Risk Assessments</i>	<i>2003</i>	<i>NCEA</i>
<i>Goal 7</i>	<i>Risk Assessment Forum Issues Paper to evaluate and identify knowledge gaps in Framework for Cumulative Risk Assessments</i>	<i>2004</i>	<i>NCEA</i>
<i>Goal 7</i>	<i>Publish EPA's Cumulative Risk Assessment Methodology</i>	<i>2008</i>	<i>NCEA</i>
<i>Goal 7</i>	<i>Updates of EPA's Cumulative Risk Assessment Methodology</i>	<i>2012 and beyond</i>	<i>NCEA</i>
Tools to Improve Cumulative Assessments (Analytical portion)			
(APG 37) Analysis of needs and research strategy for developing tools and data to characterize cumulative exposure/risks for pesticides		2004	ORD
<i>Goal 7</i>	<i>Risk Assess Forum Case Studies for assessing Framework for Cumulative Risk Assessments</i>	<i>2003</i>	<i>NCEA</i>
<i>APM</i>	<i>Report of research to identify key components and parameters for PK/PD models for interspecies extrapolation (from HH-Harmonization)</i>	<i>2002</i>	<i>NHEERL</i>
<i>APM</i>	<i>STAR Workshop on predictive approaches for assessing risks from mixtures of chemicals.</i>	<i>2003</i>	<i>NCER</i>
<i>APM</i>	<i>Identify potential common modes of actions that underlie different toxic effects (HH-Harmonization APG)</i>	<i>2003</i>	<i>ORD</i>
<i>Goal 7</i>	<i>Risk Assessment Forum Issues Paper to evaluate and identify knowledge gaps in Framework for Cumulative Risk Assessments</i>	<i>2004</i>	<i>NCEA</i>
<i>APM</i>	<i>Evaluate screening and other methods for evaluating the genotoxic effects of some metal/metal and metal/organic mixtures in OSWER and OPPT</i>	<i>2004</i>	<i>NCER</i>

APM	Evaluate innovative statistical computational and predictive approaches for assessing risks from mixtures for risk assessors in OSWER, OPPTS, OW	2004	NCER
APM	Summarize available tools (methods, measurements, models) for assessing cumulative exposures and effects	2004	NCEA
APM 228	Using current modeling tools, identify exposure measurement studies to provide critical data needed for exposure models that will be used by the Agency to conduct cumulative risk assessments	2004	NERL
APM 215	<i>Research plan for developing and evaluating data and tools for cumulative exposures for pesticides conducted by the Agency and others in the scientific community (Goal 3 APM)</i>	2004	NERL
APG	<i>Identify principles for use in scaling factors in risk assessment. (HH-Harmonization APG)</i>	2004	ORD
APG- Develop Tools and Data to Support Assessments of Cumulative exposures, dose, effects, and risks		2009	ORD
<i>Methods</i>			
APM	Develop approaches for characterizing cumulative exposures in field studies that will provide high quality exposure data to be used by the agency in conducting cumulative risk assessments	2005	NERL
APM	Peer reviewed journal publication comparing LandScan USA (a GIS data set and tool) to census data for calculating populations at risk for daytime and nighttime.	2005	NCEA
APM	Provide new or refined methods to the Agency and scientific community for measuring pollutant concentrations in environmental samples that will be used in field studies to provide high quality data for cumulative exposure assessments	2005	NERL
APM	Provide a framework for structuring evaluations of the toxicity of complex chemical mixtures for use in human health and environmental health assessments for risk assessors in OSWER and OPPT	2005	NCER

APM	Workshop report on human activity pattern survey platforms and approaches for risk assessors in EPA, state and local governments and industry	2005	NCER
APM	Papers on the feasibility of novel sampling platforms for collecting behavioral data for exposure assessors in EPA, industry and state and local governments	2008	NCER
APM	Develop/refine biomarker methods that can be used to generate measurement data on multiple exposures which will enhance, refine, and verify the Agency's cumulative risks assessments.	2008	NERL
APM	Develop Protocol for characterizing cumulative exposures in field studies that will provide high quality exposure data to be used by the agency in conducting cumulative risk assessments	2008	NERL
<i>Models</i>			
<i>APM</i>	<i>Analysis of existing children's exposure data to identify important factors for characterizing cumulative exposure to pesticides and other environmental contaminants. (Goal 3)</i>	<i>2006</i>	<i>NERL</i>
APM	Develop models to estimate exposure and dose to a set of environmental contaminants of concern so that EPA can conduct assessments of cumulative exposure and risks.	2007	NERL
APM	Report on dose modeling to estimate the critical timing and sequencing of exposures for assessment of cumulative risk	2009	NERL
<i>Data</i>			
APM	Report on important activity patterns and exposure factors and how they change over time.	2008	NERL
<i>APM</i>	<i>Provide analysis and critical measurement data needed for exposure models that will be used by the Agency to conduct cumulative risk assessments (data would be generated under other GPRG Goals or other parts of HH research.)</i>	<i>2009</i>	<i>NERL</i>
APM	Publically available data bases of human activity patterns, pesticide and product usage, and dietary consumption patterns risk assessors in EPA, state and local governments and industry	2009	NCER
<i>Toxicity Studies</i>			

APM 9	Report on studies examining interactions of carbamate pesticides in mixtures	2004	NHEERL
APM 10	Complete analysis and report on full factorial 5x5x5 study of effects of three diverse chemicals on several non-cancer endpoints	2004	NHEERL
APM 11	Report on cumulative risk of exposure to two high use pesticides on female reproductive system	2004	NHEERL
APM 12	Report of studies on modeling of dose-response curves of prototypic chemicals having similar or different modes or mechanisms of action.	2004	NHEERL
APM	Report on interactions between persistent toxicants with similar modes of action in neuronal cultures	2005	NHEERL
APM	Reports on effects of disinfectant by product mixtures in vivo and in vitro	2005	NHEERL
APM	Develop parameters to model dose-additivity for mixtures of organophosphate and carbamate pesticides	2005	NHEERL
APM	Develop in vitro methods to predict interactions of persistent environmental toxicants, including polybrominated biphenyls and dioxins	2005	NHEERL
APM	Demonstrate effects of pesticide mixtures after repeated dosing scenarios in vivo are different than those follow short-term exposure	2006	NHEERL
APM	Reports on studies to predict interactions between persistent environmental toxicants, including polybrominated biphenyls and dioxins	2006	NHEERL
APM	Proceedings from workshop on the principles of dose additivity and response-additivity to predict interactions between chemicals with similar and dissimilar modes of action, respectively.	2006	NHEERL
APM	Reports on studies to predict interactions between environmentally relevant mixtures of pyrethrins	2007	NHEERL
APM	Summary report on methods and models to predict interactions of mixtures of environmental chemicals in vivo and in vitro	2008	NHEERL

Risk Assessment Methods

APM 78	<i>Development of screening Methodology for Cumulative Risk - Case Study (under 8.2.1 Manage Environmental Hazards)</i>	2003	NCEA
APG -Provide Assessment and Analytical tools for Region and Program Offices in using biomarkers for assessing and addressing cumulative risks		2006	ORD
APM	Develop PBPK models for using exposure, biomarker, and pharmacokinetic data in risk assessments.	2006	NERL
APM	Assess approaches for relating biomarkers in blood and urine to the exposure scenarios and factors leading to observed high body burdens.	2006	NERL
APM	Report on promising new biomarkers of exposure and effects	2006	ORD
APM	Report correlating NHANES body burden measurements with effects, and evaluating co-occurrence of pollutants in bodies.	2007	NCEA
APG- Application /Evaluation of Tools		2012	ORD
APM	Report on ball clay exposure to artists in ceramics studio.	2004	NCEA
APM	<i>Pyrethroid Project (goal 3)</i>	2005	ORD
APM	Report summarizing use of EPA air monitoring data in conjunction with NHANES III health effects data (collected from 1988-1994) to examine risks from cumulative exposure to NAAQS pollutants	2006	NCEA
APM	Report on the prediction of interactions of persistent toxicants in vivo based on principles developed in vitro	2008	NHEERL
APM	Publish EPA's Cumulative RA Guidelines	2008	NCEA
APM	Proceedings from a Workshop on the use of response additivity to predict interaction of chemicals having different mechanisms of action	2009	NHEERL
APM	Apply and evaluate human exposure and dose model components in priority research areas identified by Program Offices and regions to provide cumulative exposure assessments for environmental decision (usually applied in other areas/headings, like Goal 1, Goal 3, and Goal 8.2 - Susceptibles)	2011	NERL

APG - Refined Tools/Databases		2012	ORD
APM	<i>Incorporate new data on time activity pattern, exposure factors, and exposure in to HEDS so that Program offices, Regions, States, exposure modelers and other stakeholders have access to high quality data for cumulative exposure assessments (Case studies to be conducted under other GPRA goals or other components of Human Health research.)</i>	2011	NERL
APM	Chemical mixtures report on the use of dose-additivity to predict interactions of chemicals with a common mode of action, and use of response additivity to predict interaction of chemicals having different mechanisms of action	2011	NHEERL
APM	Refine and incorporate Source Module into ORD source-cumulative exposure-effects model, and document use of the Source Module for Program Offices and public.	2011	NRMRL
APM	Peer review and publish refined versions of Human Exposure and Dose modeling tools that can be used to conduct cumulative exposure assessments for environmental decision making.	2012	NERL
Case Studies			
APG - Population-based Assessment - Dioxin		2010	NCEA
APM	Completion of the 2000 Dioxin Inventory (on books)	2003	NCEA
APM	Report on the contribution of major and minor components of animal feed to animal exposures to dioxin-like compounds	2005	NCEA
APM	Report on the testing and application of the RELMAP Model to dioxin-like compounds.	2005	NCEA
APM	Peer-reviewed publication in a scientific journal on the assessment of dioxin-like compounds present in rural background air in the US as derived from the National Dioxin Air Monitoring network	2005	NCEA
APM	Report comparing dioxin air dispersion models.	2006	NCEA

APM	Peer reviewed publication in a scientific journal demonstrating use of LandScan USA in Texas to count populations at risk, both daytime and nighttime, from cumulative exposures to air pollutants	2006	NCEA
APM	Report on field study to measure dioxin/PCB emissions from landfills and various types of fires.	2007	NCEA
APM	Quantitatively link sources of dioxin release to human exposures in the United States	2010	NCEA
Community-Based Assessment - Air Toxics			
PROPOSED INITIATIVE IN GOAL 1			
APG - Develop the methods and tools need to conduct exposure and epidemiological studies so that these studies are capable of detecting associations between air toxics exposures and health endpoints.		2006	ORD
APM	In animal and human clinical studies, identify the types of health risks associated with acute exposure to selected individual hazardous air pollutants.		NHEERL
APM	In selected communities, identify three prevalent and potentially high-risk acute exposure scenarios to mixtures of hazardous air pollutants.		NHEERL, NERL
APM	In animal and human clinical studies, identify the types of health risks associated with acute exposure to selected mixtures of hazardous air pollutants.		NHEERL
APM	Develop methods and models to classify exposure at the community level for use in epidemiological studies.		NERL
APG - Define the scope of the air toxics problem by conducting cumulative risk assessments in 5 communities to identify the critical factors driving the risks in these communities for air toxics.		2009	ORD

SUSCEPTIBLE AND HIGHLY EXPOSED LIFE STAGES AND SUBPOPULATIONS

Introduction

Over the next five to ten years, ORD's research on susceptible and highly exposed life stages and subpopulations will address the impact of variations in exposure and biological response on health risks. Research will provide the scientific support for conducting risk assessments that consider the vulnerabilities of susceptible and highly exposed life stages and subpopulations. Variation in biological susceptibility depends upon intrinsic factors, such as life stage, gender, genetic factors, and physiological state, and upon extrinsic or acquired factors, such as preexisting disease, activity levels, nutrition, stress, licit and illicit drug use, cigarette smoking, and alcohol use. Life stage, gender, occupation, geographic location, and other intrinsic and acquired characteristics may also identify distinct groups in the population with the potential for high exposure to specific environmental agents. ORD research on susceptible and highly exposed life stages and subpopulations will focus on developing a scientific understanding of the reasons for differences in exposure and response of selected groups within the general population. The impact of life stage, genetic background, and health status, as evidenced by nutritional status and preexisting disease, will be investigated.

Background

ORD has been conducting research on the first theme, vulnerabilities associated with developmental life stages, since the early 1990s. In 1994, the National Research Council's (NRC) report, *Science and Judgment in Risk Assessment* (NRC, 1994), identified variability in exposure and susceptibility as an important area where human health risk assessments could be improved. In its draft *Human Health Research Strategy* (U.S. EPA, 2002a), ORD identified susceptible and highly-exposed groups, defined by life stage, genetic factors, or health status, as one of four major areas of its human health research program. In 1993, NRC issued the report, *Pesticides in the Diets of Infants and Children* (NRC, 1993), addressing differences between children and adults in exposures and susceptibilities to pesticides. In 1996, Congress enacted two statutes requiring that EPA consider children and other potentially susceptible groups when setting health-based standards: the Food Quality Protection Act of 1996 (FQPA) and the Safe Drinking Water Act (SDWA) Amendments of 1996. Subsequently, EPA expanded its ongoing

research into susceptible and highly exposed life stages and subpopulations through 1998 and 2000 initiatives on children’s environmental health. In 2000, ORD published its *Strategy for Research on Environmental Risks to Children* (U.S. EPA, 2000), and in 2002, the Administrator released the *EPA Asthma Research Strategy* (U.S. EPA, 2002b), which addresses an endpoint of particular concern for children. Key science questions identified in the EPA strategy documents are summarized in Table HH-SS-1. In 2002, the EPA Administrator also announced that EPA is developing an Aging Initiative that will result in a national agenda designed to examine and prioritize environmental health threats to older persons.

Table HH-SS-1. Summary of Key Science Questions from US EPA Strategy Documents

<p><u>Key Science Questions for Research on Environmental Risks to Children (U.S. EPA, 2000)</u></p> <ul style="list-style-type: none"> •What are the effects from children’s exposures to environmental agents that are different from effects in adults? •What are the periods of development when exposure to environmental substances can cause adverse health effects? •What are the best in vitro models and in vivo animal models for screening for and identifying hazards to children? •To what environmental substances are children more highly exposed? What factors contribute to higher exposures? •What are the relationships between exposures to children and adverse health effects observed in childhood or later? •How can laboratory and human data be used to predict responses to childhood exposures? •What is the variation in exposure and susceptibility within members of the same age group? •What are the adverse effects from children’s exposures to mixtures? •What are the uncertainties in estimating environmental risks to children? •What are the most effective methods for communicating and reducing environmental risks to children?
<p><u>Key Science Issues on Susceptible and Highly Exposed Life Stages and Subpopulations (U.S. EPA, 2002a)</u></p> <ul style="list-style-type: none"> •What are the best and most cost-effective ways to measure human exposures in all important media, by all relevant pathways, for the general population and for susceptible subpopulations? •What must be known about human behavior and the time people spend at specific activities, in order to account for exposure in the general population and susceptible subpopulations? What are the key factors that contribute to variability in human exposure? What is the distribution of human exposure? •How can we improve the accuracy of dose estimation in the general population to describe natural genetic variability and susceptible subpopulations? •What are the determining factors underlying differential responsiveness of sensitive subpopulations of humans to chemical exposure?

Key Science Questions on Asthma (U.S. EPA, 2002b)

- What is the role of environmental agents (e.g., combustion products, bioaerosols, air toxics, and pesticides) in the induction and exacerbation of asthma?
- How do susceptibility factors including genetic susceptibility, health status, socio-economic status, exposure history, and activity patterns, influence asthmatic response to environmental agents?

ORD's research addressing the second theme, influence of genetic factors on responses to environmental agents, will benefit from recent advances in genomics and proteomics, which have the potential to increase understanding of the mechanisms by which agents exert their toxic effects.

The third theme, health status, is closely related to EPA's efforts in assessing cumulative risk with special emphasis on how non-chemical stressors, such as nutrition and health status, interact with chemical stressors to impact susceptibility.

Logic Model

The principles and processes outlined in the Logic Model (McLaughlin, 1999) shown in Figure HH-SS-1, working from right to left, were fully incorporated in this science planning activity to ensure the program delivers the right products at the right time. ORD's direct contributions within the Logic Model framework end with the Short-Term Outcomes (Change in Customer Actions). From this point forward, ORD's contributions are combined with the scientific contributions from other EPA and non-EPA scientific organizations to support the achievement of the overarching Intermediate and Long-Term Outcomes.

The Intermediate and Long-Term Outcomes identified in the Logic Model are based on Agency goals identified in the EPA Strategic Plan (U.S. EPA, 1997) that involve susceptible and highly-exposed groups. These include:

- By 2020, eliminate unacceptable risks of cancer and other significant health problems from air toxic emissions for at least 95 percent of the population with particular attention to children and other sensitive subpopulations....
- Through 2020, continue to use and improve air toxics information and tools....Develop the technical tools needed to fully implement strategies and programs to reduce air toxic exposure risk, including risk to children & other sensitive subpopulations.
- By 2020substantially reduce non-cancer risk from all sources and address disproportionate impacts on populations & areas including e.g., densely populated areas, children, and people who are highly exposed to water and food affected by air toxics.

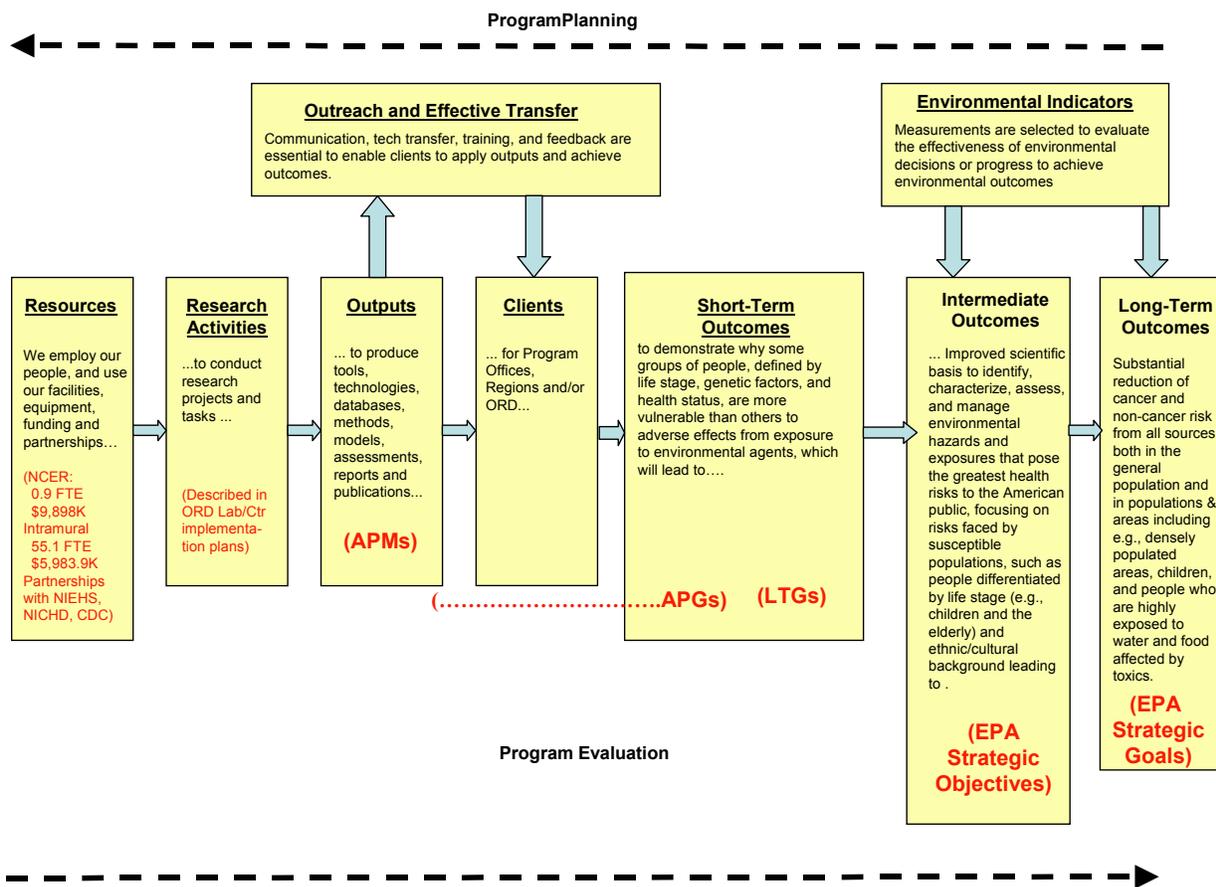


Figure HH-SS-1. MYP Logic Model

- By 2005, standards that establish protective levels for an additional ten high-risk contaminants (.g., DBP, As, Radon) will be issued and will provide increased protection to the general population as well as sensitive subpopulations such as children, elderly, and immuno-compromised.

- By 2005, 1 million children will have reduced exposure to indoor asthma triggers.

ORD's long term research program is being designed and implemented to effectively employ the Agency's unique skills and expertise in addressing the most important research questions associated with environmental risks to susceptible and highly-exposed life stages and subpopulations in a logical manner. ORD is one of very few organizations that possesses the critical skills and capacity to address the science issues related to vulnerabilities to environmental pollutants across the entire risk assessment/management paradigm. Research activities, products, and performance measures associated with implementation of ORD's research program are highlighted in the Logic Model and discussed in the next sections on long-term goal, annual performance goals, and annual performance measures.

Overview of the Long-Term Goal

To assist the Agency in achieving the long-term and intermediate outcomes discussed above, ORD has developed an integrated ORD research program with the following short-term outcome (or Long-Term Goal).

Demonstrate why some groups of people, defined by life stage, genetic factors, and health status, are more vulnerable than others to adverse effects from exposure to environmental agents

This LTG was developed by considering the scientific issues on susceptibility described in ORD's research strategies. ORD's contribution to achieving the Agency goals is to provide the scientific basis for risk characterization and reduction that often plays a key role in identifying and reducing the incidence of adverse effects resulting from exposure to environmental agents. ORD's research program on susceptible and highly exposed life stages and subpopulations will focus on developing the scientific understanding of the basis for variations in exposure and biological response of selected groups in the general population. The intermediate outcomes in Figure 1 reflect this role as described in the discussion of Goal 8 (the sound science goal) in the EPA Strategic Plan.

Under the LTG, ORD's research to improve risk assessment and risk reduction methodologies will focus on three major themes: impact of life stage, genetic factors, and health status on the variability in susceptibility and exposure. The MYP outlines critical paths to achieving the LTG for each of these themes. Much of the effort, including all of the research in the extramural program, will address the scientific risk assessment, risk management, and risk communication issues outlined in the *Strategy for Research on Environmental Risks to Children* and the *Asthma Research Strategy* as they apply to children. As implementation of the MYP proceeds, the ORD intramural program will not only address issues associated with children's risk, but will also begin to address research questions on other high-priority groups identified in the *Human Health Research Strategy*, namely, the elderly, those with genetic susceptibilities, and those with pre-existing disease.

Annual Performance Goals and Measures

This section describes ORD's Annual Performance Goals (APGs) and Annual Performance Measures (APMs) through 2014 associated with Human Health research on Susceptible and Highly Exposed Life Stages and Subpopulations that, when combined, will result in the intended LTG outcome. Figure HH-SS-2 depicts the timing and critical paths for the various APGs and demonstrates the logical design and shifts in emphasis in the research program. Table HH-SS-1 lists the APGs and corresponding ORD laboratory and center specific APMs that lead to the LTG outcome.

The MYP envisions an iterative process. Conceptual and statistical models are used to identify gaps and develop hypotheses. Methods are developed and evaluated for obtaining the data on health effects and exposure. Data are collected or generated in pilot scale hypothesis-based studies and used to develop assessment methods, protocols, and models. Laboratory studies are conducted to investigate the cellular and molecular changes resulting from exposures to environmental agents and the results used in animal models to better understand how exposures result in effects. Epidemiological and targeted field exposure studies are conducted to generate the data to fill the critical gaps and support risk assessments, test the predictiveness of the assessment methods, and provide inputs for evaluating and upgrading the models. The study results are also evaluated to identify and better understand important exposures and health endpoints and to define the state-of-the-science. The new data from these studies and other data

Human Health – Susceptible Subpopulations

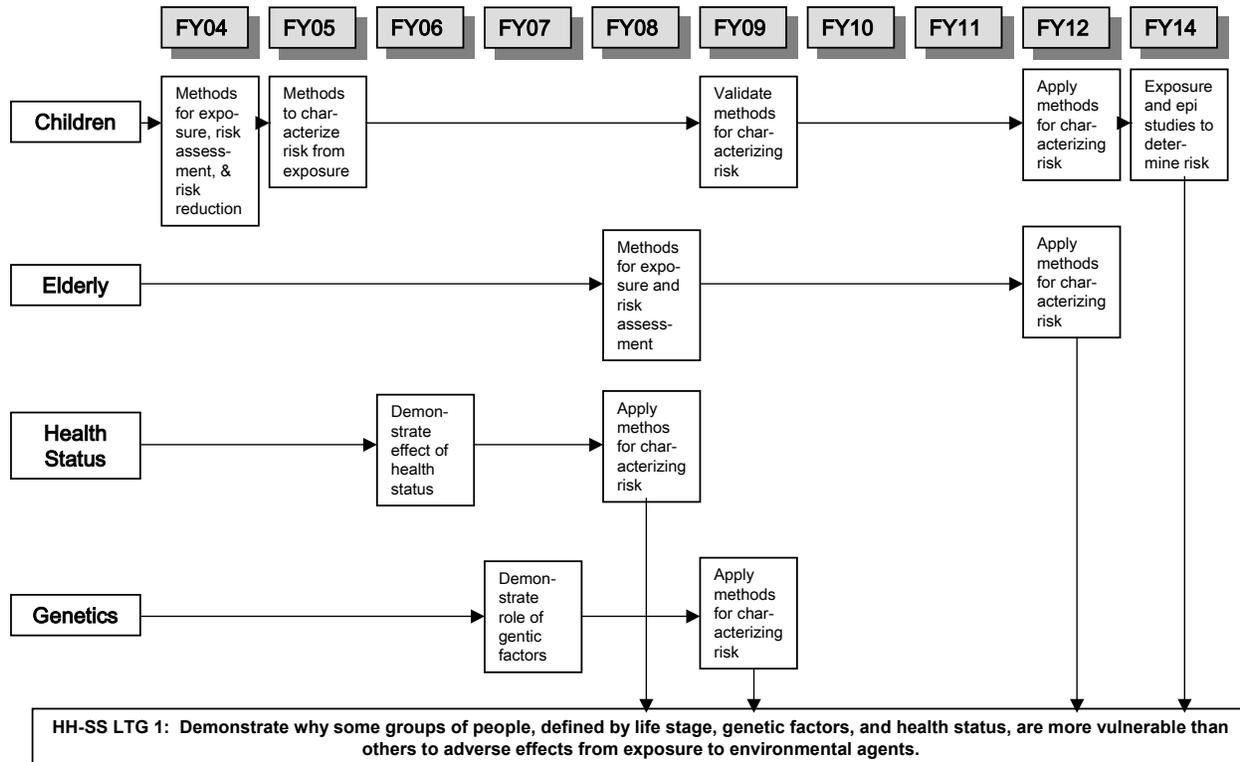


Figure HH-SS-2: Flow Chart for Human Health Susceptible Subpopulations, Long-Term Goal 4.

are used in the revised models to identify remaining and/or new critical data gaps and define future research; develop risk assessment methods, models, tools, and guidance; and assess risks. Research to fill these new data gaps (including new methods, protocols and guidance) and test the accuracy of predictive assessment methods and models is initiated, and the cycle continues until the risks are sufficiently characterized or reduced.

Over the next ten years, ORD plans to continue its emphasis on children’s health research since we have only begun to address the many scientific questions in this important area. ORD’s extramural grants program will continue to address only children’s issues. The ORD intramural program, will broaden its intramural research program addressing risks to the elderly and the influence of health status and genetic factors. This will involve a redirection of resources from children’s issues.

Life Stage

Children's Environmental Health: EPA is committed to promoting a safe and healthy environment for children by ensuring that all EPA regulations, standards, policies, and risk assessments consider special childhood susceptibilities and exposures. Windows of vulnerability exist during development, particularly during early gestation, but also throughout pregnancy, infancy, childhood, and adolescence, when toxicants may permanently alter the function of a system. Children may also be more vulnerable than adults because of differences in absorption, metabolism, storage, and excretion, with these differences possibly resulting in higher biologically effective doses to target tissues. Children can be more highly exposed than adults because of proportionately higher food intake and breathing rates, different diets, and activities such as playing on floors and a variety of hand-to-mouth activities that result in greater contact with environmental contaminants. These health threats to children are often difficult to recognize and assess because of limited understanding of when and why children's exposures and responses are different from those of adults. Research is needed to address these issues and find opportunities and approaches for risk reduction.

ORD's Children's Health Program addresses adverse effects on the developing organism that may result from exposure to environmental agents, starting with preconception exposures to parents and continuing through gestation and postnatally up to the time of maturation of all organ systems. Because organ systems reach maturity at different times, developmental phases of interest will vary by organ system. Variation in exposure resulting from age-related differences in activity patterns, diet, and physiological characteristics will also help define developmental phases of interest. The program includes effects that are not observed until adulthood. Starting in FY2005, the MYP contains four APGs that systematically address children's environmental health. The FY2005 APG is to provide methods and tools for measuring exposure and effects and characterizing risks and reducing risks from exposure to environmental agents. The 2009 APG is to complete exposure and epidemiology studies that test the methods and tools developed in the previous APG and generate new data. The 2012 APG is to develop new methods and tools based on advances in the science, and the 2014 APG is to test the new methods by conducting additional exposure and epidemiology studies.

The Children's Health Program will conduct research in the areas of high priority identified in the ORD *Strategy for Research on Environmental Risks to Children*: Mode of action

research, exposure research, epidemiology studies, risk assessment methods and models, and risk reduction methods. Research conducted pursuant to the ORD *Asthma Research Strategy* is highlighted in the MYP. This section is organized by high-priority research topics identified in the Children's Risk Strategy. The APGs for children's health research are:

By 2005, provide risk assessors and managers with methods and tools for measuring exposure and effects in children, characterizing risk to children, and reducing risks to children in schools from harmful environmental agents to support EPA risk assessment and risk management.

By 2009, complete two or more targeted epidemiological or exposure studies on children to test hypotheses, collect data, and validate methods and tools for measuring, characterizing, and reducing real world risks from exposures to harmful environmental agents to support risk assessment and risk management.

By 2012, provide risk assessors and managers with methods and tools for measuring exposure and effects in children, including adolescents, characterizing cancer and non-cancer hazards and risk to children, and reducing risks to children in schools from harmful environmental agents to support EPA risk assessment and risk management.

By 2014, complete two or more targeted epidemiological or exposure studies on children to test hypotheses, collect data, and validate methods and tools for measuring, characterizing, and reducing real world risks from exposures to harmful environmental agents to support EPA risk assessment and risk management.

MODE-OF-ACTION RESEARCH

In the intramural program, mechanism-of-action experimentation will facilitate the extrapolation of data obtained from animal and experimental models to humans, enhancing our ability to predict and study adverse effects in humans. Broadly applicable physiologically based pharmacokinetic (PBPK) models and biologically based dose-response (BBDR) models will be developed to produce more accurate risk assessments for children, making full use of pharmacokinetic and mode-of-action data.

Mode-of-action research under the Harmonization Section of the Human Health Multi-Year Plan focuses on identifying key biological events in high priority toxicity pathways that could be used to facilitate the development of molecular markers to be used in identification of chemicals for potential human health hazards. Knowledge of such key events based on the use of genomic and proteomic techniques will be coupled with emerging bioinformatic and other computer-assisted approaches to develop computational methods to prioritize chemicals for subsequent testing. Furthermore, the molecular endpoints indicative of toxicity could also be used in the development of new and more sensitive tests to be used as alternatives to current guidelines for toxicity testing. Mode-of-action research in the Susceptible Subpopulation section of the Human Health Multi-Year Plan focuses on identifying potential molecular endpoints or biomarkers that could be used to assess effects of chemicals as a function of life stage. Such information could prove to be useful in developing alternative assay approaches and the use of data developed in risk assessment, as described in “A Review of the Reference Dose and Reference Concentration Processes,” a document prepared by EPA’s Reference Dose/Reference Concentration Technical Panel (RAF, 2002). Research on mode-of-action and pharmacodynamics as a function of lifestage is intended to provide the scientific basis to develop new and more inclusive guideline protocols for toxicity at different life stages and, eventually, lead to guidance for how and when to use them.

Under the children’s health APGs for 2005 and 2012, NHEERL will conduct research on the biological basis of childhood asthma and the impacts of exposure to environmental agents (diesel particles) in animals and humans with asthma. In 2007, NHEERL will report on the mechanism of chemical-induced childhood asthma. Under the 2012 Children’s Health APG, NHEERL will examine the allergenic potential of selected indoor fungi.

Also under the 2012 APG, in 2006, NHEERL will complete reports on research to identify critical windows of susceptibility during development of major organ systems. These reports will provide data and methods to aid in the extrapolating data between animal and human studies and reduce the reliance on default assumptions. In 2007 and 2008, additional results will become available from NHEERL research on the ability of animal models to predict human life stage susceptibility, and research on modes of action by which specific groups of chemicals/pesticides increase health risks as a function of life stage. In 2010, NHEERL will

produce a report on the modes of action by which specific groups of chemicals/pesticides increase cancer or non-cancer health risks as a function of life stage.

Under the 2012 APG, the NCER grants program is supporting research on mechanism of action. In 2008, this program will produce evaluations of genetic markers and tools for assessing children's cancer risk, risks of impacts on fetal growth and development, and susceptibility to inhaled pollutants.

This work is related to mechanism-of-action research conducted under ORD's Safe Community MYP and under the Harmonization section of this MYP. These research results will be used to refine risk assessment methods for children for the guidance document produced in 2005 and 2012.

EXPOSURE METHODS, MODELS, AND MEASUREMENTS

Under the Children's Health Program APGs, NERL is addressing key research questions in the area of risk to susceptible and highly-exposed life stages and subpopulations through an iterative exposure modeling/methods/measurements process. Exposure models are used to identify key research issues and data gaps. Innovative methods and protocols are developed to address each issue. Then exposure laboratory and field studies are conducted, employing the new methods, to test the protocols and to produce high quality data to evaluate and upgrade the exposure models. The enhanced models are then used to define and/or refine the critical exposure questions that need to be addressed. Modeling tools and high quality data developed under this research program are continually applied to address specific exposure assessment questions for the program offices and regions.

In 2002, NERL completed a large-scale field study evaluating aggregate exposures of 260 young children and their primary care givers to pesticides, EDCs, and persistent organic pollutants in homes and day care centers (FY2003 APM 30). The summary results of this study will be published in 2004 along with the results from a series of related children's exposure measurements research studies conducted under the Safe Food research program (APMs 218 and 229 and APMs in the Safe Food MYP). The NERL-sponsored children's exposure measurement study results will be statistically analyzed to identify the critical factors influencing children's aggregate exposures to pesticides and other environmental contaminants. Based on results of these children's exposure field studies, an integrated exposure measurements protocol for

measuring and assessing young children's aggregate exposures to environmental contaminants has been developed and is completing peer review (2002 APM 37 and 2003 APM 244). In 2004, a relatively large longitudinal exposure measurements field study will be initiated to test this protocol and to develop distributional data on aggregate exposures and exposure factors for very young children of two different age groups (0-1 and 1-2 year old cohorts). Results will also be used to evaluate age and developmental differences in exposure. The study results will be published and data made available starting in 2005.

NERL will continue developing a toolbox of multimedia, multipathway source-to-exposure-to-internal dose models under the Aggregate/Cumulative Risk Activity Area (F-25) of Goal 8.2.1. This toolbox consists of a range of tools to facilitate simple deterministic and screening-level assessments to more complex probabilistic assessments for the general population and susceptible life stages and subpopulations. Modules are being developed for characterizing microenvironmental concentrations, human contact with contaminated media, transfer and uptake of chemicals from these media, and the resulting internal dose. Each module will be designed to receive input and produce output data in a consistent format so that the modules can be easily linked to address specific exposure issues. The Stochastic Human Exposure Dose Simulating (SHEDS) model, initially developed to assess children's exposures to pesticides in support of Goal 3 and Goal 8.2, will be applied to characterize exposures of children and other susceptible and highly-exposed groups to other key toxics and environmental contaminants. The Exposure Related Dose Estimating Modeling (ERDEM) framework provides a wide range of PBPK modeling tools for evaluating internal dose resulting from environmental exposures. Continued development and refinement of the PBPK tools in ERDEM will be conducted to address specific exposure related research questions for children and other groups. Through collaborations with NHEERL, state-of-the-art pharmacokinetic and mode-of-action data will be incorporated. SHEDS and ERDEM will be linked to characterize exposure and dose for susceptible and highly-exposed life stages and subpopulations to address specific Program Office needs. By 2004, preliminary modeling analyses of data from NERL's children's exposure measurement studies will be used to identify critical data gaps for characterizing and assessing children's environmental exposures (APM 229 and 2008 APM, as well as comparable APMs under Aggregate/Cumulative and the Safe Food MYP). One or more targeted exposure field studies will be conducted between 2005 and 2008 to fill these data gaps and to collect

additional data required for continued model development and improved exposure assessments for children. By 2008, the results of these targeted exposure field studies will be published and the data made publically available through NERL's internet accessible Human Exposure Database System.

EPIDEMIOLOGY STUDIES

The Children's Health APGs for 2009 and 2014 are to conduct exposure and epidemiology studies to test the methods and models developed previously developed and to test additional hypotheses and collect new data. The ORD children's health program will continue to conduct epidemiological and clinical studies that investigate the relationship between exposures to environmental agents and adverse health outcomes in children. The U.S. Mexico Border study is investigating pesticide exposures and effects in children along the border. Methods development and preliminary studies are currently being conducted. Preliminary data analysis will begin in 2003 and continue through 2007-2008.

In collaboration with the National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control and Prevention (CDC), and other federal agencies, ORD is planning the National Children's Study (NCS), a longitudinal cohort study called for in the Children's Health Act of 2000. The study plans to enroll 100,000 or more children before birth and follow them at least through elementary school years and preferably through adolescence or beyond. Exposure information will be collected for preconception exposures, at several times during pregnancy, and at several ages after birth. Data on outcomes will be collected during pregnancy, infancy, childhood, and beyond. Data on many different adverse outcomes potentially related to exposures to environmental agents could be collected including neurodevelopmental, reproductive, and immunotoxic effects, cancer, and respiratory effects, including asthma. Biological specimens from the parents and children will be collected and analyzed along with other relevant data to assess children's recent and past exposures to environmental contaminants. ORD is conducting methods development work for the longitudinal cohort study and plans to participate in study design and data collection. The results of these methods development activities will be published during FY 2003-2004. The Interagency study is tentatively scheduled to start during the FY 2004-2005 time period.

Analysis of the first round of data from the study is expected in 2007-2008 (Children's Health FY2009 APG).

NCER is supporting epidemiology studies in the relationship between neurodevelopmental effects and exposure to pesticides in children in rural and urban communities at the Children's Centers described below and will complete three such studies in 2005.

Because of the rising rate of asthma in the United States, especially among children, and the uncertainty as to why asthma rates are increasing, ORD is implementing the *Asthma Research Strategy* (U.S. EPA 2002b) under this multi-year plan. The current scientific database suggests that exposure to air pollutants exacerbates existing asthma while their role in causing asthma is less clear. Epidemiology studies have associated asthma aggravation as measured by increased emergency department visits with elevated levels of common air pollutants. It has been hypothesized that air pollutants may play a role as a trigger of asthma but not as a cause, although they may increase the possibility of sensitization to antigens and bioaerosols. Nevertheless, a role for common air pollutants in the development of asthma cannot be ruled out (U.S. EPA 2002b).

ORD will conduct research to understand the impact of environmental agents and factors on the induction and exacerbation of asthma. This research is closely related to research being conducted under the Particulate Matter (PM) Multi-Year Plan. Through an ongoing asthma epidemiology study in 7 U.S. communities, NHEERL and NERL are collaborating with NIAID/NIEHS through the Inner City Asthma Study to investigate effects of exposure to combustion-related products on asthmatic children. ORD will continue to analyze data from the El Paso Children's Health Study to assess geographic variation in asthma prevalence and severity. A second study modeled on the El Paso study will examine intra-urban gradients of exposure and asthma in a second major urban area. Related APMs are contained in the PM Multi-Year Plan.

ORD is planning to accomplish some of the asthma research through the National Children's Study. Successful and timely achievement of APMs through the National Children's Study is heavily dependent on EPA's collaboration with other Federal Agencies, particularly the lead agency, NICHD. ORD is currently developing methods for studying the relationship between exposure to environmental pollutants and childhood asthma under the National Children's Study.

Considerable research on asthma in children is also being conducted at several of the National Centers for Excellence in Children's Environmental Health and Disease Prevention, which are described below. In 2005, NCER will complete 5 epidemiology studies comparing levels of indoor air contaminants with incidence and severity of asthma in children in rural and urban communities.

RISK ASSESSMENT METHODS AND MODELS

Improved risk assessments methods for children will be developed under the Children's Health APGs for FY2005 and FY2012 incorporating research results from research program and related research results from other federal agencies and other sources. NCEA will continue to develop white papers on children's health issues, including use of developmental pharmacokinetic data in risk assessment, impacts of chemicals in breast milk, and use of biomarkers in risk assessment. Based on the framework for risk assessment completed in 2004, NCEA will develop the first set of approaches for conducting risk assessments for children. The guidance will address issues such as physiological parameters for children from birth through adolescence and dosimetric adjustments to correct for variability in physiology according to life stage. In 2004, an updated handbook of exposure factors for children will be completed that incorporates distributional data and critical exposure factors data generated through the NERL, NHEERL, and NCER research programs. This cycle will be repeated, with an updated guidance document for children's risk to be developed in 2012 (Children's Health APG FY2012), providing guidance on use of new mechanistic data and new exposure models in risk assessment.

RISK REDUCTION

NRMRL will conduct risk management research aimed to reduce exposure to young children in schools and kindergartens by prioritizing consumer products used in schools based on their chemical composition and potential emissions, characterizing pollutant emissions from high-risk products, providing data and models to support NERL's exposure assessment, and developing tools and databases to allow school managers to procure products and services with reduced risk to children. NRMRL will develop broadly applicable risk management methods for reducing/removing chemicals from residential environments and for preventing exposure in the residential environment (Children's Health APGs FY2005 and FY2010). Related work is being

conducted under Activity Area F-25 (Aggregate/Cumulative Risk) in Goal 8.2.1, but with different sources and objectives.

NCER is also conducting risk reduction research through the Children's Centers described below.

CHILDREN'S CENTERS OF EXCELLENCE

NCER's STAR Program will continue its support for the Centers of Excellence for Research on Children's Environmental Health and Disease Prevention. These Centers focus on the developmental effects of environmental agents including asthma, and neuro-behavioral effects. During 2003-2005, NCER will summarize the finding of these Centers through a series of workshops and reports that will provide valuable information on children's exposure, epidemiological data on asthma, and neurobehavioral effects of pesticides. In 2005, NCER will provide information on the Centers' research on intervention approaches for reducing children's exposure to environmental agents.

Risk Assessment for the Elderly: There is concern that the elderly may respond differently to environmental exposures. Therefore, ORD will conduct research to determine if the elderly represent a susceptible life stage that should be considered separately in risk assessment. There is also concern that there may be an increased risk of cancer and degenerative diseases from exposure to environmental agents as a function of age. Research is needed to examine the impact of environmental chemicals on the aging process and to develop predictive models that can be incorporated into the risk assessment process (USEPA, 2001a). The APGs for research on the elderly are:

By 2008, provide risk assessors and managers with methods and tools for assessing differences in exposures and responses to harmful environmental agents between the elderly and younger adults.

By 2012, complete two or more targeted epidemiological or exposure studies on the elderly to test hypotheses, collect data, and validate methods and tools for measuring, characterizing, and reducing real world risks from exposures to harmful environmental agents to support EPA risk assessment and risk management.

APG 135, to be completed in 2008, addresses aging as a risk factor. NHEERL will conduct research to complete research on age-dependent pharmacokinetic differences between young and older animals in 2004 and differential responses of older animals in 2006. Between 2005 and 2008, NERL will develop tools for characterizing exposure in older populations. ORD will conduct a workshop and develop guidance for conducting risk assessments for the elderly in 2008. By 2012, NERL will conduct one or more exposure studies to identical critical factors affecting exposures in aging population to test the assessment methods that have been developed. This research area is the subject of an EPA initiative.

Genetic Factors in Risk Assessment

There are a number of possible genetic factors that could predispose human subpopulations to adverse effects from exposure to environmental agents, including genetic polymorphisms for metabolizing enzymes, differing rates of DNA repair, and different rates of compensation following toxic insult. The main scientific question for this research is whether gene-environment interactions significantly increase risk of adverse effects for some segments of the population. Information concerning the influence of genetic factors on health outcomes of long-term exposure to low levels of chemicals is needed (USEPA, 2001a). The APGs for genetic factors in risk assessment are:

By 2007, analyze and demonstrate the role of genetic factors in causing cancer and non-cancer endpoints.

By 2009, provide risk assessors and managers with methods to incorporate data on interaction of genetic factors and exposure to toxic agents into risk assessments for selected health endpoints.

NHEERL is currently assessing the role of genetic polymorphisms in arsenic carcinogenesis. NHEERL will produce reports on the role of genetic factors in cancer (2005) and non-cancer (2007) endpoints. NCEA is currently analyzing data on the impact of genetic polymorphisms on metabolic pathways during different life stages. The next step will be to develop issue papers and a data base on genetic polymorphisms as a function of life stage. A report will be developed in 2009 discussing incorporation of genetic factors and their interactions with environmental exposures in risk assessment.

ORD has established a computational toxicology program that is closely related to the genetic susceptibility research being planned and implemented under this MYP. The goal of the computational toxicology program is to integrate modern computing and information technology of molecular biology and chemistry to improve EPA's prioritization of data requirements and risk assessments for toxic chemicals with emphasis on genomics and proteomics. This program will conduct research on uses of genomics and proteomics data in elucidating the role of genetic factors in sensitivity to chemical exposures and may provide invaluable data for identifying and evaluating risks of susceptible groups and individuals. The field of genomics, defined by the EPA as the study of all the genes of a cell or tissue, at the DNA (genotype), messenger RNA (transcriptome), or protein (proteome) level, has grown exponentially in the last decade. As a result, genomics technologies can now be applied to other fields including toxicology. Changes in gene expression may be used in the future to determine the health risks of a particular chemical to humans and other species. Toxicogenomics may provide information about the mode of action of a compound, the genetic pathways involved in a response to an environmental stressor, a method to identify exposure to single compounds or mixtures through detection of an expression signature for each toxic agent, and a means to identify genetic susceptibility factors that make individuals, subpopulations, or species more susceptible to an environmental contaminant.

Health Status in Risk Assessment

The third area of emphasis in the Human Health Research Strategy is the impact of health status on risk. Individuals with compromised health status may be more vulnerable to environmental agents than healthy individuals. Preexisting diseases may influence the response to environmental toxicants by altering xenobiotic metabolism or otherwise altering the host's response in a synergistic, additive, or antagonistic manner. ORD research has shown, for example, that mice challenged with influenza have increased mortality to several environmental agents such as dioxin, ozone, and ultraviolet radiation. Research is needed to develop animal models of disease having a high incidence in the human population and determine the effects of the disease on the dose-response curve to high priority environmental agents (e.g., air pollutants, pesticides) (USEPA, 2001a). The APGs for research on the impact of health status on risk are:

By 2006, evaluate the variation in vulnerability to environmental agents as a result of health status as reflected by nutritional status and pre-existing disease.

By 2008, incorporate data on presence of preexisting disease on response to environmental pollutants into risk assessment for selected health endpoints.

In 2004, NHEERL will report on the effects of diabetes on the pharmacokinetics of environmental chemicals. In 2005, NHEERL will report on effects of pre-existing disease on response to air pollutants. Leading to the 2008 APG, NCEA will examine the physiological and biochemical changes associated with common diseases as a basis for susceptibility and NHEERL will produce a report on effect of health status on risk assessment of chemicals.

Progress to Date

In 2000, ORD published the *ORD Strategy for Research on Environmental Risks to Children*, and in 2002, the *ORD Asthma Research Strategy* was published. ORD also completed an external review draft of the *Human Health Research Strategy*, which has a section on Susceptible and Highly-Exposed Subpopulations and was reviewed by the EPA Science Advisory Board in November 2002.

The ORD grants program in susceptible and highly-exposed life stages and subpopulations focuses on risks to children. The grants program, in collaboration with NIEHS, supports 12 Centers of Excellence in Children's Environmental Health and Disease Prevention. Located at universities and medical centers throughout the United States, each Center has a multidisciplinary program of laboratory research, epidemiological studies, and community-based risk reduction research. These Centers look at issues such as the relationship between asthma and air quality for children in rural and urban environments, exposure to pesticides in farmworker children and neurodevelopmental toxicity, and influence of exposure to neurotoxicants on child neurological health and development with autism and related learning disabilities as a focus. The grants program also supports smaller, more focused grants, on topics

including children's exposure to pesticides, mechanisms of action for developmental disorders, and development of biomarkers for toxic effects in children.

ORD has an intramural research program on susceptible and highly-exposed life stages and subpopulations with research in effects, exposure, risk assessment, and risk management. The following are some accomplishments of the intramural program:

- Participates on the Interagency Coordinating Committee with NICHD and CDC to design the National Children's Study.
- Developed methods for studying children's exposure and effects in the National Children's Study, including an integrated sampling method for assessing children's exposures to pesticides and other organic compounds and low cost, low burden methods for assessing children's exposures.
- Reported that urinary mutagenicity predicts risks for colorectal adenoma, indicating that individual metabolic activity of mutagens in the environment, especially the diet, pose a risk factor for cancer
- Reported that the induction of renal tumors in rats exposed to potassium bromate in drinking water was dependent on the presence of a mutant gene, raising the possibility of a vulnerable population of humans exposed to this class of environmental contaminants
- Reported differential urinary mutagenicity of male workers involved in charcoal production, suggesting differential vulnerability of humans to the formation of DNA adducts in development of cancer
- Reported that mutations in the TP53 gene in people exposed to polycyclic hydrocarbons can serve as a biomarker for adenocarcinomas
- Reported significant levels of DNA adducts in breast tissue and mutagenicity in human breast milk, suggesting a possible biomarker for possible infant exposures to carcinogenic environmental agents
- Reported suppression of immune function in adult rats exposed developmentally to organotin compounds or the pesticide heptachlor, effects that do not occur in the adult
- Reported on the partial characterization of allergens in extracts of *S. chartarum*, which provides a mechanistic link to mold-induced allergens in children
- Reported on the similarity of responsiveness of female BALB/c mice and humans sensitized to *S. chartarum*

- Reported that asthmatics have a constitutively deficient concentration of antioxidant in their pulmonary tracts, suggesting a biological basis for their differential vulnerability
- Reported that developmental exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin alters postnatal development of seminal vesicle epithelium in rats, suggesting a mechanistic basis for altered sexual morphological development in boys exposed to dioxin
- Demonstrated the importance of an inducible hepatic binding protein responsible for hepatic sequestration of dioxin, which may explain differential vulnerability to this class of agents
- Reported that low-level exposure to dioxin has effects on development of reproductive system of rats only if exposure occurs during a critical prenatal window
- Published a review paper on the relationship between endocrine disruption and developmental cancers
- Reported that developmental alteration of thyroid development produces long-term effects in regions of the brain known to mediate learning and memory
- Reported that the developmental exposure to chlorpyrifos produced long-term biochemical, morphological and behavioral changes not observed in adult animals
- Reported that neurotoxicant-induced inflammation in the nervous system may be associated with different vulnerability of younger animals to organotins
- Published a review on vulnerable processes of nervous system development, markers and methods of assessment
- Reported differences between rats and mice in response to TH-glucuronidation inducers, suggesting a genetic basis for differential vulnerability to PHAH compounds
- Reported for the first time transgenerational effects of di(2-ethylhexyl)phthalate in the male rat
- Reported that metabolites of arsenic are toxic and that the rate of metabolism may be genetically determined, suggesting a biological basis for differential vulnerability to the carcinogenic effects of arsenic
- Reported ethnic differences in secondary sexual characteristics and menses in US girls
- Developed and evaluated immunochemistry and rapid screening methods for characterizing children's exposures to selected pesticides and other environmental contaminants
- Developed and evaluated improved dietary methods for assessing children's exposures to pesticides and other environmental contaminants

- Developed and evaluated methods for characterizing particle transfer (hand-to-mouth and outdoor-to-indoor) that can be used to assess children's exposures to environmental contaminants
- Developed and evaluated computational methods for assessing exposure associated with urinary biomarker results
- Completed and reported the results from the Minnesota NHEXAS children's study
- Completed and reported the results from the Children's Total Exposure to Pesticides and Other Persistent Organic Pollutants (CTEPP) study assessing pesticide exposures to 260 children in OH and NC
- Completed a series of pilot field studies to fill critical data gaps and identify the key factors influencing children's exposures
- Completed a field study with HUD and CPSC examining children's exposures to pesticides, lead, and allergens in randomly selected US daycare centers
- Developed a peer reviewed protocol for assessing children's aggregate exposures to pesticides and other persistent pollutants
- Completed a series of field exposure studies assessing exposures to children who live along the US/Mexico border and in other high-use agricultural communities
- Provide reference exposure data for children along the US/Mexico border
- Completed and reported the results from a series of PM panel studies examining PM exposures and selected health effects metrics by elderly subpopulations
- Analyze and report on factors for children's exposures to pesticides that may lead to high-level, short-term exposures to pesticides
- Developed a prototype source-to-exposure-to-dose modeling framework that enables the complex computation of exposures to environmental pollutants
- Developed and published first and second generation multimedia, multipathway exposure models for infants, children, and the general population
- Developed and improved the Stochastic Human Exposure Dose Estimating (SHEDS) model for pesticides and PM including two stage Monte Carlo sampling for estimating exposures and addressing both uncertainty and variability
- Developed and improved the Exposure-Related Dose Estimating Model (ERDEM) for characterizing internal doses resulting from multimedia, multipathway exposures

- Developed improved modeling modules for the Dietary Exposure Potential Model for estimating dietary exposure and identifying sources
- Developed improved modeling modules for dermal and gastrointestinal exposure and dose characterization within ERDEM
- Developed improved modeling module for assessing cholinesterase inhibition resulting from OP exposures within ERDEM
- Employed the SHEDS model to assist OPPTS assess children's risks to chlorpyrifos and CCA treated wood
- Employed ERDEM to assist OPPTS assess risks to malathion from selected commercial products
- Developed and made publically available the Consolidated Human Activity Database (CHAD)
- Developed and made publically available NERL's Human Exposure Database System (HEDS) containing NERL's children exposure data, CHAD, other relevant data including the field exposure and meta data from NHEXAS, CTEPP, and other key NERL studies
- Completed a framework for assessing risks to children, which is serving as the basis for a more detailed and comprehensive methodology that is currently being developed.
- Published *Child-Specific Exposure Factors Handbook*, which provides EPA risk assessors with data on factors such as activity patterns, physiological factors, and ingestion rates for various age groups.
- Completed a workshop and published resulting papers on critical windows of vulnerability to toxic agents during development
- Developed database on pharmacokinetic data in children
- Completed report on use of pharmacokinetic data in risk assessments for children
- Published reports on chemicals in breast milk
- Under the Buy Clean Initiative, developed a searchable database for hard-surface cleaners, containing formulation data for over 300 products and properties of over 150 chemicals found in the formulations. School managers can use this stand-alone database as a tool to reduce pollutant exposure to school children by procuring less hazardous products.

Changes from 2001 MYP

The three long-term goals, in the susceptibility section of the 2001 MYP, which addressed risk assessment, risk management, and asthma, were combined into one long-term goal. The risk management work performed in NRMRL and NCER is closely related to the risk assessment program and did not warrant a separate LTG. It was inconsistent to break out asthma in a separate LTG because other equally important endpoints did not warrant their own LTGs and much of the asthma work was being done either in the STAR Centers for Excellence or was planned under the NCS, which were reported under the risk assessment LTG.

The APGs were rewritten to reflect three paths to obtaining the LTG. These paths involved understanding the roles of life stage, genetic factors, and health status in interindividual variability in susceptibility and exposure. Completion of any one of these paths would be sufficient to achieve the LTG, and the number of paths included reflects the judgment of the writing team on what ORD can accomplish with existing resources, which have decreased since the last Children's Health Initiative in 2000. APGs reflect a period of measurement methods development, laboratory studies, analysis of available data, and model development followed by epidemiology and exposure studies to test the methods and models and to generate new data. Each path is envisioned as a cycle alternating between the two phases until either the risks have been adequately identified and assessed or reduced to acceptable levels.

The third major change is that we no longer expect to continue work on the impact of health status on variability in risk. Resources have been decreasing in ORD's core susceptibility program, and this reflects the decrease. Resources will be used to continue research on life stage and genetic factors.

Potential Additional Work

With additional resources, ORD would expand its research on the impact of various non-chemical stressors on response to exposure to environmental agents. Based on the results of this research, ORD would develop methods for incorporating these responses into EPA's risk assessments.

On November 20-22, 2002, the EPA Science Advisory Board (SAB) met to discuss ORD's draft *Human Health Research Strategy*. The SAB commented at length on the discussion of health status as a factor in susceptibility. The reviewers felt that ORD's focus on

pre-existing disease was too limited. They strongly recommended that we expand the section to include other potential indicators of health status that are not clinical diseases, such as nutrition and socioeconomic status. With additional resources, ORD would expand to include other stressors of this type in its research program.

Combining different types of stressors (e.g., chemical and non-chemical) can be a problem. Certain stressors cannot be evaluated using existing methods, and little attention has been given to how to combine different types of stressors. Research is needed on risks of non-chemical stressors, how exposure to non-chemical stressors affects risks of chemical stressors, and methods for conducting population-based cumulative risk assessments.

Many stressors fall outside EPA's regulatory purview. But these stressors often need to be assessed because they may interact with regulated stressors and affect risk. For example, poor nutrition may impact absorption of environmental agents in the G-I tract, increasing internal dose and risk. These stressors may also need to be assessed in order to determine whether, for example, chemicals released from industrial plants, are the main sources of risks as opposed to other stressors in the environment that may not be within EPA's jurisdiction.

Several reports have highlighted the importance of understanding the accumulation of risks from multiple environmental stressors. These include the National Research Councils 1994 report *Science and Judgment in Risk Assessment* and the 1997 report by the Presidential/Congressional Commission on Risk Assessment and Risk Management entitled *Risk Assessment and Risk Management in Regulatory Decision-Making*. In addition, legislation such as the Food Quality Protection Act of 1996, has directed the Environmental Protection Agency to move beyond single chemical assessments and to focus, in part, on the cumulative effects of chemical exposures occurring simultaneously.

In response to the increasing focus on cumulative risk, several EPA programs have begun to explore cumulative approaches to risk assessment. The Office of Pesticide Programs has developed cumulative risk assessment guidance focused on implementing certain provisions of FQPA and recently completed an assessment of risks from exposure to organophosphorus pesticides. The Office of Air Quality Planning and Standards is performing a national-scale cumulative assessment of human health risks posed by outdoor air exposures to a set of 33 priority urban air toxics. ORD has produced a draft dioxin reassessment that considers combined risks from exposure to dioxins, furans, and dioxin-like polychlorinated biphenyls. The

EPA Science Policy Council has asked the Risk Assessment Forum to begin developing Agency-wide cumulative risk assessment guidance that builds from these ongoing activities. As a first step, a technical panel convened under the Risk Assessment Forum has developed a draft Framework for Cumulative Risk Assessment (<http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=29570>).

We propose to conduct research and develop risk assessment methods to support risk assessments of susceptible life stages and subpopulations defined by exposure to non-chemical stressors that may exacerbate responses to exposure to environmental agents. Science questions that would be addressed include

- How the vulnerability of a population and its members affects risk considering
 - Communities with high numbers of susceptible members
 - Communities with special or heavy exposures
 - Differential preparedness to withstand toxic insult and differential ability to recover:
 - Based on coping mechanisms of community and individual
 - Relevant to human health assessments in terms of impact of health care, health insurance, income, survival rates in community
- Stressor interactions, (e.g., Impact of noise on response to ototoxic chemical exposure)
- Joint assessment of chemical and non-chemical stressors
 - Common metrics
 - Ranking systems
 - Comparative risk assessment
 - Probabilistic risk assessment
- Interactions between environmental agent stressors and other factors
 - Current health status
 - Past exposure history
 - Economic status
 - Community property values
 - Lifestyle factors
 - Stress of living near waste site, incinerator, etc.
- Stresses on the ecological system that impact the human community

Links to Other Multi-Year Plans

Research on susceptible and highly-exposed life stages and subpopulations described in this MYP has significant links to other research programs on human health (i.e., aggregate/cumulative toxicity, harmonization), new research initiatives (i.e., computational toxicology), and several other research programs (i.e., safe food and safe communities, and endocrine disruptors). Information from all of these areas will contribute to the overall goal of demonstrating why some groups of people, defined by life stage, genetic factors, and health status, are more vulnerable than others to adverse effects from exposure to environmental agents.

The Safe Food MYP includes research on children's exposure to pesticides and includes measurement studies and modeling activity to support assessments in OPP that are closely allied with research on age-related susceptibility. The Safe Communities MYP describes ORD's program for development of toxicity tests and includes testing for developmental effects and elucidation of mechanisms of action of toxic effects. The EDC MYP includes research on reproductive effects in children related to exposure to endocrine disrupting chemicals.

Links to Research Initiatives

The Administrator has announced an EPA initiative on aging and the impact of aging on responses to exposure to environmental agents in the elderly. ORD will participate in this initiative and is starting a work group to develop a plan for this program.. EPA has assembled an inventory of research and activities related to the elderly. Much of the current research program focuses on impacts of exposure to particulate matter.

The EPA Genomics Task Force asked ORD to take the lead for integrating genomics information into how the Agency performs its risk assessments. ORD is focusing on the application of genomics to revolutionize risk assessment in regulatory decisions. In meeting this challenge, ORD's research to develop emerging technologies will address the need to apply genomic approaches to characterize toxicity pathways to determine human and ecological risks.

The goal of ORD's computational toxicology initiative is to integrate modern computing and information technology with the technology of molecular biology to improve the Agency's prioritization of data requirements and risk assessments for toxic chemicals. Application of

genomics and proteomics methods to risk assessment has application for identifying susceptible subpopulations.

Interaction between ORD and Other Agency Offices

Intramural Coordination:

- For intramural research, it is assumed that investigator-initiated responses will be consistent with the relevant ORD research strategies, this Multi-Year Plan, and individual laboratory/center implementation plans.
- Research on susceptibility in the Intramural and STAR programs will complement each other
- Coordination within the intramural program is crucial for research that cuts across laboratories and centers within ORD and will require coordination and collaboration through individual investigator-initiated collaborations, scientist-to-scientist meetings, and trans-ORD research teams.
- Biannual updating of this Multi-Year plan will facilitate integration of research efforts and assist ORD in alignment of research to be consistent with the highest priority areas and help shape the research program to address high priority research needs raised by Program and Regional Offices.

Intramural and Extramural Coordination:

- Integration of the intramural research program with STAR-supported research is important to maintain the balance of research to address cutting-edge, high priority research needs.
- RFAs for extramural research support should be consistent with themes outlined in the relevant ORD research strategies
- Interactions between recipients of STAR grants and intramural investigators will be encouraged, since it is likely that such an exchange of information would help focus the program and provide opportunities for future collaborations.

Coordination with Program and Regional Offices

- Results will be transmitted to Program and Regional Offices in several ways, including annual briefings, scientist-to-scientist meetings, website information, and publication of peer-reviewed products.

Summary of Non-EPA Research

The research program of the National Institute of Environmental Health and Safety (NIEHS) is closely allied with that of ORD in studying the impact of environmental contaminants on public health. Under their extramural programs, EPA and NIEHS jointly sponsor twelve Centers for Children's Environmental Health and Disease Prevention Research. The centers conduct research to improve detection, treatment, and prevention of environmentally related diseases in children. The NIEHS Intramural Division conducts basic and applied research on how environmental exposures affect biological systems and human health, on the identification of susceptible life stages and subpopulations, and on the interaction between the environment, genes, and age. NIEHS is sponsoring the Environmental Genome Project, which investigates the interaction of genes and environmental contaminants in causing human disease. In 2000, NIEHS created the National Center for Toxicogenomics to facilitate the application of gene and protein expression technology and work to understand the relationship between environmental exposures and human disease susceptibility. NIEHS also has programs directed at issues related to aging.

The National Institute for Child Health and Human Development (NICHD) supports research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children and adults. The NICHD program includes research on the effects of exposure to environmental agents on human development. NICHD, EPA, CDC, and other federal agencies are designing the National Children's Study, a large longitudinal epidemiology study of children's exposure to environmental agents. EPA and NICHD jointly sponsor research on genetic susceptibility and variability of human malformations. EPA's efforts in this area focus on identifying environmental agents that cause birth defects and other developmental disorders, the molecular mechanisms of birth defects, and how to use mechanistic and other data in the risk assessment process.

NCI is the primary sponsor of research on the biology of cancer. Investigations are focused on identifying and understanding the genes whose activity allows DNA changes that result in a normal cell becoming a cancer cell. NCI is developing and using experimental biological models that mimic the wide variety of human cancers. NCI also supports population-based research on environmental and genetic causes of cancer and on the role of biological, chemical, and physical agents in the initiation, promotion, and inhibition of cancer. NCI's Agricultural Health Study (AHS) is a large epidemiology study of cancer in farm workers and their families. ORD is participating in the AHS through an exposure study of a subgroup of participants. NCI also supports human-subject research aimed at understanding the molecular causes of specific cancers in children and the reasons for treatment failure. The pediatric Clinical Trials Cooperative Groups (Children's Cancer Group, Pediatric Oncology Group, National Wilms' Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group) develop research protocols used in the treatment of the majority of children with cancer in the United States and represent a significant portion of the U.S. clinical research on childhood cancers. A significant portion of children with cancer in the United States are enrolled in Federal programs. NCI also supports grants including laboratory and epidemiological studies of pediatric cancer survivors. To date, these studies have not focused on possible environmental causes of childhood cancer.

The National Center for Environmental Health (NCEH) of the Centers for Disease Control and Prevention (CDC) tracks asthma emergency room visits, asthma hospitalizations, and asthma mortality on a national level and in four geographic regions in partnership with State and local governments. Hospitals and clinics routinely report obvious birth defects. NCEH surveys children aged 3 to 10 in metropolitan Atlanta to document developmental disabilities that require time to appear, including mental retardation, vision and hearing impairment, and cerebral palsy, and conducts surveillance and epidemiology studies of human exposure to lead, radiation, air pollution, and other toxicants. A major focus of the NCEH Strategic Plan is the incorporation of advances in genetics into its research, epidemiology studies, and disease prevention programs. NCEH has a laboratory with expertise in analyzing biological samples for environmental contaminants, which is developing improved analytical methods for blood and urine samples from children.

CDC's National Center for Health Statistics (NCHS) is conducting the fourth National Health and Nutrition Examination Survey (NHANES IV), a national survey of health and

nutrition. The NHANES surveys have about 30,000 respondents and include sufficient numbers of children in selected age ranges and other potentially sensitive subgroups to allow statistical inferences about their health, nutrition, and food intake, and the concentrations of some environmental contaminants in their blood and urine. ORD is collaborating with NCHS to collect information on children's exposure to pesticides and other environmental contaminants. NHANES has been conducted since 1971.

GOAL 8.2 Human Health Research (Susceptible and Highly-Exposed Life Stages and Subpopulations)

Long-Term Goal: Demonstrate why some groups of people, defined by life stage, genetic factors, and health status, are more vulnerable than others to adverse effects from exposure to environmental agents.

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS			
<i>(Note: Italics indicate a linkage with another HH or GPRA area)</i>			
APG 34 - Deliver state-of-the-science reports, interim exposure data, and methods for measuring and assessing exposure and susceptibility of children to ORD and EPA program and regional offices, to provide the scientific foundation for measuring and assessing risks to children.		2003	ORD
<i>APM 35</i>	<i>Assessment of children's dietary exposure based on data from the Minnesota NHEXAS (APG 4; Goal 3 and 8.2)</i>	<i>2002</i>	<i>NERL</i>
<i>APM 37</i>	<i>Develop a protocol for conducting an assessment for children to pesticides addressing critical pathways associated with inhalation, dermal absorption and non-dietary exposure (Also Goals 3 and 8.3)</i>	<i>2002</i>	<i>NERL</i>
<i>APM</i>	<i>Report on risk of birth defects in selected US populations- CDC studies (APM Goal 2 Drinking Water)</i>	<i>2002</i>	<i>NHEERL</i>
APM 69	Provide preliminary report and consultation on use of emerging technology for collecting and storing data for Longitudinal Cohort Study	2003	NCEA
APM 70	Provide state-of-the-science paper on chemicals in breast milk as related to risk assessment.	2003	NCEA
APM 80	Complete an external review draft report on the effect of pesticide mixtures on immunologic response in mice at different life stages	2003	NCEA
APM 228	Report on use of pharmacokinetic data in risk assessments for children	2003	NCEA
APM 10	Summary of publications from the EPA/NIEHS Centers fo Excellence for Children's Health and Disease prevention - exposure studies	2003	NCER

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THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS			
<i>(Note: Italics indicate a linkage with another HH or GPRA area)</i>			
APM 11	Report from an interagency workshop on children's health sponsored by the EPA/NIEHS Centers for Children's Health and Disease Prevention Research.	2003	NCER
APM 30	Complete field monitoring study (CTEPP) to evaluate aggregate exposures of 260 young children in their homes and daycare centers to persistent organic pollutants.	2003	NERL
APM 253	Analysis and report on factors for children's exposure to pesticides that may lead to high-level, short-term exposure to pesticides.(APGS 4 & 28; also under Goals 3 and 8.3)	2003	NERL
<i>APM 244</i>	<i>Peer-reviewed design for field study to evaluate protocols for obtaining reliable data on children's exposure to pesticides, EDCs, and other persistent pollutants (APG 4; Share with Goal 3 and 8.3)</i>	<i>2003</i>	<i>NERL</i>
APG 44 - Contribute to protecting children from harmful environmental agents in their daily lives by providing risk assessors and risk managers with better data on children's aggregate exposures in their homes and daycare settings and improved exposure factors for estimating children's risk		2004	ORD
APM 107	External review draft of an updated Exposure Factors Handbook for Children, incorporating new data from ORD-supported studies.	2004	NCEA
APM 10	Compare pesticide exposure and body burden in children of different ages to those of adults in the same home.	2004	NCER
APM 11	Provide data on pesticide exposure among children in agricultural communities	2004	NCER
APM 218	Analysis of the "Children Total Exposure to Pesticides and Persistent Organic Pollutants (including EDCs) Study" to estimate aggregate exposures and identify critical exposure factors. (Also Goals 3 and 8.3)	2004	NERL

ANNUAL PERFORMANCE GOALS AND MEASURES THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS		YEAR	LAB/ CENTER
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APM 229	Conduct modeling analysis of children's studies to identify key uncertainties and data gaps for use by EPA and science community to plan future measurement studies to specifically address these gaps. (Also Goals 3 and 8.3)	2004	NERL
APM 230	Provide innovative, low burden exposure research tools that can be used by the Agency and the scientific community in designing and implementing the National Children's Study	2004	NERL
APM 119	Provide indoor emission characterization methods and protocols for use by investigators to determine children's exposure to indoor contaminants to support a long-term study of children's health	2004	NRMRL
APG 176	Deliver emission model to ORD and EPA program and regional offices to aid decision-makers in reducing exposure and risks to children	2004	NRMRL
APM 335	Complete emission model on a cleaning product used in schools to help officials select products that reduce children's exposure to air pollutants associated with asthma and other respiratory problems.	2004	NRMRL
APG 2005	By 2005, provide risk assessors and managers with methods and tools for measuring exposure and effects in children, characterizing risk to children, and reducing risks to children in schools from harmful environmental agents to support EPA risk assessment and risk management.	2005	ORD
APM 143	Annual report from the EPA/NIEHS/CDC Children's Research Centers	2002	NCER
<i>APM</i>	<i>STAR grantees will report on research on: Particulate air pollution and initiation of asthma (6779).... (PM MYP, APG X, 2002)</i>	2002	<i>NCER</i>

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THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS			
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<i>APM</i>	<i>STAR grantees will report on research to: Determine the cardiopulmonary response to exposure to concentrated ambient PM in 12 asthmatic subjects. (7531 NYU) (PM MYP, APG X, 2002)</i>	2002	NCER
APM 202	Provide proof of concept for use of a biologically based, dose response model of a specific cellular, developmental event to predict the risk of adverse outcome (i.e., toxicant induced limb defects)	2002	NHEERL
<i>APM</i>	<i>STAR grantees will report on research to: understand effects of inhaled ultrafine particles on asthma (6785) (PM MYP, APG 20, 2003)</i>	2003	NCER
<i>APM 185</i>	<i>Report on the acute respiratory health effects of particulate matter and co-pollutants among asthmatic children in seven U.S. communities (ICAS). (PM MYP, APG X, 2005)</i>	2003	NHEERL
APM 189	Complete evaluations of at least 2 approaches for assessing age dependent vulnerability of children to environmental toxins	2004	NCER
<i>APM</i>	<i>STAR grantees will report on research assessing the health effects of concentrated fine/ ultrafine aerosols in clinical studies of susceptible populations including those with asthma, COPD, heart disease. (7352 UCLA) (PM MYP, APG X, 2004)</i>	2004	NCER
APM 225	Develop next generation models to estimate exposure and dose to pesticides and other environmental contaminants so that EPA can produce improved exposure and risk assessments (Also Goals 3 and 8.3)	2004	NERL
<i>APM 226</i>	<i>Provide refined methods to the Agency and scientific community for measuring children's exposures to pesticides and other environmental contaminants (Also Goals 3 and 8.3)</i>	2004	NERL
APM 22	Report on the biological basis of childhood asthma	2004	NHEERL

ANNUAL PERFORMANCE GOALS AND MEASURES THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS		YEAR	LAB/ CENTER
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24	Report on the health effects associated with exposure of animals and humans with asthma to diesel exhaust particles	2004	NHEERL
APM	External review draft report on conducting risk assessments for children as a sensitive subpopulation and summary of supporting ORD research	2005	NCEA External NHEERL NERL NCER NRMRL
APM	Complete the evaluation of new biomarkers for assessing children's exposure and risk that utilize less invasive approaches	2005	NCER
APM 192	Complete the evaluation of at least eight (8) approaches for reducing children's exposure to indoor pollutants (EPA/NIEHS Children's Research Centers)	2005	NCER
APM	Report on the health effects associated with exposure of diesel exhaust particles in asthma animal model	2005	NHEERL
<i>APM</i>	<i>Methodology to Guide the Replacement of Agency Default Uncertainty Factors With Factors Based on Data (Goal 2?)</i>	<i>2005</i>	<i>NCEA</i>
APM	Compile exposure factors, methods, and measurement data to be used by EPA exposure assessors to conduct aggregate exposure assessments. (Also Goals 1, 3, 4, and 8.3)	2005	NERL
<i>APM</i>	<i>Provide OPPTS with the available NERL sponsored children's exposure data and tools for assessing aggregate exposure to residential-use pesticides in support of the August 2006 reassessment (Goals 3)</i>	<i>2005</i>	<i>NERL</i>
APM 16	Report on at least 1 method to test for effects in the National Children's Study, including the assessment of respiratory health outcomes such as asthma.	2004	NHEERL
APM 17	Report on assessing health effects in children under five years of age exposed to pesticides	2004	NHEERL

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APM 17	Report on methods to collect, store, and transport biologic specimens from surrogate tissues in humans and rodent models for protein and gene expression analysis	2004	NHEERL
APM	Develop and demonstrate methods that will enable school systems (or managers of other building types) to reduce the exposure of children with respiratory problems to indoor contaminants from one additional source type that could exacerbate the children's adverse health effects	2005	NRMRL
APG 100	By 2009, complete two or more targeted epidemiological or exposure studies on children to test hypotheses, collect data, and validate methods and tools for measuring, characterizing, and reducing real world risks from exposures to harmful environmental agents to support EPA risk assessment and risk management.	2009	ORD
<i>APM</i>	Summary of Publications from the EPA/NIEHS Centers of Excellence for Children's Health and Disease Prevention: <i>Asthma</i> Epidemiology Studies	2004	NCER
APM	Report on determinants of susceptibility to the acute respiratory health effects of combustion-related pollutants among asthmatic children in 7 U.S. communities.	2003	NHEERL
APM 18	Report on field ready test system based on classical conditioning for use in testing developmental neurological disorders in human infants.	2004	NHEERL
APM 23	Peer-reviewed scientific publication on intra-urban variations in the prevalence of childhood asthma associated with intra-urban gradients of combustion-related pollutants and air toxics in El Paso, TX	2004	NHEERL
APM 191	Complete three (3) epidemiology studies comparing levels of pesticide exposure with evidence of neurobehavioral effects among children aged 0-5 years in both rural and urban communities	2005	NCER

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APM 193	Complete five (5) epidemiology studies comparing levels of indoor air contaminants with the incidence and severity of asthma among children aged 0-5 years in both rural and urban communities	2005	NCER
APM	Complete field monitoring study of longitudinal aggregate exposures for infants and toddlers that will be used to evaluate measurement approaches and to provide the Agency with critical data to substantially improve aggregate exposure assessments for young children to pesticides and other environmental contaminants. (Also Goals 3 and 8.3)	2006	NERL
APM	Report on the characterization of physicochemical properties of the allergenic protein from selected indoor fungi and compare to other well-characterized proteins for hazard identification	2006	NHEERL
APM	Conduct analysis of longitudinal exposure study” to estimate aggregate exposures, to evaluate exposure algorithms, to evaluate approaches for measuring exposure and to identify critical exposure factors that can be used by the Agency to improve exposure and risk assessments. (Also Goals 3 and 8.3)	2007	NERL
APM	Identify and describe factors that contribute to high-end aggregate exposures to residential-use pesticides that can be used by exposure assessors to identify highly-exposed sub-populations and by exposure modelers to predict exposure and dose for these subpopulations (Also Goals 3 and 8.2)	2007	NERL
APM	Report on prevalence of asthma and low pulmonary function levels among 4th and 5th grade schoolchildren in a second major urban area.	2007	NHEERL
APM	Report on analysis of National Children’s Study data on relationship between exposure to environmental agents and adverse health outcomes	2008	NCEA NERL NHEERL NRMRL

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APM	Complete a comprehensive epidemiological study of the relationship between PCB and mercury exposure and adverse health outcomes in a population of Hmong and Laotian in northeastern Wisconsin	2008	NCER
APM	Complete a comprehensive study of the exposure of children in Cincinnati, Ohio to lead, mercury, pesticides, PCBs, and environmental tobacco smoke (ETS)	2008	NCER
APM	Complete two assessments of the relationships between pre and post natal exposures to neurotoxic chemicals in the environment and brain development and injury (including autism) among children in New Jersey and California.	2008	NCER
APM	Provide ORD with an assessment of key factors influencing aggregate exposures of young children in one or two cohorts along the US/Mexico border	2008	NERL
APM	Report on a validation of field-collected diesel exposure biomarkers	2008	NHEERL
APG 2012	By 2012, provide risk assessors and managers with methods and tools for measuring exposure and predicting effects in children, including adolescents, characterizing cancer and non-cancer hazards and risk to children, and reducing risks to children in schools from harmful environmental agents to support EPA risk assessment and risk management.	2012	ORD
APM 20	Report on the use of genomics for monitoring expression of health status through analysis of accessible tissues and cells	2004	NHEERL
APM 21	Report on the long-term persistent effects of developmental exposure to environmental chemicals on cancer and non-cancer endpoints	2004	NHEERL
APM 19	Report on role of maternal folate status during early pregnancy on response to developmental toxicants	2004	NHEERL
APM 25	Report on proteins from several indoor fungi that pose a hazard with respect to allergenicity	2004	NHEERL

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APM	Report on long-term effects of in utero insult on adult health and reproduction to assess adequacy of current testing guidelines for reproductive toxicity	2005	NHEERL
APM	Report on the assessment of the relative potency of several indoor fungal allergens to obtain quantitative information for risk assessments	2005	NHEERL
APM	Issue papers on biomarkers of exposure and effect in children	2006	NCEA
APM	Complete a longitudinal characterization of permethrin concentrations in a multipathway study of young children	2006	NCER
APM	Provide new models of longitudinal dietary intake of pyrethroid and organophosphate insecticides by children	2006	NCER
APM	Provide new or refined methods to the Agency and scientific community for measuring cumulative exposures to chemical contaminants that will be used in field studies to provide high quality data for exposure assessments (Also Goals 3 and 8.2)	2006	NERL
APM	Identify available tools for characterizing adolescent exposures to environmental contaminants and identify key uncertainties and critical data gaps for use by ORD research in planning future research to reduce uncertainty in exposure assessments for adolescents.	2006	NERL
APM	Report on age-related pharmacokinetic and pharmacodynamic changes in developing animals	2006	NHEERL
APM	Report on the identification of molecular endpoints for use in predicting adverse outcomes as a function of life stage	2006	NHEERL
APM	Report on development of principles to be used to assess cancer risks in children	2006	NHEERL

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APM	Report on critical windows of susceptibility during development of major organ systems (i.e., reproductive, respiratory, immune, nervous, cardiovascular, and/or endocrine) between rodents and humans to reduce reliance on default assumptions in risk assessment.	2006	NHEERL
APM	Report on development of principles to be used to assess cancer risks in children	2006	NHEERL
APM	Report on identification of molecular endpoints for use in predicting adverse outcomes as a function of life stage	2006	NHEERL
APM	Develop and demonstrate methods that will enable school systems (or managers of other building types) to reduce the exposure of susceptible children to indoor contaminants from additional source types that could exacerbate the children's adverse health effects.	2006	NRMRL
APM	Report on the ability of animal models to predict human life stage susceptibility to agent exposure resulting in organ system dysfunction or cancer	2007	NHEERL
APM	Report on the mechanism of chemical-induced childhood asthma	2007	NHEERL
APM	Report on the application of the principles in assessing cancer risk in children	2007	NHEERL
APM	Evaluate a new genotoxicity assessment tool for children's cancer risk	2008	NCER
APM	Evaluate genetic markers for susceptibility related to fetal growth and development	2008	NCER
APM	Evaluate the genetic basis for increased susceptibility of children to inhaled pollutants	2008	NCER
APM	Evaluate two new biomarkers for assessing the susceptibility of children to asthma	2008	NCER

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APM	Develop/refine biomarker methods that can be used to generate measurement data on multiple exposures which will enhance, refine, and verify the Agency's cumulative risks assessments. (Also Goals 3 and 8.2)	2008	NERL
APM	Provide refined tools for characterizing adolescent exposures to environmental contaminants	2008	NERL
APM	Demonstrate the use of NERL's human exposure modeling tools and databases to assess young children's exposures to pesticides and other environmental contaminants. (Also Goals 3 and 8.3)	2008	NERL
APM	Summary report on state of science and application to risk assessment of pharmacokinetics and pharmacodynamics as it relates to children's health	2008	NHEERL
APM	Develop and demonstrate broadly applicable risk management methods for reducing/preventing children's exposure to hazardous pollutants in the indoor environments	2008	NRMRL
APM	Evaluate the refined exposure tools for characterizing adolescent exposures to environmental contaminants through one or two targeted pilot studies	2010	NERL
APM	Report on mode(s) of action by which specific groups of chemicals/pesticides increase cancer or non-cancer health risks as a function of life stage.	2010	NHEERL
APM	Report on use of molecular endpoints as alternatives to currently existing testing guidelines to assess toxicity as a function of life stage	2010	NHEERL
APM	External review draft report on conducting risk assessments for children, incorporating new research results	2012	NCEA

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS			
<i>(Note: Italics indicate a linkage with another HH or GPRA area)</i>			
APG 2014	By 2014, complete two or more targeted epidemiological or exposure studies on children to test hypotheses, collect data, and validate methods and tools for measuring, characterizing, and reducing real world risks from exposures to harmful environmental agents to support EPA risk assessment and risk management.	2014	ORD
APM	Provide an analysis of the results of one or two targeted studies to assess key factors influencing adolescent exposures to environmental contaminants	2012	NERL

ANNUAL PERFORMANCE GOALS AND MEASURES THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS		YEAR	LAB/ CENTER
<i>(Note: Italics indicate a linkage with another HH or GPRA area)</i>			
APG 135	By 2008, provide risk assessors and managers with methods and tools for assessing differences in exposures and responses to harmful environmental agents between the elderly and younger adults.	2008	ORD
APM 67	State-of-the-science paper on aging as it relates to risk assessment	2003	NCEA
APM 128	Workshop report on application of PBPK modeling to quantify pharmacokinetic variance as a component of uncertainty factors in risk assessment.	2004	NCEA
APM 14	Report on modeling for age-dependent pharmacokinetics in risk assessment	2004	NHEERL
APM	Identify available tools for characterizing exposures throughout the life span and to identify uncertainties and data gaps in exposure assessments for adolescents.	2007	NERL
APM	Report on age-dependence of protective repair and plasticity mechanisms in aged animal models	2005	NHEERL
APM	Report on latent adverse health effects of developmental exposures	2005	NHEERL
APM	Report on differential response of older animals to environmental agents	2006	NHEERL
APM	Report on gene expression changes correlated with latent adverse health effects of developmental exposures	2006	NHEERL
APM	Issue papers on biomarkers of exposure and effect in the elderly	2007	NCEA
APM	Report on the physiological and biochemical changes as a result of aging as a basis for susceptibility	2007	NCEA
APM	Report on mechanisms of susceptibility to environmental insult in models of aging	2007	NHEERL
APM	Provide the Agency with new/updated tools for characterizing life-span exposures to environmental contaminants for use in future field measurement studies.	2008	NERL

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS			
<i>(Note: Italics indicate a linkage with another HH or GPRA area)</i>			
APM	Draft external review report on conducting risk assessments for the elderly.	2008	NCEA
APG 2012	By 2012, complete two or more targeted epidemiological or exposure studies on the elderly to test hypotheses, collect data, and validate methods and tools for measuring, characterizing, and reducing real world risks from exposures to harmful environmental agents to support EPA risk assessment and risk management.	2012	ORD
APM	Provide ORD and the Program Offices with an assessment of the results of one or two pilot exposure studies to identify critical factors influencing exposures of aging subpopulations to environmental contaminants.	2012	NERL
APG 2007	By 2007, analyze and demonstrate the role of genetic factors in causing cancer and non-cancer endpoints	2007	ORD
APM 49	Report on contributions of genetic polymorphisms of metabolic pathways to susceptibility and population variance	2002	NCEA
APM 197	Report on genetic polymorphisms that might alter human risk of arsenic carcinogenesis	2002	NHEERL
APM 68	Report comparing polymorphisms of metabolic pathways and population variance in different life stages	2003	NCEA
<i>APM</i>	<i>Report on interindividual variation in arsenic metabolism (Drinking Water)</i>	2003	<i>NHEERL</i>
<i>APM</i>	<i>Report on role of specific polymorphisms in metabolism and repair and the relative increase/decrease in tumorigenic risk associated with them for POMs and how these factors influence low-dose linearity (Air Toxics)</i>	2005	<i>NHEERL</i>
APM	Report on gene array data from animal and human polymorphisms and relation to disease susceptibility and underlying oxidative stress	2007	NHEERL
APM	Report on the role of genetic factors in cancer endpoints	2007	NHEERL

ANNUAL PERFORMANCE GOALS AND MEASURES THEME: LIFE STAGE: PRENATAL, INFANTS, CHILDREN, ADOLESCENTS		YEAR	LAB/ CENTER
<i>(Note: Italics indicate a linkage with another HH or GPRA area)</i>			
APM	Report on the role of genetic factors in non-cancer endpoints	2007	NHEERL
APG 2009	By 2009, provide risk assessors and managers with methods to incorporate data on interaction of genetic factors and exposure to toxic agents into risk assessments for selected health endpoints	2009	ORD
APM	External review draft report on use of genetic information in risk assessment	2009	NCEA
APG 126	By 2006, evaluate the variation in vulnerability to environmental agents as a result of health status as reflected by nutritional status and pre-existing disease.	2006	NHEERL
APM 19	Report on role of maternal folate status during early pregnancy on response to developmental toxicants	2004	NHEERL
APM 13	Report on the effects of diabetes on pharmacokinetics of environmental chemicals	2004	NHEERL
APM	Report on the effects of pre-existing respiratory disease on response to air pollutants	2005	NHEERL
APM	Report on comparative dose-response toxicity data for susceptible hypertensive rats and role of oxidative stress	2005	NHEERL
APG 2008	By 2008, incorporate data on presence of preexisting disease on response to environmental pollutants into risk assessment for selected health endpoints	2008	ORD
APM	Report on the feasibility of identifying basic physiologic and biochemical changes associated with prevalent diseases and their impact on the toxicity of common environmental contaminants.	2006	NCEA
APM	Report on the physiological and biochemical changes associated with common diseases as a basis for susceptibility.	2008	NCEA
APM	Report on effect of health status on risk assessment of chemicals	2008	NHEERL

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EVALUATION OF PUBLIC HEALTH OUTCOMES

Introduction

ORD's current Human Health core research program does not now include specific efforts to evaluate the public health outcomes of our research and Agency policies. The issue of "accountability" – of making sure that our research and our pollution control programs produce measurable benefits in public health – is, however, an important issue. In order to better protect the country's air, water, and land resources, the Environmental Protection Agency must go beyond its current reliance on process indicators such as decreased emissions or discharges and measure actual changes in the status of ecological condition and human health. This issue is fundamental to the very first goal of ORD's Strategic Plan, to support the Agency in protecting human health and the ecosystems on which health depends. For this reason, a description of the research toward evaluation of environmental public health outcomes, and a discussion of potential approaches to evaluate the effectiveness of Agency efforts are included in this Multi-Year Plan.

In its risk assessment and risk management process, EPA often attempts to estimate the benefits of Agency decisions in terms of preventing or reducing risks posed by environmental contaminants; however, the Agency generally has not conducted evaluations as to whether those intended benefits in protecting public health were realized. With the advent of GPRA and calls for EPA to demonstrate measures of success, research is needed to enable the evaluation of actual benefits to public health, as measured by changes in morbidity, mortality, or other metrics such as QALYs or DALYs, resulting from Agency decisions.

The Presidential Commission on Risk Assessment and Risk Management (1997) has supported the need for EPA to measure the effectiveness of public health intervention. The National Research Council (1997) also noted a lack of consensus concerning appropriate indicators of health status that could be used to measure the performance of environmental health programs. This has led the Council of State and Territorial Epidemiologists, the CDC, the Agency for Toxic Substances and Disease Registry, and the EPA to begin the development of a set of public health indicators to track adverse health events related to the environment. The Pew Environmental Health Commission (Pew, 2000) has also recommended a nationwide tracking of priority chronic diseases, such as asthma and respiratory diseases, and exposures to

environmental pollutants such as PCBs, metals, and pesticides. The Presidential Commission on Risk Assessment and Risk Management (1997) supported this need in its recommendations on environmental health, recognizing the inherent difficulties of such evaluations. The other sections of this Human Health Multi-Year Plan outline steps to improve the science of human health risk assessment to enable improved risk management decisions. We need, also, to complete the cycle by improving the science that will enable reliable estimations of the *actual* reduction in risk. Great similarities in information needs exist for both parts of the process because, essentially, evaluating the efficacy of a decision requires comparing risk assessments before and after implementation of the risk management actions.

Research Goal and Objectives

The goal of research in this area is to be able to measure (or reliably estimate) changes in human health risk with sufficient precision and accuracy so that we can determine the degree to which Agency decisions and actions contributed to those changes. The figure of the Source-Exposure-Dose-Effects continuum (Figure HH-I-1 in the Introduction) shows the chain of movement of a contaminant from source to effects and provides a framework for this discussion. To predict or evaluate the outcomes of the Agency's risk management decisions, it is necessary to (1) measure or reliably estimate the changes in effects (or dose, or exposure, or environmental concentrations, or emissions—striving to measure as close to the outcome as possible, but recognizing that such measurements are not always feasible), (2) have confidence that the observed changes were due to the risk management efforts, and (3) determine the significance of the changes and whether or not the changes were effective in protecting human health. Two main objectives of ORD's research program emerge: (1) to establish the linkages between sources, environmental concentrations, exposure, effects, and outcomes such that a change in public health outcome consequent to a regulation/rule can be measured by measuring any one of these linked steps, and (2) to provide better methods/approaches by which others can measure or model changes in outcomes consequent to a regulation. It should be noted that a substantial part of the research on the complex relationship between sources and environmental quality (i.e., fate, transport, and transformation) is part of other programs (e.g., particulate matter, air toxics, hazardous waste, and ecosystem risks). Evaluation of public health outcomes clearly depends on the insight and research efforts under other GPRA research areas to provide significant

components of the underlying science. Further, evaluation of public health outcomes will depend on partnerships with the Centers for Disease Control (CDC) and other health agencies.

Approaches to Evaluating Public Health Outcomes

Assessment of the public health impact of an environmental decision should answer two questions: (1) did the environmental decision actually prevent, reduce, eliminate, or modify exposure to the pollutants of concern? And (2) did this prevention, reduction, elimination, or modification result in disease prevention and improved public health?

Four types of approaches might be used to assess the public health benefits of environmental decisions: (1) population studies of morbidity/mortality, (2) population exposure studies, (3) field sampling of environmental media, and (4) measuring changes in source emissions. These approaches are ordered in terms of ability to determine human exposures and link them with health outcomes; however, this order does not mean that an approach listed earlier than another approach is necessarily more feasible. Enabling these approaches to be used effectively to estimate risk reduction will require linking them in the development of a model. Each of these areas can be improved, in some cases as a result of the risk assessment research program discussed elsewhere. However, there are some special needs for evaluating regulatory efficacy for public health protection. Thus, a careful prioritization analysis is needed.

Population Studies of Health Outcomes

The optimal approach is that of epidemiologic study, which has the advantage of being able to evaluate whether exposure to a pollutant can actually be related to a public health outcome in a specific population, as measured by changes in morbidity and/or mortality or other metrics. Several types of epidemiologic study are possible, including cohort studies, case-control studies, time-series studies, and molecular (biomarker) studies. An epidemiologic study could utilize several assessment measures of disease or the continuum of disease (e.g., morbidity, mortality, clinical examination, biomarkers of effect) and determine exposure to individuals in the study population from multiple pollutants through different exposure pathways. A disadvantage of this approach is that there may be limitations related to the sensitivity of methods available to measure exposure or the effect. In particular, short-term health effects

(asthma etc) will much easier to measure (in the short-term) than long-term health effects like cancer.

In considering an epidemiologic approach, three approaches should be considered. The first is the use of available data for both exposure and effects. Examples of such databases include (for exposure) air monitoring networks, proximity to hazardous waste sites, and drinking water quality, and (for effects) cancer registries, birth defects registries, and infectious disease surveillance. A second approach is to consider the development of a database or surveillance program to monitor over time changes and fluctuations in the exposure and disease of interest. The first two options have strength when the data cover several years prior to the environmental management action and several years after the management action. They also have strength if they are implemented over several geographic regions or are national in scope. A disadvantage is there may be incompleteness in the data, relatively insensitive methods may be used to assess the effect, and the surveillance systems may be costly to implement and maintain. Also, because of the lack of scientific linkages between these environmental quality measurements and actual exposure, it is often difficult to precisely and accurately detect changes in outcomes. A third approach is the conduct of an epidemiologic study or series of studies specifically designed to examine the effect of the environmental management policy. Choosing an appropriate study design is based on the size of the population to be studied, the magnitude of the effect associated with the exposures of interest and the prevalence of the disease to be studied. Epidemiologic studies can be retrospective, prospective, or bidirectional. Whether to use existing data establish de novo a new surveillance database, develop partnerships with agencies collecting similar data, or conduct an epidemiologic study or series of studies will be driven by issues of data availability, methods available to measure exposure and effect, and resources. Also, the feasibility of measuring reduction in illness incidence will depend on the degree to which such incidence is affected by risk factors other than environmental pollution and the biological mechanisms and time courses involved in the pathogenesis of the illnesses in question.

Because of the statistical difficulty of detecting small changes in population effects, developing more sensitive health indicators would be quite useful. For example, early indicators of disease or more sensitive methods (both for measuring exposure, effects and statistically analyzing effects) are needed.

Population Exposure Analysis (Biomonitoring)

The second epidemiological approach is to examine populations for exposures to pollutants of concern. This approach would include biomarkers of exposure and *personal* exposure-related media (e.g., food, drinking water, air) and has the advantage of discovering what people are actually exposed to and evaluating the pathways and sources of exposure. It is not sufficient, however, from a public health outcomes perspective, to measure simply biomarkers in the population. Without information about the exposures leading to those biomarkers, no evaluation of the effectiveness of Agency risk management decisions can be made. A program of biomarker measurements must be augmented with a program of exposure measurements in order to evaluate the effectiveness of regulatory programs. Examples of such a program would be the recently completed pilot program of the National Human Exposure Assessment Survey (NHEXAS) and the National Human Exposure Monitoring Survey (NHEMS). If done on a longitudinal basis in a sufficiently large population, this approach has the advantage of evaluating the impact of environmental decisions on human exposure. This approach does not measure changes in public health directly, but depends upon an understanding of the exposure-dose-response relationship to extrapolate the changes in exposure to changes in public health.

Research advances are needed to enable more accurate models of exposure with known uncertainty and variability. These are dependent on having more cost-effective methods and approaches to measure population exposure so that exposure surveillance approaches are feasible. Early efforts to establish a National population exposure network at the CDC have begun. It will be important to join with these activities to facilitate sufficient depth to allow State by State comparisons. For example, while NHANES provides a National snapshot of exposures, it does not allow a geographical picture to be drawn, and cannot therefore be linked to emission profiles except at the crudest of scales.

Measuring Toxicants in Environmental Media

A third approach is to examine concentrations in media of relevance to humans (e.g., air at a stationary monitor, finished water). However, this does not measure actual exposure to people, and without appropriate information, some key pathways and media of exposure may be missed. Like the preceding approach, it also does not examine disease or indicators of health in

the population. This approach can be more useful, however, when the linkages between environmental media, exposure, and effects have been established. The feasibility and utility of this approach could be improved with knowledge of what pathways and media are of importance to the risk being reduced. The development of analytic methods for contaminants that meet data quality objectives at small cost are equally important. These data have been collected by EPA for many years, and analyses to reveal temporal and spatial trends will be valuable. Much work will need to be done to assure data compatibility with new data on exposure databases and health-effect databases.

Measuring Toxicants in Source Emissions

Measuring changes in source emissions is an approach that is less expensive and noninvasive compared to some of the other approaches, but like the second and third ones discussed above, it does not examine disease or indicators of health in the population. It also does not evaluate exposure to a population or even concentrations in the media (e.g., food, water, air) that may be of relevance to human exposure; it is at best a very crude surrogate for potential exposure. This approach is not without difficulty and should not be construed as easy, but it may be the easiest to achieve of the four approaches identified. If this approach is used, it is essential to understand the relationship between the source being measured and the exposure to the person or population, to ensure that unmeasured source emissions do not predominate. This area presents an added difficulty because many pollutants of interest are not emitted directly; rather they are formed in fate processes. Thus, the linkage between the source and the pollutant of interest must be clearly understood through research on fate, transport, and transformation. Some of this latter research is part of other ORD research programs.

Linkages Between the Risk Assessment Elements and Modeling

Although the approaches are discussed as discrete entities, perhaps the most important research is to provide the linkages among them. Ultimately, this will vastly increase the feasibility and accuracy of both “before” and “after” assessments. Given the immense number of scenarios to be evaluated, models of this process are needed. Such models are under development as part of the Human Health base program, but additional modules are likely to be needed to incorporate the special needs of an “after” assessment.

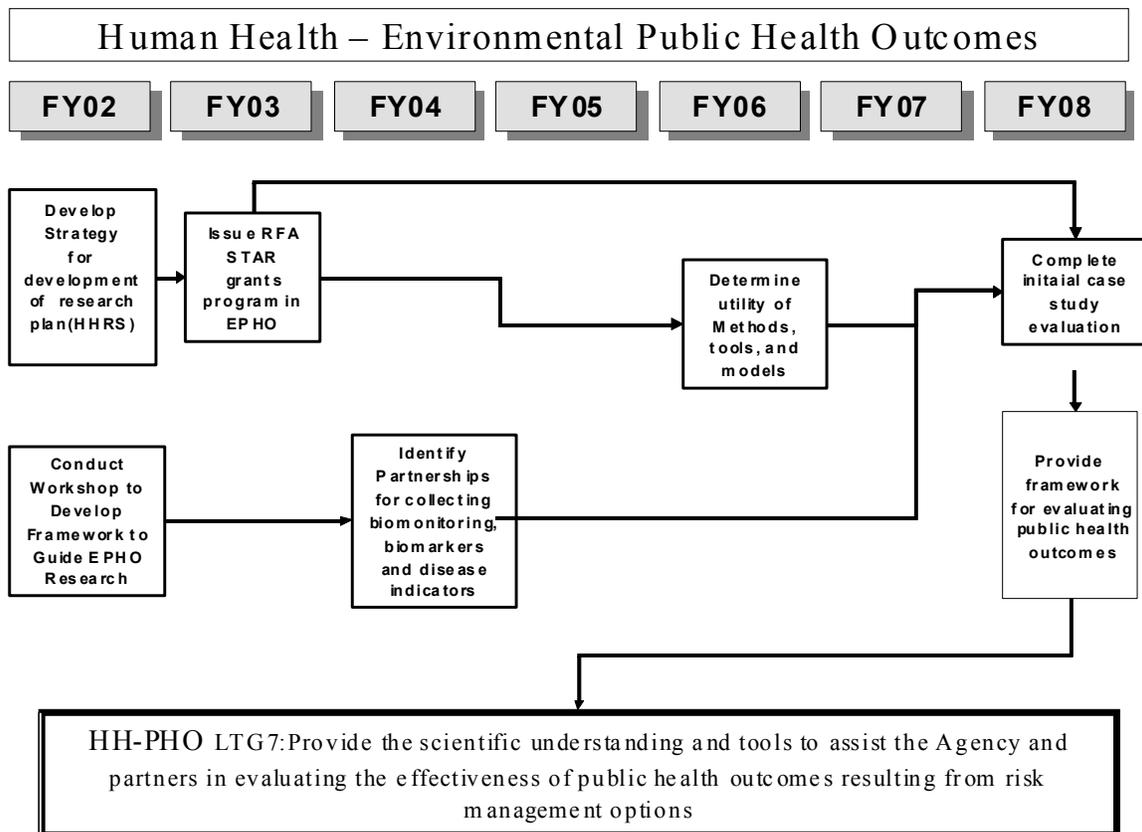
Case Studies

To evaluate the strengths and weaknesses of our ability to estimate the effectiveness of EPA’s regulatory activities, a logical first approach is to use existing approaches and evaluate existing databases that compile pollutant emissions information or environmental concentrations, health endpoints, or both. Case studies will reveal database discontinuities, data gaps as well as the need for partnerships with outside agencies for data collection.

Research Program

The environmental public health outcome research program will feature a number of program elements supporting the Long Term Goal including:

Case Studies (APGI) – A variety of case studies will be selected and a “before” and “after” analysis of public health risk will be conducted using available methodologies. Some case studies may be geographic, some temporal, and some following single toxicants or single



priority outcomes.

New Modeling Tools (APG2)– A modeling framework to link models all the way from source to effects which will provide more confidence in exposure-dose-response relationships through thorough understanding of the critical processes within, and linkages between each component of the human exposure-dose-response sequence; be well-grounded in science and evaluated with data from measurement programs, put regulatory actions into context by accounting for all pathways and routes of exposure and effects; provide for inclusion of variability and uncertainty. The World Health Organization Environmental Burden of Disease (EBD) methodology is an example of one of the potential early methods.

New Measurement Programs and Tools (APG3)– Better ways to measure changes in effects (or in indicators of effects, exposure, and indicators of exposure, environmental concentrations, or source strength), together with measurement programs (NHEMS) to measure the effects before and after implementation of the Agency’s policies. Establishing the necessary partnerships with “sister agencies” will be an important early step.

Summary of Non-ORD Research

A variety of Federal Agencies are conducting research related to the analysis of the public health outcomes of environmental exposures. There are also some Non-Federal agencies in partnership with the US Government conducting public health surveillance activities. An example is the 1999; Pew Charitable Trusts’ Health and Human Services program, an initiative to help rebuild the nation’s neglected public health system. Within EPA, the Office of Environmental Information is conducting a “data inventory” on public human health data in 2003, which coupled with the APM on the exposure “data inventory” will reveal opportunities for linkages. The Centers for Disease control is expanding the number of chemicals included in the NHANES population exposure analysis. The *National Report on Human Exposure to Environmental Chemicals* provides an ongoing assessment of the U.S. population’s exposure to environmental chemicals using biomonitoring. The first *National Report on Human Exposure to Environmental Chemicals (First Report)* was issued in March 2001 and included 27 chemicals. The 27 included lead, mercury, cadmium, and other metals; dialkyl phosphate metabolites of organophosphate pesticides; cotinine; and phthalates. This *Second Report*, released in January 2003, presents biomonitoring exposure data for 116 environmental chemicals for the

noninstitutionalized, civilian U.S. population over the 2-year period 1999-2000. Polycyclic aromatic hydrocarbons (PAHs) Dioxins, furans, and coplanar polychlorinated biphenyls (PCBs), Non-coplanar PCBs, Phytoestrogens, Selected organophosphate pesticides, Organochlorine pesticides, Carbamate pesticides, Herbicides, Pest repellents and disinfectants. Unfortunately, this data is not available in a suitable geographic format, and exposures can not be linked to emissions or other EPA data. EPA is working with NIEHS and CDC on the NHEMS (National Human Exposure Monitoring Survey) which may correct some of these deficiencies.

Resources:

The Environmental Public Health Outcomes Initiative is ramping-up from FY02, where the budget was 100K, to FY05, where the projection is 10% of the total Goal 8.2 funding, or 3.5M. Some of this growth would result from shifting APMs from other research areas here, where there would be a better fit. The most significant portions of the resources would be devoted to NCER grants (and joint solicitations with partners). Funding needs for FY03 are 1.5M, for FY04, 2.0M, for FY05 3.5M.

Goal 8.2 Human Health Research (Public Health Outcomes)

LONG TERM GOAL: By 2008; provide the scientific understanding and tools to assist the Agency and others in evaluating the effectiveness of public health outcomes resulting from risk management options.

ANNUAL PERFORMANCE GOALS AND MEASURES	YEAR	LCR
APG1: Establish linkages between emissions, exposures, effects and effectiveness such that public health outcomes can be measured or modeled.	2006	ORD
APM1: Establish a data inventory for human exposure biomonitoring and bioindicator databases.	2003	NRMRL
APM2: Establish Ranking of Priority Environmental Public Health Outcomes (EPHO) through Environmental Burden of Disease (EBD)Methods.	2003	NRMRL
APM3: Identify pilot projects as case studies to evaluate Agency environmental management decisions using currently available information and approaches.	2004	ORD
APG2: Provide improved tools, systems, methods, models into framework by which EPA and others can measure or model changes in public health from risk management options.	2008	ORD
APM1: Develop a strategy for conducting Environmental Public Health Outcomes (EPHO) research	2002	ORD
APM2: Conduct a workshop to identify elements of a framework or strategy for conducting public health outcomes research.	2002	NRMRL
APM3: Develop statistical techniques using environmental and human health data in evaluating health outcomes through the STAR program.	2003	NCER
APM4: Assess state-of-the-art approaches for evaluating how human health is impacted by risk management options.	2006	ORD

APM5: Publish a solicitation on development of environmental public health outcomes related indicators and indices for evaluating regulatory and pollution control programs	2003	NCER
APM6: 305: Hold workshop on the state of human health indicators to determine where future extramural research is needed.	2004	NCER
APM 7: Publish a summary of advances in the development of environmental public health outcomes related indicators and indices for evaluating regulatory and pollution control programs	2006	NCER
APG3: Develop partnerships for data collection and new indicators and metrics for exposure and health effects	2005	ORD
APM1: Publish new suites of public health and public exposure indicators that reflect early detection of public health effects.	2005	ORD

SUMMARY

This MYP lays out research over the next five to ten years that is needed to address critical issues in core human health research. The anticipated resources are not adequate to do everything. Nor can everything be done at this time, since some issues are extremely difficult: resolution of those issues awaits additional scientific insight and innovation – both of which take time. Choices about the focus in this core research program have been made – based on (a) ORD’s assessment of client needs and time-lines, (b) the scientific feasibility of success, and (c) the breadth and applicability of the results. Many of the choices to date have resulted in a strong focus on children and on the effects of pesticides in the current program. ORD recognizes the needs to expand the focus to other groups (*e.g.*, the elderly) and stressors (*e.g.*, stressors other than pesticides or even chemicals).

The shape of the program will undoubtedly continue to evolve over time, as new scientific findings and technologies change the landscape of what is feasible, and as new problem areas rise or fall in importance and urgency. Indeed, the discussions in this version of the MYP include frequent references to “Computational Toxicology,” an initiative area that ORD is developing for better understanding and predicting environmental hazards for both humans and ecosystems. The “Comp Tox” efforts will improve our ability to measure, to assess, and to predict risk from a variety of environmental factors – concepts that are critical to all of our Goal 8.2 Human Health research areas, and especially to the Harmonization effort. This core Human Health research will both benefit from, and contribute to, the “Comp Tox” effort. In addition, EPA’s Aging Initiative will undoubtedly change the focus of the Susceptible Subpopulations research program over the next few years to account for changes in risk as people age from one life-stage to another. Also, EPA’s Risk Assessment Forum has recently set out a Framework for Cumulative Risk Assessment, and in so doing broadened the definition of “cumulative” well beyond the understanding of the word found in the Food Quality Protection Act. The Aggregate / Cumulative research plan has already responded to the framework document and its recommendations.

This is the third iteration of the Human Health Multi-Year Plan. Many improvements in ORD’s Human Health research planning have already manifested themselves in the process of developing the three versions of the MYP. As ORD continues to iterate these plans, the research

will become even better focused at delivering real, beneficial outcomes for protecting Human Health.