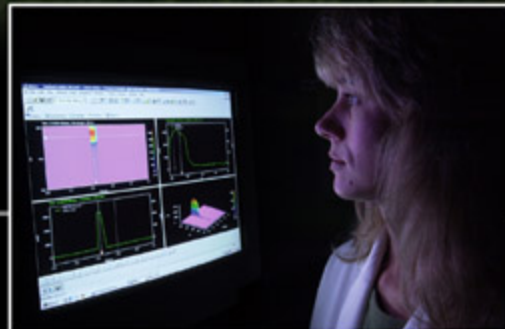
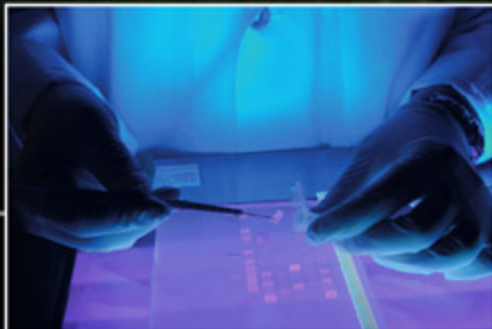
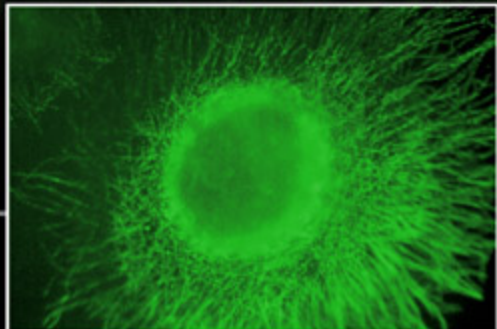


# HUMAN HEALTH

## RESEARCH STRATEGY



## RESEARCH AND DEVELOPMENT



# **Human Health Research Strategy**

Office of Research and Development  
U.S. Environmental Protection Agency  
Washington, DC 20460

## **Disclaimer**


This document has been subjected to review by the National Health and Environmental Effects Research Laboratory and the Science Advisory Board and has been approved for publication. It does not constitute an EPA position or policy concerning human health risk assessment research. Any mention of trade names does not constitute EPA endorsement.

## FOREWORD

The 2003 EPA Human Health Research Strategy identifies and prioritizes research needed to improve the scientific foundation for health risk assessments. The Human Health Research Strategy identifies two overall strategic objectives: research to improve the scientific foundation of human health risk assessment and research to enable evaluation of public health outcomes from risk management decisions. The Strategy provides a conceptual framework for future human health research by the Office of Research and Development (ORD) and was prepared by a team of scientists from ORD with input from EPA's Office of Prevention, Pesticides, and Toxic Substances, the Office of Water, and the Office of Children's Health Protection.

The Human Health Research Strategy focuses on developing a multidisciplinary, integrated program to improve linkages between exposure, dose, effect, and risk assessment methods. ORD efforts in computational toxicology, predicting aggregate and cumulative risk (exposure to mixtures of pollutants from multiple sources), protecting susceptible subpopulations (i.e., children, older adults) and accountability reflect the timeliness of this plan.

This research plan is an important planning and accountability tool because it makes clear the rationale for and intended products of EPA's human health research program. This research strategy also provides the basis for the development of a multi-year plan on human health research, which outlines specific research goals and measures to be accomplished over the next 5-10 years.



Paul Gilman, Ph.D.  
Assistant Administrator

# TABLE OF CONTENTS

	<u>Page</u>
FOREWORD .....	iii
LIST OF FIGURES .....	vi
AUTHORS, CONTRIBUTORS, AND REVIEWERS .....	vii
PEER REVIEW HISTORY .....	viii
ABBREVIATIONS AND ACRONYMS .....	ix
GLOSSARY .....	x
EXECUTIVE SUMMARY .....	E-1
1. INTRODUCTION .....	1-1
1.1 PURPOSE OF THE STRATEGY .....	1-1
1.2 CURRENT RESEARCH PROGRAM ON HUMAN HEALTH .....	1-2
1.3 FUTURE RESEARCH PRIORITIES .....	1-4
1.3.1 Framework for an Integrated Research Program in ORD .....	1-4
1.3.2 Research Themes .....	1-8
1.4 STRATEGIC PRINCIPLES .....	1-9
2. RESEARCH TO IMPROVE THE SCIENTIFIC FOUNDATION OF HUMAN HEALTH	
RISK ASSESSMENT .....	2-1
2.1 RESEARCH ON HARMONIZING RISK ASSESSMENT APPROACHES .....	2-1
2.1.1 Scientific Uncertainties .....	2-1
2.1.2 Research Objectives .....	2-2
2.1.3 Research Approach .....	2-2
2.2 RESEARCH ON AGGREGATE AND CUMULATIVE RISK .....	2-6
2.2.1 Scientific Uncertainties .....	2-6
2.2.2 Research Objectives .....	2-7
2.2.3 Research Approach .....	2-7
2.3 RESEARCH ON SUSCEPTIBLE AND HIGHLY-EXPOSED	
SUBPOPULATIONS .....	2-12
2.3.1 Scientific Uncertainties .....	2-13
2.3.2 Research Objectives .....	2-14
2.3.3 Research Approach .....	2-14
3. RESEARCH TO ENABLE EVALUATION OF PUBLIC HEALTH OUTCOMES FROM	
RISK MANAGEMENT ACTIONS .....	3-1
3.1 SCOPE AND DEFINITIONS .....	3-2
3.2 SCIENTIFIC UNCERTAINTIES .....	3-4
3.3 SCIENTIFIC OBJECTIVES .....	3-5

3.4	RESEARCH APPROACH .....	3-6
3.5	RESEARCH IMPLEMENTATION .....	3-7
4.	REFERENCES .....	4-1

APPENDICES

APPENDIX A-	ORD Research Plans and Strategies .....	A-1
APPENDIX B-	EPA’s Office of Research and Development-Organizational Chart .....	A-3
APPENDIX C-	Examples of Mechanistic Data Used in Risk Assessment .....	A-4
APPENDIX D-	Agencies Having Research Programs Complementary to ORD .....	A-5
APPENDIX E-	Examples of Health and Environmental Databases to Evaluate Public Health Outcomes From Risk Management Actions .....	A-7

## LIST OF FIGURES

<u>Figure</u>		<u>Page</u>
1-1	Relationship Between Core and Problem-Driven Research .....	1-1
1-2	The Risk Assessment-Risk Management Paradigm .....	1-2
1-3	The Exposure-Dose-Effect Continuum .....	1-5
1-4	ORD's Approach to Solving Agency Problems .....	1-6
1-5	ORD's Integrated Research Program .....	1-7
1-6	Integrated ORD Research Program on Molds and Asthma in Children .....	1-8
1-7	Role of Research in Assessment of Health Outcomes .....	1-9
	in the Risk Assessment and Risk Management Process	
3-1	Role of Analysis of Health Outcomes in the Risk Management Process .....	3-3



## AUTHORS, CONTRIBUTORS, AND REVIEWERS

### Executive Lead

Harold Zenick, National Health and Environmental Effects Research Laboratory (NHEERL), Office of Research and Development (ORD), U.S. Environmental Protection Agency (EPA)

### Authors

Hugh Barton, ORD/NHEERL  
Jerry Blancato, ORD/National Exposure Research Laboratory (NERL)  
Michael Callahan, formerly with ORD/National Center for Environmental Assessment (NCEA)  
Larry Cupitt, ORD/NERL  
Judith Graham, formerly with ORD/NERL  
Karen Hammerstrom, ORD/NCEA  
Jonathan Herrmann, ORD/National Risk Management Research Laboratory (NRMRL)  
Robert Kavlock, ORD/NHEERL  
Gary Kimmel, ORD/NCEA  
Hugh McKinnon, ORD/NRMRL  
Hugh Tilson, ORD/NHEERL  
Vanessa Vu, formerly with ORD/NCEA  
Jennifer Orme-Zavaleta, ORD/NHEERL

### Contributors

Linda Birnbaum, ORD/NHEERL	Patricia Murphy, ORD/NCEA
Rebecca Calderon, ORD/NHEERL	Dale Pahl, ORD/NERL
Robert Chapman, formerly with ORD/NCEA	Julian Preston, ORD/NHEERL
Gary Foureman, ORD/NCEA	Chris Saint, ORD/National Center for Environmental Research (NCER)
Herman Gibb, ORD/NCEA	John Schaum, ORD/NCEA
Annie Jarabek, ORD/NCEA	Linda Sheldon, ORD/NERL
Carole Kimmel, ORD/NCEA	William Steen, formerly with ORD/NERL
Suzanne McMaster, ORD/NHEERL	Michel Stevens, ORD/NCEA

### Reviewers

Tom Barnwell, ORD/NERL	Steven Hedtke, ORD/NHEERL
William Farland, ORD/NCEA	Robert Menzer, formerly of ORD/NCER
Elaine Francis, ORD/NCER	Lee Mulkey, ORD/NRMRL
Fred Hauchman, ORD/NHEERL	Kevin Teichman, ORD/Office of Science Policy (OSP)

## PEER REVIEW

Peer review is an important component of research strategy development. The peer review history for this research strategy follows:

**ORD Science Council:** March 21, 2001, Elaine Francis and Kevin Teichman, Lead Reviewers

**External Peer Review:** Science Advisory Board/Human Health Research Strategy (HHRS) Review Panel, November 20-21, 2002

### **External Peer Review Panel Members:**

- Dr. James Klaunig, Panel Chair, Professor of Toxicology and Director of Toxicology, Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, IN
- Dr. Paul Blanc, Professor of Medicine and Endowed Chair in Occupational and Environmental Medicine, University of California-San Francisco, San Francisco, CA
- Dr. James Gibson, Research Professor of Pharmacology and Toxicology, The Brody School of Medicine, East Carolina University, Greenville, NC
- Dr. Michael Jayjock, Senior Research Fellow, Rohm and Haas Co., Springhouse, PA
- Dr. George Lambert, Associate Professor of Pediatrics and Associate Director of the Clinical Research Center, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway, NJ
- Dr. Joseph Landolph, Associate Professor of Molecular Pharmacology and Toxicology, School of Pharmacy, University of Southern California in Los Angeles, Los Angeles, CA
- Dr. Steve Lewis, Distinguished Scientific Associate, Exxon Mobil Biomedical Sciences, Inc., Annandale, NJ
- Dr. Randy Maddalena, Indoor Environment Department Lawrence Berkeley National Laboratories, Berkeley, CA
- Dr. Maria Morandi, Assistant Professor, University of Texas Houston Health Sciences Center, School of Public Health, Houston, TX
- Dr. Beate Ritz, Associate Professor, Department of Epidemiology and Center for Occupational and Environmental Health, School of Public Health, University of California in Los Angeles, Los Angeles, CA
- Dr. Herbert Rosenkrantz, Professor, Environmental and Occupational Health and Pharmacology, University of Pittsburgh, Pittsburgh, PA
- Dr. Robert Spengler, Associate Administrator, Agency for Toxic Substances and Disease Registry, Atlanta, GA
- Dr. Bernard Weiss, Professor, Environmental Medicine and Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, NY

### **Peer Review Coordinator:**

- Dr. Sue Shallal, Designated Federal Officer, Environmental Health Committee EPA Science Advisory Board, Environmental Protection Agency, Washington, DC

## ABBREVIATIONS AND ACRONYMS

Ah	Arylhydrocarbon
ATSDR	Agency for Toxic Substance and Disease Registry
BBDR	Biologically Based Dose Response Modeling
CCL	Contaminants Candidate List
CDC	Centers for Disease Control and Prevention
EPA	U.S. Environmental Protection Agency
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GPRA	Government Performance and Results Act
HUD	Housing and Urban Development
IPCS	International Programme on Chemical Safety
MOE	Margin of Exposure
NAS	National Academy of Science
NCEA	National Center for Environmental Assessment (EPA/ORD)
NCEH	National Center for Environmental Health
NCER	National Center for Environmental Research (EPA/ORD)
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCT	National Center for Toxicogenomics
NCTR	National Center for Toxicological Research
NERL	National Exposure Research Laboratory (EPA/ORD)
NHANES	National Health and Nutrition Examination Survey
NHEERL	National Health and Environmental Effects Research Laboratory (EPA/ORD)
NHEXAS	National Human Exposure Assessment Survey
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No-Observed-Adverse-Effect Level
NRC	National Research Council (NAS)
NRMRL	National Risk Management Research Laboratory (EPA/ORD)
NTP	National Toxicology Program
OPP	Office of Pesticide Programs
ORD	Office of Research and Development (EPA)
OSP	Office of Science Policy
PBPK	Physiologically Based Pharmacokinetic Modeling
PK	Pharmacokinetic
QSAR	Quantitative Structure-Activity Relationship
RfC	Reference Concentration
RfD	Reference Dose
SAB	EPA's Science Advisory Board
STAR	EPA/ORD Science to Achieve Results Extramural Grants Program
TSCA	Toxic Substances Control Act
TEF	Toxicity Equivalent Factor
UF	Uncertainty Factor

## GLOSSARY

**Aggregate Exposure:** The combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and sources (working definition developed by EPA Science Policy Council).

**Aggregate Risk:** The risk resulting from aggregate exposure to a single agent or stressor (working definition developed by EPA Science Policy Council).

**Biological Markers or Biomarkers:** Indicator signaling events in biological systems or samples. There are three classes of biomarkers: exposure, effect, and susceptibility. A marker of exposure is an exogenous substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism. A marker of effect is a measurable biochemical, physiological, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease. A marker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic.

**Biologically-Based Dose Response (BBDR) Model:** A model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.

**Childhood:** Nominally, the period from birth through the onset of puberty. However, the *Human Health Research Strategy* addresses adverse effects on the developing organism that may result from exposure to environmental agents, starting with preconception exposures of the parents and continuing through gestation and postnatally up to the time of maturation of all organ systems.

**Cumulative Risk:** The combined risks from aggregate exposures to multiple agents or stressors (working definition developed by EPA Science Policy Council).

**Dose:** The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The *potential dose* is the amount ingested, inhaled, or applied to the skin. The *applied dose* is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having crossed the outer boundary of the organism). The *absorbed dose* is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of the skin, lung, and digestive tract) through uptake processes. *Internal dose* is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the pollutant available for interaction by any particular organ or cell is termed the *biologically effective dose* for that organ or cell.

**Effectiveness:** The improvement in health outcome that a prevention strategy can produce in typical community-based settings.

## GLOSSARY (Continued)

**Efficacy:** The improvement in health outcome that a prevention strategy can produce in expert hands under ideal circumstances

**Exposure:** Contact of a pollutant, physical, or biological agent with the outer boundary of an organism; exposure is quantified as the concentration of the agent in the medium over time.

**Margin of Exposure:** The ratio of the critical NOAEL to the expected human exposure level.

**Mechanism of Action:** The complete sequence of biological events that must occur to produce a toxic effect.

**Mode of Action:** A less-detailed description of the mechanism of action in which some, but not all, of the sequence of biological events leading to a toxic effect is known.

**Nonthreshold Effect:** An effect for which it is assumed that there is no dose, no matter how low, for which the probability of an individual's responding is zero.

**No-Observed-Adverse-Effect Level (NOAEL):** The highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control.

**Outcome Measure:** The final health consequence (e.g., cases prevented, quality-adjusted life years) resulting from an intervention.

**Pharmacodynamics:** The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (also called toxicodynamics).

**Pharmacokinetics:** The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of pollutants (also called toxicokinetics).

**Physiologically-Based Pharmacokinetic (PBPK) Model:** A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution between target organs and tissues, metabolism, and excretion.

**Program Office:** An EPA organizational unit that administers a major EPA program (i.e., Air and Radiation; Water; Prevention, Pesticides, and Toxic Substances; and Solid Waste and Emergency Response).

**Reference Concentration (RfC):** An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of the human population (including sensitive subpopulations) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

## GLOSSARY *(continued)*

**Reference Dose (RfD):** An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure of the human population (including sensitive subpopulations) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

**Susceptibility:** Increased likelihood of an adverse effect related to intrinsic (i.e., life stage, genetic predisposition) or extrinsic determinants (i.e., preexisting disease) unique to the organism.

**Threshold Effect:** An effect for which there is some dose below which the probability of an individual's responding is zero.

**Uncertainty Factor (UF):** One of several factors used in calculating an exposure level that will not cause toxicity from experimental data. For example, UF's are used to account for the variation in susceptibility among humans, the uncertainty in extrapolating from experimental animal data to humans, and the uncertainty in extrapolating data from studies in which agents are given for less than a lifetime.

**Vulnerability:** Synonymous with susceptibility

## EXECUTIVE SUMMARY

The mission of the U.S. Environmental Protection Agency (EPA) is to protect public health and safeguard the natural environment. Risk assessment is an integral part of this mission in that it identifies and characterizes environmentally related human health problems. The *Human Health Research Strategy* document presents a conceptual framework for future human health research by EPA's Office of Research and Development (ORD). This research strategy outlines ORD's core research effort to provide broader, more fundamental information that will improve understanding of problem-driven health risk issues encountered by the EPA's Program and Regional Offices. The scope of this research document is strategic in that it discusses broad themes and general approaches. Implementation of an integrated research program on human health is described in greater detail in ORD's Multiyear Plan on Human Health Research. The Multiyear Plan identifies specific performance goals and the measures needed to achieve those goals over a 5- to 10-year period. Each Laboratory and Center in ORD is also developing an approach linking research at the project level to the goals and measures in the Multiyear Plan and the general themes outlined in this research strategy document.

Based on the needs of the EPA's Program and Regional offices, recommendations made by external advisory groups, and goals established by EPA in response to the Government Performance and Result Act (GPRA) under Sound Science (Goal 8), ORD has identified two strategic research directions that will be pursued over the next 5 to 10 years (see text box).

### Strategic Research Directions

- Research to Improve the Scientific Foundation of Human Health Risk Assessment, including:
  - Harmonizing Cancer and Noncancer Risk Assessments
  - Assessing Aggregate and Cumulative Risk
  - Determining Risk to Susceptible Human Subpopulations
- Research to Enable Evaluation of Public Health Outcomes from Risk Management Decisions.

Research in these strategic areas will improve the scientific foundation for EPA's risk assessments and lead to principles that can be used to evaluate the effectiveness of risk management actions aimed at improving environmental public health. Chapter 1 of the *Human Health Research Strategy* document provides background information regarding the regulatory and scientific basis for a core research program on human health risk assessment. Chapter 1 also develops the need for a multidisciplinary, integrated research program and describes how ORD will formulate problems and approaches to study complex questions related to human health. Chapter 2 describes the scientific uncertainties, objectives, and approaches that ORD will use to harmonize risk assessments, assess aggregate and cumulative risk, and determine risk to susceptible subpopulations. Chapter 3 describes ORD's public health outcomes research program that will work toward providing more scientifically defensible assessments of *actual* reduction in risk.

ORD will focus on developing a multidisciplinary, integrated program that will build linkages between exposure, dose, effect, and risk assessment methods to provide the scientific basis for harmonizing risk assessment approaches, predicting aggregate and cumulative risk, and protecting susceptible subpopulations. In addition, ORD will develop an integrated research program utilizing its intramural scientific capacity in conjunction with extramural grants, cooperative agreements, and interagency agreements. Efforts have been and will continue to be made to identify and foster collaboration with other Federal and State agencies, as well as academic and private organizations having research programs that complement ORD's research efforts.

### **Research to Improve the Scientific Foundation of Human Health Risk Assessment**

ORD's human health risk assessment program is based on the assumption that major uncertainties in risk assessment can be reduced by understanding and elucidating the fundamental determinants of exposure and dose and the basic biological changes that follow exposure to pollutants leading to a toxic response. Research in this area will provide the scientific knowledge and principles to improve the risk assessment of all human health endpoints, aggregate and cumulative risk, and susceptible and highly exposed subpopulations.

### ***Harmonizing Risk Assessment Approaches***

ORD's research in this area will address the disparate approach for the risk assessment of cancer and noncancer endpoints. Research on harmonizing risk assessment approaches will lead to a common set of principles and guidelines for drawing inferences about risk based on mechanistic information. The overall goal of this research is that Program and Regional

Office risk assessors will use mechanistic data in a harmonized manner for risk assessments for all health endpoints. Specific research objectives include the following:

- ❑ Develop emerging technologies or methods to study mode or mechanism of action;
- ❑ Develop the biological basis for understanding mode or mechanism of action;
- ❑ Develop a basis for comparing risk across all health endpoints using mechanistic information;
- ❑ Develop principles for the use of mechanistic data to select the most appropriate risk assessment model; and
- ❑ Develop principles for the use of mechanistic data to reduce or replace uncertainty factors in risk assessments, especially for inter- and intraspecies extrapolation, including approaches for linking dosimetry models, such as pharmacokinetic models, with empirical or pharmacodynamic models for effects of pollutants with similar or different modes of action.

### ***Aggregate and Cumulative Risk***

ORD's research program on aggregate and cumulative risk will address the fact that humans are exposed to mixtures of pollutants from multiple sources. Research will provide the scientific support for decisions concerning exposure to a pollutant by multiple routes of exposure or to multiple pollutants having a similar mode of action. ORD will also develop approaches to study how people and communities are affected following exposure to multiple pollutants that may interact with other environmental stressors. Specific research objectives include the following:



- ❑ Determine the best and most cost-effective ways to measure human exposures in all relevant media, including pathway-specific measures of multi-media human exposures to environmental contaminants across a variety of relevant microenvironments, exposure durations, and conditions;
- ❑ Develop exposure models and methods suitable for EPA and the public to assess aggregate and cumulative risk, including mathematical and statistical relationships among sources of environmental contaminants, their environmental fate, and pathway-specific concentrations; models linking dose and exposure from biomarker data; and approaches to assess population-based cumulative risk, including those involving exposure to stressors other than pollutants; and
- ❑ Provide the scientific basis to predict the interactive effects of pollutants in mixtures and the most appropriate approaches for combining effects and risks from pollutant mixtures.

### ***Susceptible and Highly-Exposed Subpopulations***

ORD research on susceptible subpopulations will focus on developing a scientific understanding of the biological basis for differing responsiveness of subpopulations within the general population, including factors associated with their differential exposure. Research on biological susceptibility will focus on the role of intrinsic factors, such as life stage and genetic background, and extrinsic factors, such as preexisting disease, on responsiveness to environmental pollutants. Specific research objectives include the following:

- ❑ Identify the key factors that contribute to variability in human exposure, including the distribution of human exposures and behavior associated with exposure to pollutants;

- ❑ Improve the accuracy of dose estimation in the general population;
- ❑ Identify the biological basis underlying differential responsiveness of sensitive subpopulations of humans to pollutant exposure; and
- ❑ Determine how exposure, dose and effect information can be incorporated into risk assessment methods to account for interindividual variability.

### **Research to Enable Evaluation of Public Health Outcomes from Risk Management Actions**

Generally, EPA has not prepared retrospective evaluations to determine if the intended benefits in protecting public health were realized once an EPA decision had been in place for a period of time. With the advent of GPRA and calls for EPA to stress and demonstrate outcome-oriented goals and measures of success, research is needed to enable evaluation of actual public health outcomes from risk management actions. Estimating public health benefits of EPA regulatory decisions and rule making or, in a more general sense evaluating public health outcomes from risk management actions will be a challenging undertaking. It will involve a number of disciplines grounded in both the physical and social sciences and increasingly must take into account the economic and behavioral aspects of human decision-making.

The long-term goal of ORD's research on public health outcomes will be to provide the scientific understanding and tools to EPA and others for use in evaluating the effectiveness of public health outcomes resulting from risk management actions. Research will focus on identifying, discovering, or developing the most effective methods and models; determining how they can be integrated into a decision-making framework to assist Federal, State, and local decision-makers in evaluating changes in

public health as a result of risk management actions; and developing a framework to quantify such changes accurately. Specific research objectives include the following:

- ❑ Establish the linkage between sources, environmental concentrations, exposure, adverse effects or disease, and effectiveness such that a change in a human health outcome consequent to a risk management action can be determined by measuring or modeling any one of these linked steps; and
- ❑ Improve methods and models by which others can measure or model changes in public health outcomes following various risk management actions.

Because of the novelty of the long- term goal and research objectives and the requirement for an unusually high degree of interdisciplinary coordination, ORD will develop a multiyear implementation plan for the public health outcomes research program. This plan will provide considerable details on the development, investigation, and delivery phases of the research.

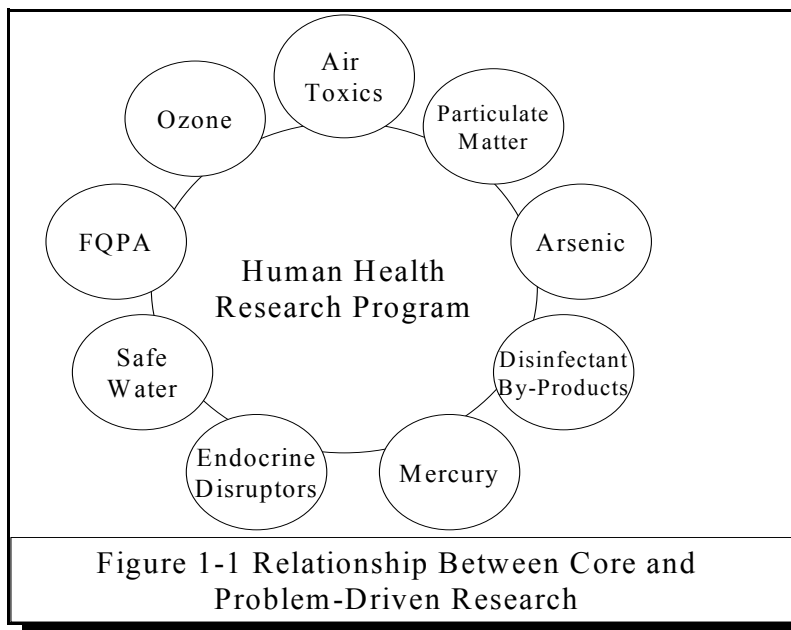
# 1. INTRODUCTION

The mission of the U.S. Environmental Protection Agency (EPA) is to protect public health and safeguard the natural environment (i.e., air, water, and land) upon which life depends. Risk assessment is an integral part of this mission in that it identifies and characterizes environmentally related health problems. EPA's Office of Research and Development (ORD) conducts research that contributes to the scientific foundation for risk assessment and risk management decisions in EPA's regulatory programs. Since 1996, ORD has used a risk-based strategic planning process in consultation with EPA's Program and Regional Offices and the external scientific community to set research priorities. From this process, research to improve human health risk assessment was identified as one of six priority research areas in the *1997 Update to ORD's Strategic Plan* (U.S. EPA, 1997a) and *ORD Strategic Plan* (U.S. EPA, 2001b). As such, fundamental human health research is also part of the ORD Sound Science Program under Goal 8, which is one of EPA's 10 strategic environmental goals in accordance with the requirements of GPRA (see text box).

**Goal 8: Sound Science, Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems - EPA will develop and apply the best available science for addressing current and future environmental hazards as well as new approaches toward improving environmental protection.**

## 1.1 PURPOSE OF THE STRATEGY

The *Human Health Research Strategy* presents a conceptual framework of ORD's future research directions in human health risk assessment and risk management. This



strategy identifies the broad, overarching questions that will guide ORD's core human health research program over the next 5 to 10 years. Core research aims to provide broad, fundamental scientific information that will improve understanding of problem-driven human health issues arising from risk assessment in EPA's Program and Regional Offices. Core research consists of understanding the fundamental processes that underlie environmentally related health problems; the development of broadly applicable research and risk assessment tools and approaches; and the design, implementation, and maintenance of appropriate measures of environmental exposure (NRC, 1997). Approximately 40% of ORD's research program has been defined as core research. Problem-driven human health issues associated with specific contaminants, media, or issues (e.g., particulate matter, arsenic in drinking water, disinfection byproducts, endocrine disruptors) are addressed in separate ORD Research Strategies and Plans (see Appendix A). Fundamental research issues that cut across those research strategies must often be addressed before more problem-driven

questions can be studied. There will be a constant need to integrate problem-driven and core research as illustrated in Figure 1-1. For example, problem-driven research is being conducted to study the interaction of pesticides in mixtures because the Food Quality Protection Act (FQPA, 1996) indicates that EPA should consider the risk associated with cumulative exposures of pesticides having a common mechanism. However, core or basic research on the mode or mechanism of action of these pollutants will have to be done before addressing more problem-driven questions concerning the interaction of pesticides based on their mechanism or mode of action.

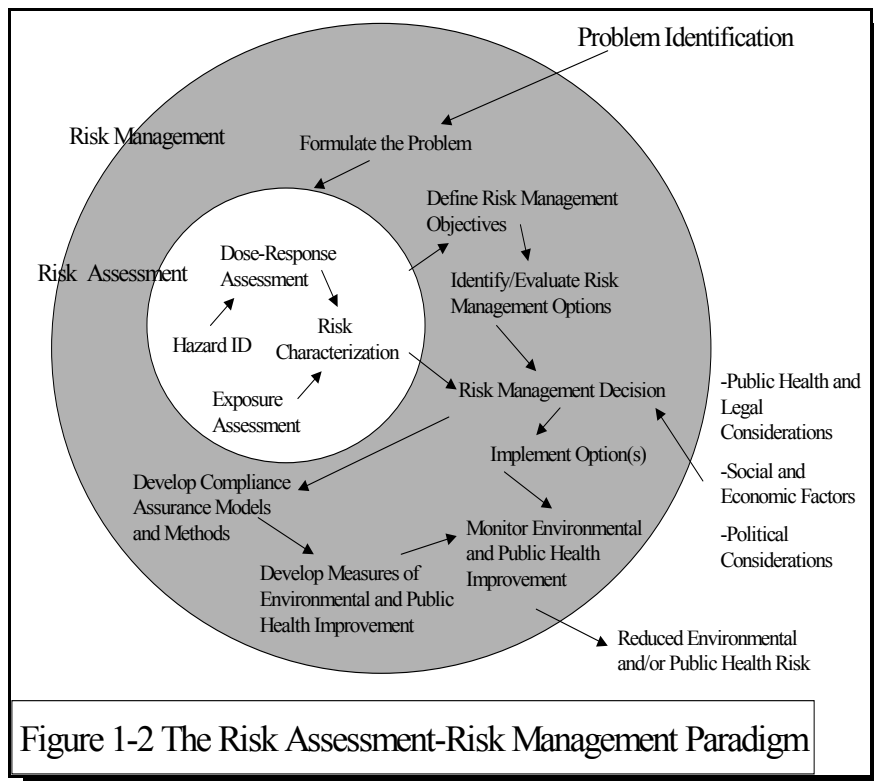


Figure 1-2 The Risk Assessment-Risk Management Paradigm

The *Human Health Research Strategy* is not intended to be a technical document. The target audience includes EPA and other federal agency scientists, managers, and policymakers, as well as the scientific community at large. It describes the scientific uncertainties, objectives and general approaches that will be taken by ORD's core research program on human health. ORD has developed a Multiyear Plan for Human Health Research that describes anticipated goals and measures over a 5- to 10-year period. In addition, each Laboratory and Center within ORD is developing its own approach to link specific projects and tasks to the ORD Multiyear Plan and the themes described in this research strategy document.

## 1.2 CURRENT RESEARCH PROGRAM ON HUMAN HEALTH

Human health risk assessment provides a qualitative and quantitative characterization of the relationship between environmental exposures and effects observed in exposed individuals. In 1983, the National Research

Council (NRC) described four primary steps in the process of risk assessment, i.e., hazard identification, dose-response assessment, exposure assessment, and risk characterization (Figure 1-2). Risk assessment is the primary scientific input to the risk management process, which involves the recognition of a potential new risk and development, selection and implementation of EPA actions to address the risk. Risk management often considers a wide variety of other factors. The overall process of risk assessment and risk management is often called the Risk Assessment-Risk Management Paradigm.

Over the last several years, ORD has aligned its organizational structure and research program to be consistent with the Risk Assessment-Risk Management Paradigm (Appendix B)(see text box on next page). ORD is organized into three national Laboratories and two Centers. The National Exposure Research Laboratory (NERL) focuses on measuring exposures and

### Laboratories and Centers in ORD

<u>Major Focus</u>	<u>Lab/Center</u>
Exposure and Dose	NERL
Dose and Effects	NHEERL
Risk Assessment	NCEA
Risk Management	NRMRL
Extramural Research	NCER

producing scientifically defensible exposure models that reduce the gaps in scientific knowledge related to actual human exposure to pollutants. In 1995, EPA's Science Advisory Board (SAB) (U.S. EPA, 1995) reviewed the state of exposure assessment science and reported that this area was hampered by a variety of technical limitations, including lack of exposure measurement techniques, a paucity of exposure databases and other exposure-relevant data, and reliance on numerous default assumptions with little justification for their selection. The SAB also found that available exposure models had rarely been evaluated against actual human exposure measurements. In addition, there were no comprehensive human exposure models that could describe the complex relationships between pollutant sources, environmental concentrations, exposure pathways, actual human exposures, and the dose that results from exposure to pollutants by multiple pathways. The SAB also found that the methods available for both human exposure measurements and exposure modeling were too intrusive or costly to implement routinely. Much of the work conducted by NERL over the last several years has been directed at these data and methodological gaps.

In the Risk Assessment-Risk Management paradigm, dose-response assessment is the process for determining the likelihood of an adverse effect at a particular exposure or dose. A primary concern for dose-response

assessment is an understanding of the dose of the pollutant that reaches its target organ, tissue, cell, or biomolecule. Research on issues related to dose is largely conducted at NERL and the National Health and Environmental Effects Research Laboratory (NHEERL). Research at NERL focuses on pharmacokinetic (PK) modeling to estimate internal dose metrics for multiroute aggregate exposure. Research at NHEERL focuses on determining the basis for metabolic differences between species. This information is crucial for extrapolating toxicological data from animals to humans in risk assessment and determining the biologically effective dose of the parent compound or metabolite(s) of the pollutant.

The goal of hazard identification is to describe and ultimately predict in humans the toxicological effects of pollutants that might occur due to exposure to environmental agents. Research related to hazard identification is largely conducted at NHEERL and focuses on test methods development and characterization of hazard potential in animal models. Clinical or epidemiological studies are also used to identify potential risks in the human population and generate testable hypothesis for future studies in animal or *in vitro* models. Risk assessment is often confounded by a number of uncertainties related to the risk assessment methodology, including extrapolation across species, extrapolation from short-term to lifetime exposures, and variability of response within the human population. A significant component of research at NHEERL focuses on reducing or eliminating uncertainties in the risk assessment process. Research at NHEERL also seeks to understand the cascade of events between the presence of a pollutant at a target site and the ultimate manifestation of toxicity. Knowledge of the sequence of biological events that must occur to produce an adverse effect [i.e., the mechanism of action, or an understanding of some, but not

all, of the key biological steps leading to toxicity, i.e., the mode of action (U.S. EPA, 1996; U.S. EPA, 1999a; IPCS, 1999; Schlosser and Bodganffy, 1999)] is being used with increasing frequency in risk assessment (see Appendix C). Procedures for the use of mechanistic data are defined in the EPA's draft Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999a).

The National Center for Environmental Assessment (NCEA) performs complex risk assessments of national interest and develops risk assessment methods, databases, and tools based on results produced by ORD and others. NCEA also serves an integrating function within ORD, bringing together results from hazard identification, dose-response assessment, and exposure assessment on issues related to the risk assessment process. The risk assessment program includes development of dose-response and exposure models, factors, databases, and guidance for conducting risk assessment. Issues confronting the risk assessment program include how to use exposure, pharmacokinetic, and mechanistic data in risk assessment; harmonizing cancer and noncancer risk assessment methods, and conducting cumulative risk assessments of multiple pollutants.

The National Risk Management Research Laboratory (NRMRL) focuses on providing the most effective and useful risk management options and improving the linkage between risk assessment and risk management efforts.

Intramural research conducted by NERL, NHEERL, NCEA, and NRMRL is complemented by extramural research sponsored by ORD's National Center for Environmental Research (NCER). Through the Science to Achieve Results (STAR) Program, NCER supports grants that focus on specific research needs consistent with

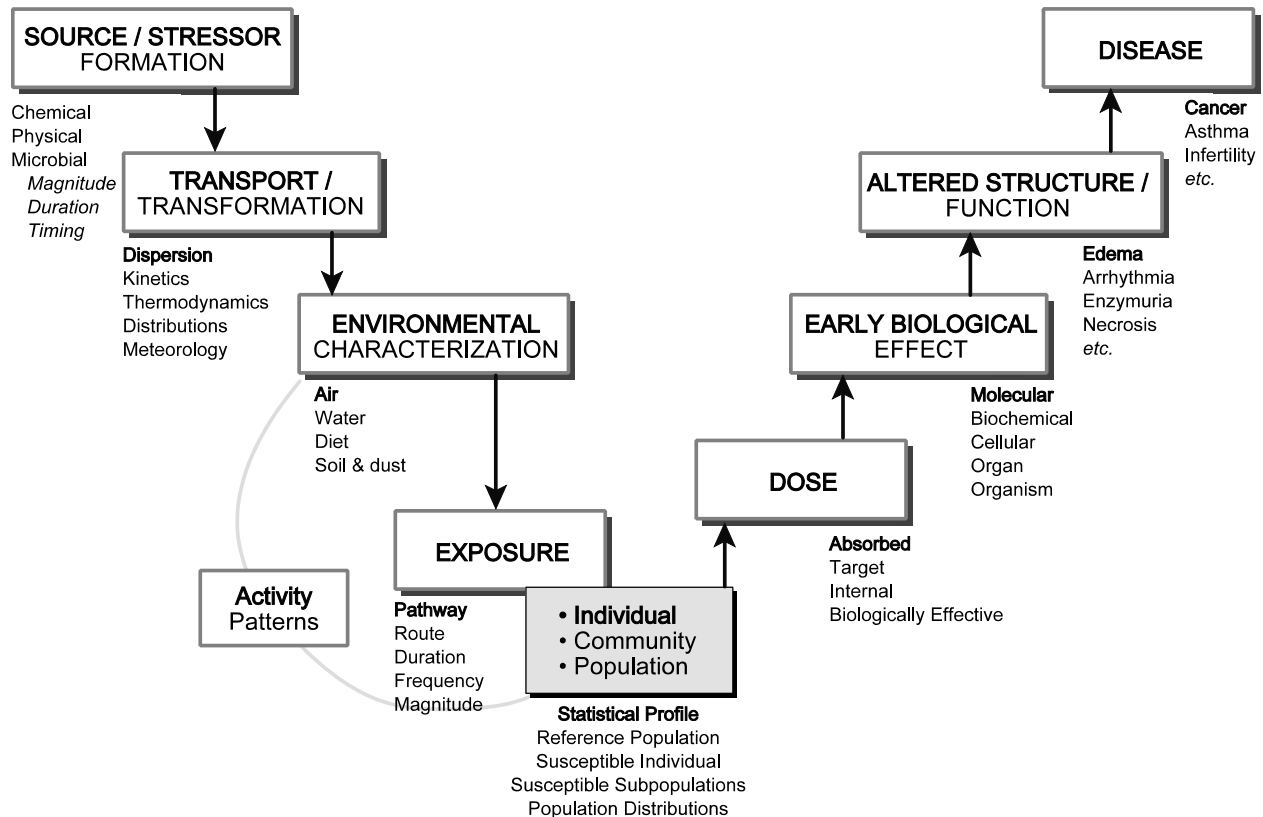
the mission of the EPA. For example, the STAR Program provides support to extramural scientists to develop statistical and predictive approaches for assessing risks from pollutant mixtures. Other examples of STAR research include 12 EPA/National Institute of Environmental Health Sciences (NIEHS)-supported Centers for Children's Health and Disease Prevention Research and individual studies, such as the development of biomarkers for risk assessment in children.

### **1.3 FUTURE RESEARCH PRIORITIES**

#### **1.3.1 Framework for an Integrated Research Program in ORD**

ORD will develop a multidisciplinary research program that addresses linkages lying along a continuum from the source of an agent through exposure and dose to adverse outcome such as disease (Figure 1-3). One example of the need for an integrated research program arises from the opportunities and challenges associated with data in recent reports by the Centers for Disease Control and Prevention (CDC, 2001, 2003). The first publication, the *National Report on Human Exposure to Environmental Chemicals*, provided an ongoing assessment of the U.S. population's exposure to environmental chemicals using biomonitoring. This report contains blood and urinary values on 27 pollutants collected as part of the National Health and Nutrition Examination Survey (NHANES). The second report, which was released in January 2003, presents biomonitoring exposure data for 116 environmental chemicals for the U.S. population divided into age, gender, and race/ethnicity groups. The exposure information should help prioritize research on the relation between exposure and health effects and help identify population groups with unusually high exposure for health effects evaluation. Efforts will be made to link the biomonitoring data back to

# Scientific Elements of Human Health Risk Assessment



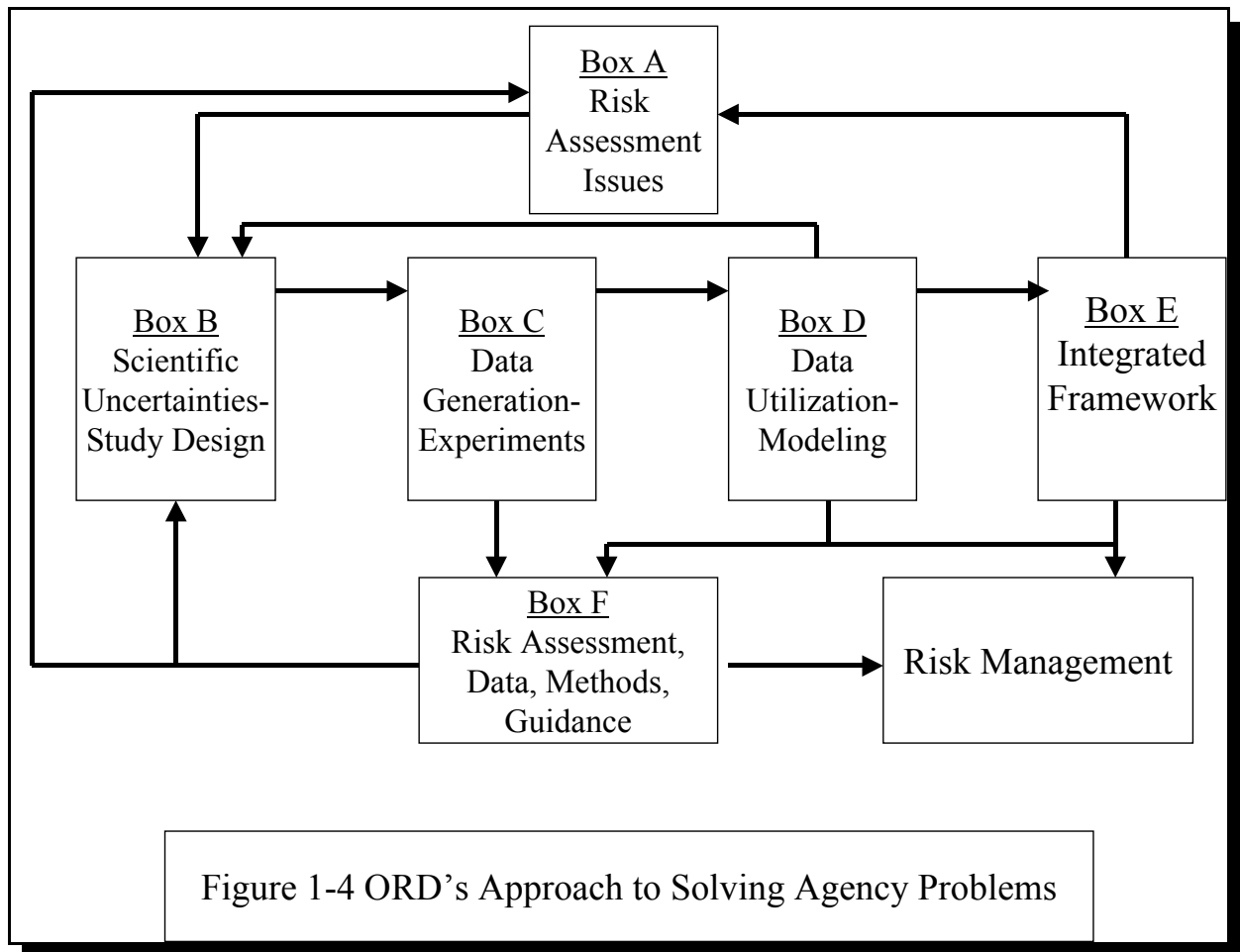
**Figure 1-3 The Exposure-Dose-Effect Continuum**

pathway and source to guide risk management interventions.

ORD's evolving integrated approach to problem formulation and research planning is illustrated in Figure 1-4. Risk assessment issues arising from Regional or Program Offices, through legislative or regulatory mandates or ORD research results will be evaluated to determine the scientific questions (Figure 1-4, Box A). This evaluation will lead to the design of studies to address those uncertainties (Box B). Results from these studies (Box C) will be used to refine additional studies and/or generate models (Box D) to inform the development of better risk assessment methods. Efforts to construct modules or compartments of models (Box D) will feed back onto the design and execution of additional experiments. Ultimately, results from all experiments and models will be used to develop

risk assessment methods (Box F) and develop an integrated framework (Box E) that will form the scientific basis for risk assessment guidance and risk management decisions. Consolidated information resulting from the integrated framework may also be used to inform or redefine the original risk assessment issue.

A conceptual model illustrating a completely integrated research program is illustrated in Figure 1-5. As this figure shows, analysis of risk assessment issues gives rise to scientific questions concerning exposure, dose, effects, and risk assessment methods. For example, risk assessment questions related to exposure might require studies involving the development of analytic methods and the execution of pilot-scale laboratory or field exposure research followed by larger scale population or epidemiological studies to gain important

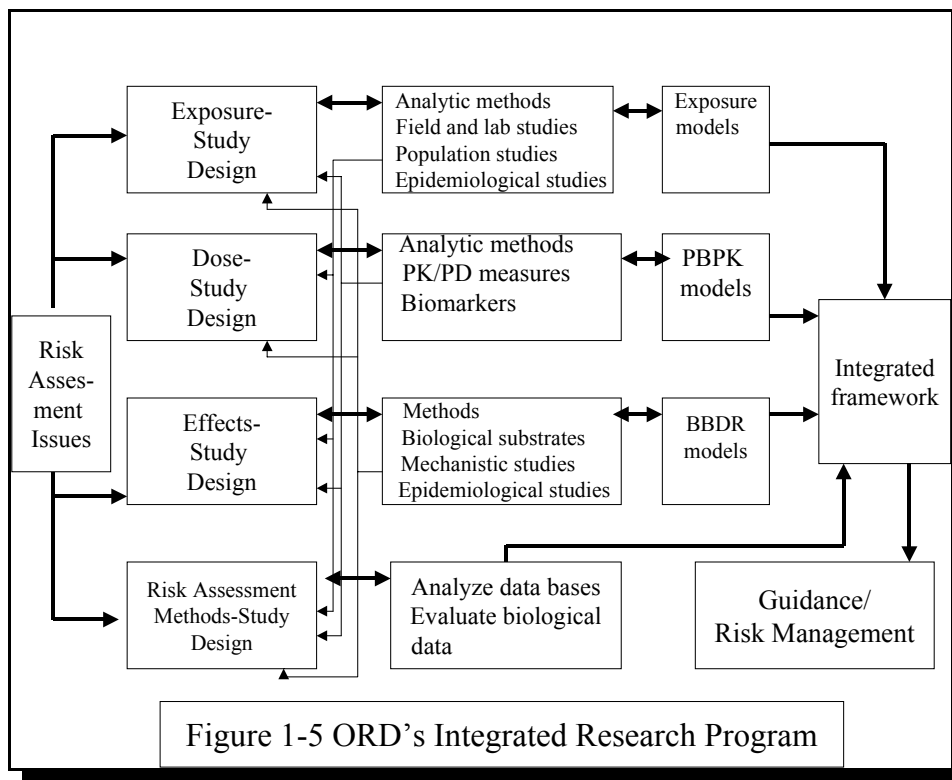


exposure and/or exposure factor data. The results of this research could be used to help develop exposure assessment models. Research questions related to dose might involve experiments to develop analytical methods, obtain pharmacokinetic data, or identify biomarkers. The results of these experiments would be used to develop physiologically based, pharmacokinetic models for estimating internal dose. Effects research may require the development of sensitive and specific methods to help understand the biological substrates underlying the mode or mechanism of action of environmentally relevant pollutants. Epidemiological studies may provide the basis for confirming possible health-related adverse effects in the human population and generate testable hypotheses for subsequent confirmation in animal or *in vitro* models. The results of effects research would be used to develop biologically based dose-response models linking effects observed at

the cellular or molecular level to adverse health effects. Assessment of data generated from exposure, dose and effects research would be used to formulate better risk assessment methods. All of the data generated from research on exposure, dose, effects, and risk assessment methods would be used to help develop an integrated framework for the development of guidance for risk assessment and scientific support for risk management options.

Figure 1-5 also shows that results from various experiments and models may feed back at any time through an iterative process to improve the design of future experiments. Results from experiments and outputs from models in any area of analysis (i.e., exposure, dose, effect, risk assessment) may influence the design of studies and the generation of data in other areas. For example, the results of field studies concerning exposure of children to pesticides might





constituents of mold are associated with allergenicity. The third objective of this research program is to demonstrate parallels between human and rodent responses to the mold in order to facilitate interspecies extrapolation. Epidemiological and clinical studies evaluate the exposures of children to fungi that might lead to asthma using a cohort of children to address the hypothesis that

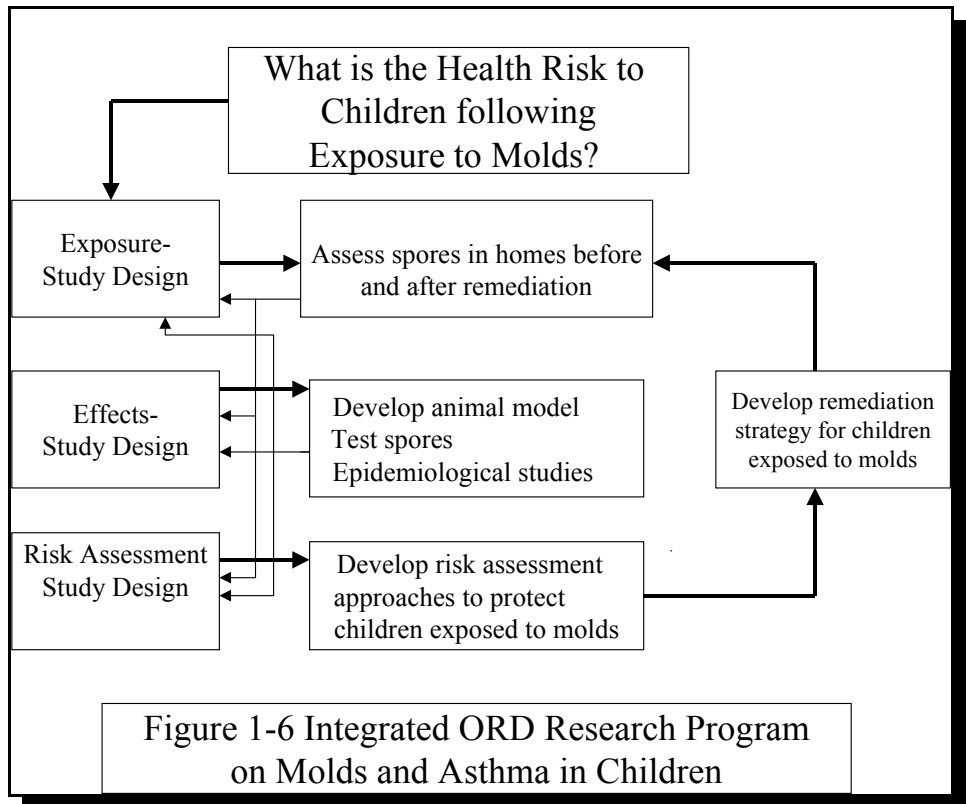
influence the choice of dose or concentration of pollutants for future research.

ORD's ongoing research on asthma and exposure of children to fungi and molds serves as a specific example of a multidisciplinary, integrated research program that uses the scientific expertise and resources from the various ORD Laboratories and Centers to address a high priority research issue (Figure 1-6). In 1998, a team of researchers from NERL, NHEERL, NCEA and NRMRL was organized to address the effects of the *S. chartarum* fungus, a common indoor contaminant, on children's health. The first objective of this program was to determine, before and after remediation, the quantities of *S. chartarum* spores in dust from homes of children with asthma or pulmonary hemosiderosis and assess specific antibodies to mold proteins in these children. A second objective was to establish a mouse model of allergic lung disease to characterize IgE-inducing proteins from three fungi, including *S. chartarum*, immunologically, and identify any common characteristics using advanced proteomics. This research addresses the hypothesis that differences in protein

participants in the fungal-exposed cohort will have significantly more asthma than control participants. Other objectives of this research are to test methods to reduce spore release and growth of fungus and to begin to develop a risk assessment model. The ultimate goal is develop a model that can be used to address risk assessment and risk management approaches for indoor molds associated with asthma and other health conditions.

Figure 1-6 illustrates the integrated multidisciplinary approach that has been developed to address this high priority need of EPA. Exposure data from field studies identify and characterize exposures to fungi that might be associated with childhood asthma. These studies also help define the relationship between exposure and effects and provide important exposure information for the design of effects studies and risk assessment approaches. Research on effects focuses on developing animal models of allergic lung disease that can be extrapolated to humans and on studies providing a causal link between the potential mode of action or mechanism and allergic lung disease. Mechanistic effects research helps confirm

the associations observed in the exposure assessment and could lead to the identification of specific fungi species involved in producing allergic lung disease. Epidemiological studies in children provide important information for the design of risk assessment approaches to protect children exposed to fungi and help shape the design of future studies. Risk assessment approaches are being developed based on results from the exposure assessment and effects research, all of which provide the scientific basis for development of risk management options and remediation strategies, if necessary. Once a remediation strategy has been implemented, future studies will be designed to evaluate the effectiveness of the strategy. Depending on the outcome of these studies, additional research on exposure, effects, and risk assessment models may be initiated to devise a more effective risk assessment-risk management approach.



### 1.3.2 Research Themes

Based on input from Regional and Program Office risk assessors and ORD scientists, future ORD research will focus on two strategic directions (see text box), including research to improve the scientific foundation of human health risk assessment and research to enable evaluation of public health outcomes from environmental risk management decisions. Research to improve human health risk assessment will emphasize three themes, i.e., harmonizing cancer and noncancer risk assessments, assessing aggregate and cumulative risk, and evaluating risks for susceptible and highly exposed subpopulations. ORD has determined that there is a need to develop the scientific basis for harmonizing the use of mechanistic information in cancer and noncancer risk assessments. Research on assessing aggregate and cumulative risk addresses the need to develop risk assessment/risk management approaches to

#### Strategic Research Directions

- ☐ Research to Improve the Scientific Foundation of Human Health Risk Assessment:
  - Harmonizing Cancer and Noncancer Risk Assessments
  - Assessing Aggregate and Cumulative Risk
  - Evaluating the Risk to Susceptible Human Subpopulations

evaluate multichemical/multipathway exposures to environmental agents, while research on risks to susceptible and highly exposed subpopulations focuses on understanding variability in human responses to environmental agents. Susceptible subpopulations also include populations of people that are differentially exposed to environmental agents. These themes are discussed in greater detail in Chapter 2.

ORD will also initiate research to enable the evaluation of public health outcomes from risk management actions. This program will include new EPA efforts to measure and monitor improvements in environmental public health following risk management actions as underscored by requirements that EPA evaluate the success of its environmental programs and decisions. Success will be measured by changes in health outcomes and indicators resulting from risk management decisions. EPA has traditionally relied on “process” measures (e.g., decreased emissions, number of sites cleaned up) to measure public health benefit indirectly. ORD’s future research program will seek to identify and validate health events that can serve as true public health outcome measures (Figure 1-7). The regulatory and scientific bases for this part of the research program are described in greater detail in Chapter 3 of this document.

#### 1.4 STRATEGIC PRINCIPLES

The following strategic principles will be used in developing and implementing ORD’s research program on human health:

**Collaboration across ORD** - As described previously, the intramural ORD program is organized around the Risk Assessment-Risk Management Paradigm, i.e., NERL, NHEERL, NCEA and NRMRL

(Figure 1-2). ORD’s future research program will focus on more complex environmental problems requiring collaboration and synergy between the various Laboratories and Centers in ORD. Scientists in Program and Regional Offices are viewed as collaborators as well as clients, and collaborative relationships will be established to design and conduct studies related to human health risk assessment and risk management.

**Focus and Broad Application** - A research strategy to improve human health risk assessment and management must emphasize selected high-priority issues with outcomes expected to have a wide effect on risk assessment. ORD will focus the core human health research program on environmental pollutants, which is consistent with the expertise and infrastructure ORD has developed over the last several years. However, as knowledge gaps are identified for other classes of environmental agents, such as microbes and bioaerosols, research will be initiated to address specific questions related to those agents.

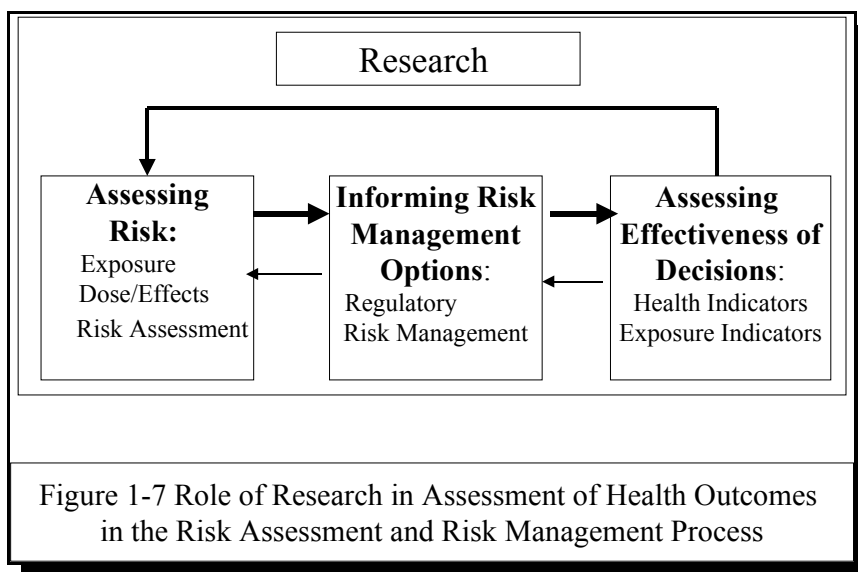


Figure 1-7 Role of Research in Assessment of Health Outcomes in the Risk Assessment and Risk Management Process

***Support EPA's Mission*** - The research must address knowledge gaps in risk assessment identified by Program and Regional Offices or raised by specific regulatory or legislative requirements. Results should have tangible benefits to all groups interested in improved risk assessments (i.e., states, local governments, industry, nongovernmental environmental organizations, communities, international governments). ORD's research will result in products and information that have direct and practical applications in risk assessment. ORD scientists will also identify issues that may be important to the future of risk assessment that are not major concerns to programs and regions at the present time.

***Outreach, Coordination, and Partnership with External Scientific Community*** - ORD will develop an integrated research program utilizing its intramural scientific capacity in conjunction with extramural grants and cooperative and interagency agreements. In addition, efforts have been and will continue to be made to identify and foster collaboration with other federal and state agencies, as well as academic and private organizations, that complement ORD's research efforts (see Appendix D).

## **2. RESEARCH TO IMPROVE THE SCIENTIFIC FOUNDATION OF HUMAN HEALTH RISK ASSESSMENT**

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; how much of the toxic moiety arrives at the target site; and 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 1-3). The overall objective of ORD's human health research program is to link exposure, dose, and effect approaches along this continuum in order to provide an integrated information base for scientifically defensible risk assessment and risk management decisions.

### **2.1 Research on Harmonizing Risk Assessment Approaches**

#### **2.1.1 Scientific Uncertainties**

Assessment of health risk from exposures to environmental agents has traditionally been performed differently depending upon whether the response is a cancer or a noncancer health effect. This practice has been based on a limited understanding of the mode of action of toxic substances. Historically, cancer was thought to be largely the consequence of the direct interaction of a carcinogen with DNA to produce a heritable change in a single cell that eventually produced a tumor. It was thought, therefore, that the dose-response for such a mechanism would not show a biological threshold but would be linear at low doses. This led EPA to employ a science policy that cancer risk

should be estimated by a linear, nonthreshold dose-response method.

On the other hand, a threshold has been generally assumed for noncancer effects based on considerations of compensatory homeostasis and adaptive mechanisms. The threshold concept assumes that a range of exposures can be tolerated up to some finite level without adverse effects. This threshold will vary from one individual to another, so that there will be a distribution of thresholds in the population. Except for some pollutants, such as the criteria air pollutants, evaluating human risks for noncancer effects has generally involved the determination of a level of daily exposure that is likely to pose no appreciable risk of deleterious effect during a lifetime.

The disparate approach for assessment of cancer and noncancer endpoints has been questioned (e.g., NRC, 1994). It now appears that carcinogens can affect many cellular targets and biochemical and biological processes that eventually lead to the formation of tumors. Such targets may include DNA, which contains the genes that control cell growth, or biochemical processes involved in cell growth regulation, cell signaling, and cell-to-cell communication. Other mechanisms may involve cell toxicity and death, perturbation of hormonal systems, and suppression of the immune system. Many of these mechanisms may have thresholds of response, as discussed in the proposed new cancer risk assessment guidelines (U.S. EPA, 1996, 1999a). It has also been hypothesized that threshold considerations may not be applicable to all noncancer effects, e.g., lead-induced cognitive deficits in children. Furthermore, our emerging understanding of the mechanisms of carcinogenesis and other health effects suggests that the underlying

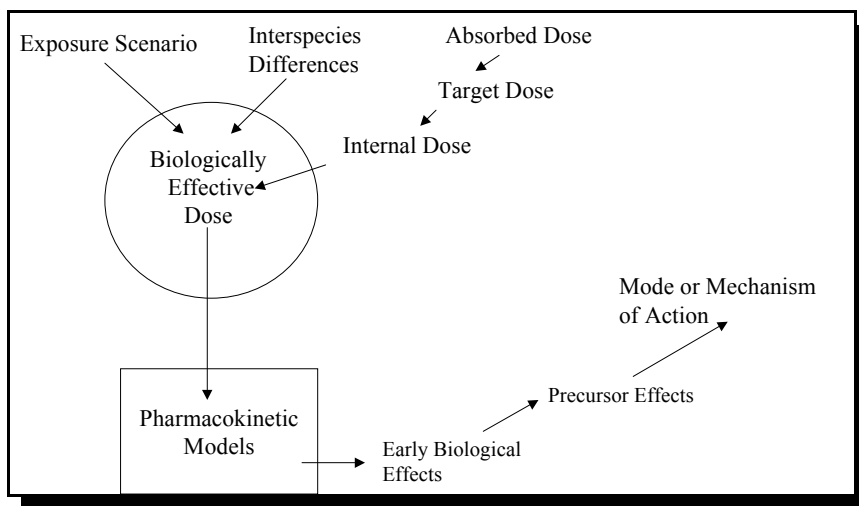
basis for certain noncancer and cancer endpoints may have common precursors. For example, pollutant-induced toxicity can cause altered biological function, cell death, and tissue regeneration while surviving cells compensate for that injury by increasing cell proliferation which may result in tumor formation if continued unchecked. Thus, the primary precursor effect may be related to both the cancer outcome and other types of noncancer biological effects.

Understanding an agent's mechanism of action will be crucial to a more accurate prediction and characterization of hazard and risk and will be the basis for developing harmonized approaches for all health endpoints. *Harmonization* in this context refers to the development of a consistent set of principles and guidelines for drawing inferences from scientific information. It does not mean that a single methodology should be used for the assessment of all toxicities and pollutants. Instead, it emphasizes the need for consistent application of all pertinent information on toxicity, dosimetry, mode of action, and exposure in all risk assessments regardless of the nature of toxicities or pollutants. ORD will focus its research to improve the foundation of these risk assessment methods by seeking to better understand the mechanisms or modes of action that are common to cancer and noncancer health effects. One of the goals of ORD's research on harmonization is to improve general understanding of mechanisms and modes of toxic action.

### 2.1.2 Research Objectives

The following research objectives provide the framework needed to develop an integrated research program that will harmonize risk assessment approaches:

- ❑ Develop, validate, and standardize emerging technologies or methods to study mode or mechanism of action;
- ❑ Develop the biological basis for understanding mode or mechanism of action;
- ❑ Develop a basis for comparing risk across all health endpoints using mechanistic information;
- ❑ Develop principles for the use of mechanistic data to select the most appropriate risk assessment models; and
- ❑ Develop principles for the use of mechanistic data to reduce or replace uncertainty factors in risk assessments, especially for inter- and intra-species extrapolation, including approaches for linking dosimetry models, such as pharmacokinetic models, with empirical or pharmacodynamic models for effects of pollutants with similar or different modes of action.



### 2.1.3 Research Approach

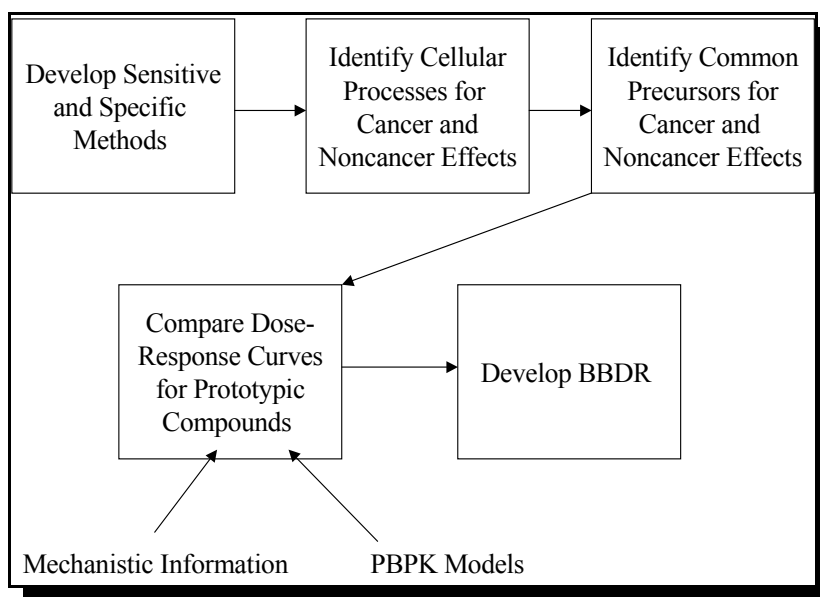
*Exposure Research.* Specific exposure issues have not been identified within the context of the harmonization of risk assessment approaches. Research to characterize the various exposure pathways to relevant pollutants is described in Section 2.2 under the theme of Aggregate and Cumulative Risk and includes a description of the magnitude and nature of the pollutants to

which people are exposed, as well as the timing and sequence of those exposures. Research on differential exposure of susceptible and highly exposed subpopulations is described in Section 2.3.

*Dose Research.* It is hypothesized that there may be common biological effects that serve as precursors to various health effects. For example, some pollutants may cause multiple effects, both cancer and noncancer, through initially similar mechanisms, such as adduction of DNA or binding to a receptor. Subsequent events must differ in order to produce different effects. Other pollutants can cause multiple effects through multiple mechanisms, often through the formation of metabolites with different biological activities. In either case, knowing the biologically effective dose of the active pollutant at the target site is crucial for elucidating mechanisms and modes of cancer and noncancer health effects for risk assessment. Research on dose will identify the biologically effective dose of parent compound or metabolites in target tissue and attempt to relate those levels to the presence of early biological and precursor effects at the molecular, biochemical, cellular, organ, and organismal levels (see schematic on previous page). This information will, therefore, be crucial for studies attempting to elucidate mode or mechanism of action. The development of pharmacokinetic models to inform studies on mode or mechanism of action must also take into account variables such as the duration of exposure and possible interspecies differences in sensitivity.

*Effects Research.* Central to the question of harmonizing risk assessment approaches is whether various modes or mechanisms of action have a similar necessary step (e.g., cell proliferation, receptor interaction, response to injury or stress, alterations in DNA repair mechan-

isms, apoptosis) leading to the adverse effect. Virtually every toxic event in a tissue or organism exposed to a pollutant is modulated by a finite number of damage-response pathways by which cells sense the status of their internal environment. Through these sensors, critical processes that activate specific genes or proteins to cause the cell to migrate, proliferate, differentiate, or die are made by a cell's biochemical machinery. Progress in this area depends upon a clear understanding of the changes in the biology of the cell following delivery of the active chemical moiety to target cells and the relationship of responses with dose. Determining the presence of the active toxic moiety at specific target sites will be crucial for these studies.



A significant first step in effects research on harmonization will be the development of sensitive and specific methods (see schematic above) to study mechanism or mode of action based on the application of emerging technologies, especially proteomics and genomics. Bioinformatic approaches will also have to be developed to help interpret the meaning of changes coming from multigene, microarray assays used in hazard identification and quantitative dose-response assessment. Effects

research will initially focus on identifying cellular processes (e.g., regeneration, proliferation) that may be similar for cancer and noncancer health effects. This research will lead to studies that will identify common biochemical or molecular pathways associated with those cellular processes. Research will then focus on studies concerning the effects of environmentally relevant doses or concentrations of prototypic pollutants with similar putative modes or mechanisms of action or on pollutants sharing similar structure-activity relationships. If a common cellular target can be identified for specific adverse outcomes, physiologically based pharmacokinetic (PBPK) models will determine target tissue levels and the influence of duration of exposure and interspecies variation on adverse effects. One of the long-term goals of ORD's research is the development of models that take into account the sequence of early biological events leading to adversity (i.e., mechanisms or modes of action) for multiple endpoints, the shape of the dose-response curves at low doses, and the influence of interspecies differences. ORD research will study both high and low doses in order to elucidate the likely shape of the dose-response curve and to determine whether different modes or mechanisms may be operating at different doses. ORD will also focus on developing animal models that can be extrapolated directly to humans.

Mechanistic effects research based on emerging technologies such as proteomics, genomics, and bioinformatics will also feed directly into ORD's efforts to set mechanistically based priorities for pollutant risk assessments and optimize *in vivo* and *in vitro* testing requirements through the use of computational methods and molecular profiling, i.e., computational toxicology (see text box). For example, computational methods, such as quantitative structure-activity relationships (QSAR), could be used

### Computational Toxicology

The application of models from computational and systems biology and computational chemistry for prediction and understanding mechanisms of action

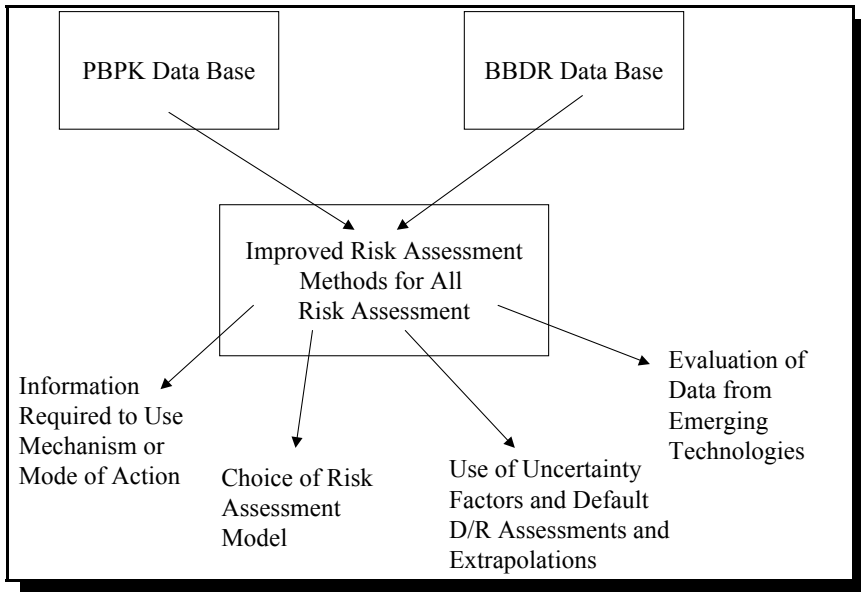
to determine which set of chemicals out of a larger population [e.g., Toxic Substances Control Act (TSCA) inventory] might have the potential to produce an adverse effect (e.g., cancer or reproductive toxicity). This information could be used to prioritize subsequent testing of this subset of chemicals for potential human health or environmental effects. Emerging technologies such as genomics and proteomics could be used to generate molecular profiles that would serve as diagnostic tools to discriminate toxicological pathways leading to different adverse effects. Diagnostic tools could be used to design *in vitro* and *in vivo* tests to confirm the toxicological pathway involved in producing the adverse effects. This information would then be used to guide the selection of specific testing protocols for risk assessment. ORD will initially demonstrate the feasibility of this approach by focusing on prioritization and screening assays and models for endocrine disrupting chemicals. This class of pollutants was chosen because ORD has considerable experience in determining environmental exposure levels to these chemicals, as well as developing *in vivo* and *in vitro* tests in response to provisions of the Food Quality Protection Act (FQPA). The primary focus of these studies will be on endocrine-mediated reproductive and developmental effects following exposure to environmentally relevant concentrations.

*Risk Assessment Methods.* In developing harmonized approaches for the assessment of risk to different health endpoints, a key issue is to determine how much information is needed to show that a



particular toxic effect is mediated by a specific mode of action and that the pollutant or its metabolite is present in sufficient quantities in the target tissue (see schematic).

or proteomic methods. This “translational” research will be a major challenge for EPA as the onslaught of data generated by these new approaches will far outpace the research and guidance on interpretation and application in risk assessment.



Recent EPA guidance to improve risk assessments has emphasized the importance of providing risk managers with a fuller characterization of risk. Current default approaches to express risk for health effects presumed to be mediated by threshold or nonlinear modes of action include the use of reference toxicity values [e.g., chronic oral Reference Dose (RfD), inhalation Reference Concentration (RfC), or the concept of the margin of exposure (MOE)], i.e., the ratio of the critical NOAEL to the expected human exposure level.

Although these risk assessment models consider all the available data, they do not provide an explicit estimate of variability and uncertainty or provide information on the consequences of exposures that exceed the reference values or have a small MOE.

For example, the proposed cancer risk assessment guidelines (U.S. EPA, 1999a, 1996) provide for judging the plausibility and adequacy of available evidence for a postulated mode of action, identifying susceptible subpopulations, and determining the most appropriate approaches and methods for low-dose extrapolation. ORD research on risk assessment methods will focus on how to incorporate mode-of-action information for other health endpoints. Guidance will also be developed to determine how different endpoints of toxicity could develop through common biological processes or modes of action. One high priority for ORD research on risk assessment methods will be prototype assessments for both data-rich and data-poor pollutants to illustrate how mode of action, PBPK, and biologically based dose response (BBDR) models may be used *in lieu of* default approaches. Risk assessment research is also needed to develop principles to evaluate the results of studies in which the data have been generated using genomic

or proteomic methods. This “translational” research will be a major challenge for EPA as the onslaught of data generated by these new approaches will far outpace the research and guidance on interpretation and application in risk assessment.

An important focus of ORD’s risk assessment research on harmonization will be the development of approaches to characterize variability and uncertainty in reference toxicity values and to provide a probabilistic framework for estimating risks associated with exposures above reference toxicity values. This research will examine data underlying the various uncertainty factors commonly applied in setting reference values, including factors for inter-species and intra-species extrapolation (including pharmacokinetic and pharmacodynamic variability) and variability in responses due to changes in exposure duration. As an example, this research would explore the use of probability distributions that can be com-

bined to characterize the variability and uncertainty around the reference values for health effects. Various statistical approaches will be explored as a means for estimating risks above the reference toxicity values for informing risk management decisions and supporting economic benefits analyses. Risk assessment methods on risk predictive models for cancer and noncancer effects will also be investigated.

## 2.2 Research on Aggregate and Cumulative Risk

### 2.2.1 Scientific Uncertainties

The development of risk assessment methodology during the 1970s and early 1980s closely followed EPA's strategy for pollution control. Historically, EPA evaluated the risks of a single pollutant in a single exposure medium, such as lead in outdoor air or drinking water. In reality, people are constantly exposed to mixtures of pollutants. Furthermore, exposure to the same pollutant may occur from a variety of routes, including the air, water, and food. In addition, 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 environmental exposure to pollutants occurs via multiple exposure routes and pathways, including inhalation, ingestion, and uptake through the skin. Research on aggregate and cumulative risk will focus on defining the multitude of ways in which people are exposed to pollutants and characterizing the subsequent effects and risks.

The FQPA directed 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 pesticide exposure. However, EPA's efforts to assess aggregate and cumulative risk go far beyond the FQPA and pesticides. For example, the Office of Water must assess risks from 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 Office needs methods to assess risks from mixtures of criteria air pollutants and sources containing a mixture of hazardous air pollutants. The Waste Program Office deals with mixtures of many different chemical classes found together in the soil, water, and air of waste sites and their surroundings. In addition, EPA's Program and Regional Offices deal with communities 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. To encompass all these concerns, this document defines aggregate exposure and cumulative risk broadly in accordance with the working definitions developed by EPA's Science Policy Council (see text box).

#### **Working Definitions Developed by EPA Science Policy Council**

**Aggregate Exposure:** The combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and sources.

**Aggregate Risk:** The risk resulting from aggregate exposure to a single agent or stressor.

**Cumulative Risk:** The combined risks from aggregate exposures to multiple agents or stressors.

The traditional approach to assessing aggregate and cumulative risk is to focus primarily on individual pollutants and their sources. The pollutants are initially traced through the environment, and the concentrations and doses of each chemical are estimated separately. The toxicity and risks from the multiple stressors are added or combined using the basic methods in EPA's *Chemical Mixtures Guidelines* (U.S. EPA, 1986, 2000c) to determine risk. This pollutant-based approach has most often been applied for estimating exposures and risks for specific locations or scenarios (e.g., risks associated with a hazardous waste site).

The objective 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 EPA can protect the health of the public and environment more effectively. ORD's research program on aggregate and cumulative risk will take two approaches: chemical-focused and population-based. The chemical-focused approach may be better suited to address the likely effects of a specific source or a pollution control strategy when the key variables associated with that source can be well characterized for specified human exposure scenarios. A population-based approach may be better at revealing total exposures and identifying when important sources or important pathways of exposure may not have been identified. A population-based approach may also be useful in assessing public health outcomes because the objective of any control policy is to decrease public exposure and risk. ORD research will build on these two approaches to develop scientifically robust aggregate and cumulative risk assessment methods, including how to identify important stressors to a population, combine risk over several stressors, define risks that accumulate over time, and assess the interaction between stressors. The research program for aggregate and cumulative

research consists of several interrelated research efforts, all of which add critical components to the overall aggregate/cumulative risk assessment effort.

### 2.2.2 Research Objectives

The following research objectives provide the framework to develop an integrated research program on aggregate and cumulative risk:

- ❑ Determine the best and most cost-effective ways to measure human exposures in all relevant media, including pathway-specific measures of multimedia human exposures to environmental contaminants across a variety of relevant microenvironments and exposure durations and conditions;
- ❑ Develop exposure models and methods suitable for EPA and the public to assess aggregate and cumulative risk, including mathematical and statistical relationships among sources of environmental contaminants, their environmental fate, and pathway-specific concentrations; models linking dose and exposure from biomarker data; and approaches to assess population-based cumulative risk, including those involving exposure to stressors other than pollutants; and
- ❑ Provide the scientific basis to predict the interactive effects of pollutants in mixtures and the most appropriate approaches for combining effects and risks from pollutant mixtures.

### 2.2.3 Research Approach

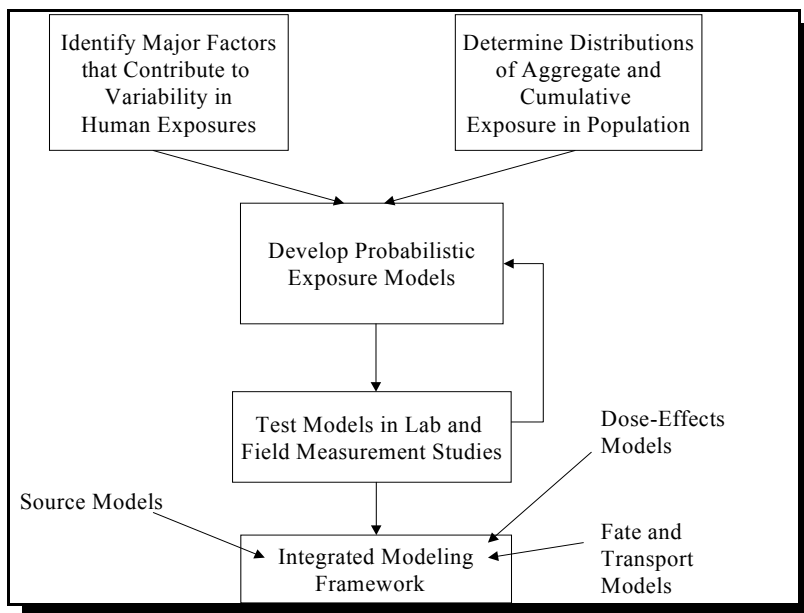
*Exposure Research.* One goal of ORD's research program is to develop methods and approaches for measuring exposures and identify exposure factors accounting for aggregate and cumulative exposure. In assessing aggregate and cumulative risk, the focus will be on measuring exposure and

estimating biologically relevant doses in exposed individuals. Considerable progress has been made over the past two decades toward developing personal measurement-based methodologies for assessing human exposures in either a population of concern, or in the population at large. The Total Exposure Assessment Methodology program and the National Human Exposure Assessment Survey (U.S. EPA, 1999b) have demonstrated the techniques and values of measuring personal exposures. In addition, the CDC continues to improve their methods for measuring pollutants and their metabolites in blood and urine and have recently begun reporting exposure data for a representative sample of the U.S. population. These measurement-based methods add to our arsenal of approaches to address aggregate and cumulative risk.

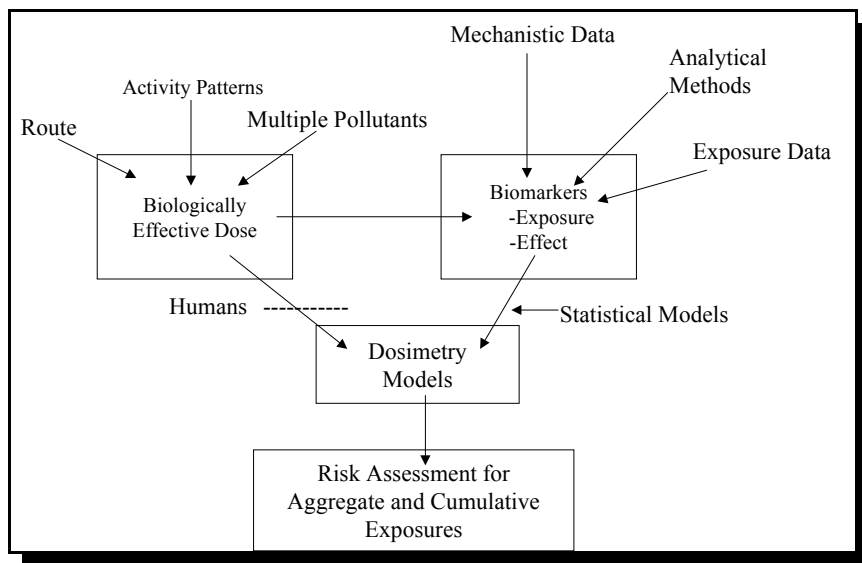
Exposure research on cumulative and aggregate risk will build upon the problem-driven research being conducted under other research strategies (see Appendix A) and focus principally on describing how people come into contact with pollutants. As a result of this emphasis, important components of this research will be to: (1) identify and characterize major factors, including time-activity patterns, that contribute to human variability in aggregate and cumulative exposure, and (2) to conduct studies to determine distributions of aggregate and cumulative exposure for the general population and for specific susceptible or targeted subpopulations (see schematic). Exposure research will integrate an understanding of exposure pathways and human contact with pollutants into probabilistic human exposure models that account for both aggregate and cumulative exposures. These exposure models will then be tested against the exposure and exposure factor data generated through targeted laboratory and field measurement studies, including population and epidemiological studies.

The resulting data will be used to improve our understanding of human exposure and refine the exposure models. The ultimate objective of this research will be to assemble and integrate a knowledge of human exposures into models that describe those exposures and to combine the source models, the transport and fate models, and the probabilistic exposure models into an integrated modeling framework that can be linked and effectively employed by the risk assessor. The framework is designed to link a variety of source, exposure, exposure-dose, and dose-effect modules into a comprehensive source-to-effects modeling framework characterizing and assessing user-specified aggregate and cumulative exposures and risks. The resulting tools, models, and framework will then be disseminated to scientists and risk assessors as they work to solve specific programmatic problems as outlined in ORD's research strategies (see Appendix A).

*Exposure to Dose Research.* When exposures to an agent occur via multiple routes, they must be converted to a common basis, usually some measure of dose, to evaluate the risk of aggregate and cumulative exposure. Ideally, the common



metric would be the biologically effective dose, that is, the dose to the target organ, tissue, cell, or molecule that causes the toxic or adverse health effect (see schematic).



The biologically effective dose may be the pollutant itself or one or more metabolites and may be affected by many factors. For example, contemporaneous exposure of a single pollutant by more than one route can result in different proportions of parent compound or metabolites than would be predicted from one route alone. The route of exposure may also modulate the internal dose of systemic toxicants at the target tissue due to alterations in physiological parameters (e.g., breathing rate due to an irritant) or pharmacokinetic parameters (e.g., induction of enzymes). Human activity patterns may also affect the biologically effective dose. A pesticide, for example, may contact the body through inhalation of dust from contaminated surfaces, the diet, and as a result of hand-to-mouth activity. People may be exposed occupationally as well as incidentally away from their place of work. People may also be exposed to low background levels and also, by virtue of special intermittent activities, to bursts of higher exposure. Finally, the biologically effective dose may

be affected by exposure to more than one pollutant. Multiple pollutant exposures might change the metabolic transformation of the pollutants in the mixture, resulting in different biologically effective doses than seen after exposure to the pollutants in isolation. Ingestion of otherwise innocuous substances, because of enzyme induction, might also increase the rate of formation of a toxicologically relevant metabolite of a pollutant of environmental concern. Knowledge of the biologically effective dose provides the basis for developing dosimetry models that can be used in assessing risk of aggregate and cumulative exposures.

Measuring the biologically effective dose in humans, however, is not easily accomplished and is therefore not usually attempted. More often, a surrogate for the biologically effective dose, such as the absorbed dose (the amount of substance crossing an absorption barrier such as the skin, the lining of the lung, or the lining of the gastrointestinal tract) or the level of pollutant in human blood, urine, or other biological tissue is measured or estimated and used in the aggregate assessment as the common metric. In some notable cases (e.g., concentration of lead in the blood, carboxyhemoglobin), the human biomarker can also be used as a quantitative predictor of effects. An exposure biomarker is an exogenous substance or its metabolite(s) measured in a compartment within an organism, whereas an effects biomarker is a measurable change within an organism that can be recognized as an established or potential health impairment. Exposure biomarkers are actual evidence of internal dose. However, only a few biomarkers, such as urinary metabolites, are relatively easy to measure in exposure field studies.

With proper research, such biomarkers can be used with pharmacokinetic models to estimate, via a “back calculation,” the biologically effective dose and even the exposure that occurred. Thus here, the exposure-to-dose continuum is actually used in reverse for “dose-to-exposure” estimations.

Identification and characterization of biomarkers and development of methods to use them will be a high priority for ORD’s research on aggregate and cumulative risk. Development of analytic methods to measure biomarkers and methods for their analysis and interpretation will be necessary for exposure and dose assessment. This will require contributions from ORD’s research on effects to provide the scientific basis for the development of sensitive and specific biomarkers based on mechanistic studies. Combined with proper modeling techniques and some knowledge of possible exposure patterns and measurements, biomarker data can be used to estimate dose and exposure. Research in this area will also focus on the development and/or implementation of advanced statistical methods to help formulate and use dosimetry models for estimating exposure from biomarkers. This is especially important as more and more biomarker measurements are taken and their results are made available. For example, CDC is publishing on the internet the results of such measurements taken in the population. Those data, often representing “snap-shots in time” will have to be interpreted using a variety of modeling and statistical tools to determine the meaning of these data with respect to exposure and dose.

Initially, ORD’s dose research will focus on the development of a suite of route-specific models for use in dose-response assessment of cumulative and aggregate exposures. This will build upon the dosimetry-based approach in the current risk

assessment guidelines, extend it to oral and dermal exposures, and use it to evaluate aggregate exposures. As the program progresses, dose models will be expanded to describe and predict chemical disposition within the body resulting from aggregate and cumulative exposures. ORD’s dosimetry models will enable users to estimate biologically relevant doses resulting from exposure to multiple pollutants and multiple pathways of exposure. The most immediate phases of this research will concentrate on aggregate exposures. In addressing cumulative risk, models will be first developed for those cases involving exposure to multiple compounds with common modes of action. The next phase will begin to address those cases in which compounds may act with different modes of action.

ORD realizes that there must be significant integration between research on exposures, dose, and effects to study the problem of aggregate and cumulative risk adequately. ORD has already implemented plans to facilitate a multidisciplinary approach to this problem. For example, scientists from NERL, NHEERL and NCEA, as well as scientists from the Office of Pesticide Programs (OPP), are working on a collaborative research project to develop methods and models for assessing the exposure, dose, and aggregate and cumulative risk of pyrethroid mixtures. In addition, NERL and NHEERL sponsored an Exposure to Dose Modeling Workshop in July 2001 to begin linking quantitative modeling in a Human Health Risk Assessment context. This meeting examined a number of issues related to source, exposure pathways, doses in toxicology and epidemiological studies, pharmacokinetic modeling of mode of action, effects, and dose-response modeling. Presentations at the meeting were followed by a discussion of research directions and options for linking models. Significant

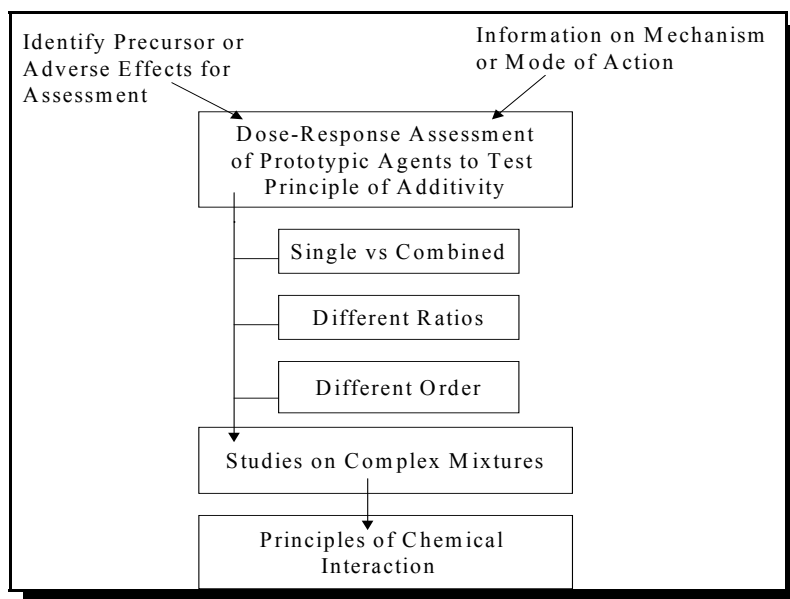
opportunities for collaboration and model-sharing between principal investigators in both laboratories were identified. Projects have been initiated to integrate to a greater extent the modeling efforts of the two laboratories. Interactions between the exposure, dose, and effects research programs and the risk assessment methods are also being developed.

*Effects Research.* The FQPA indicates that EPA must consider the cumulative effects of pesticides and other chemicals having a common mode or mechanism of toxicity. Understanding cumulative risk requires knowledge about mechanisms or modes of action and an understanding of how chemicals will interact in mixtures. The principal effects issue for cumulative risk is the possibility that chemicals in mixtures may interact in a nonadditive manner. There is evidence that the assumption of dose additivity may not hold for all mixtures of pollutants. For example, research has indicated that antagonism can occur at high concentrations of some mixtures of pollutants; whereas synergistic interactions have been noted at the low end of the dose-response curve for other mixtures. Understanding the conditions under which nonadditive interactions will occur between pollutants is needed to support risk assessment approaches for cumulative exposures.

ORD's effects research program on mixtures will test various assumptions concerning the behavior of pollutants in defined mixtures containing major or key known constituents at concentration ratios resembling real-world mixtures. To develop quantitative models, it is crucial in these studies to understand dose-response behavior and the pharmacokinetic characteristics of each pollutant. Much of this information can be derived from projected work on the development of methods and mechanistically based dose-response

models. It is likely that a systematic approach to the study of mixtures will require the development of new investigative tools such as genomics and proteomics so that effects of multiple pollutant interactions can be studied in rapid fashion.

The overall approach of ORD's effects research on chemical mixtures will be to identify key biological processes (see schematic) that could be used in testing for various health endpoints and in determining



effects of pollutants based on their mechanism or mode of action and environmental relevance. Initial studies will focus on dose-response curves for pollutants in isolation, and then pollutants will be tested for evidence of antagonism, potentiation, or synergism with other pollutants in the mixture. Two key questions are where on the dose-response curve interactions occur and whether interactions vary with the ratio of the pollutants in the mixture. Additionally, fit will be important to determine the influence of the order of presentation of pollutants in the mixture. Studies on interactions between pollutants in mixtures

will be used to develop principles for the assessment of real-world mixtures.

*Risk Assessment Methods.* Human populations are most frequently exposed to multiple environmental pollutants (e.g., particulate matter, pesticides, microbes, climatic stressors). Exposure to multiple stressors could change health risks through combining effects arising from similar modes of action or through interactions between nonchemical stressors that increase or decrease the potency of environmental agents. Research will be designed and conducted to evaluate population-based approaches to assess effects of total exposures in the environment and the interaction of chemicals with nonchemical stressors. Because this is an emerging area, case studies will be conducted and a conceptual framework will be developed incorporating results from ORD aggregate/cumulative research and addressing issues of aggregate and cumulative exposure, mechanisms of action, and PBPK and dose-response modeling. The objective of this research is to develop guidance and EPA guidelines for population-based cumulative risk that will incorporate cumulative and aggregate exposure to multiple stressors.

### **2.3 Research on Susceptible and Highly Exposed Subpopulations**

The goal of ORD's program on susceptible and highly exposed subpopulations is to understand why some people and groups are more susceptible or highly exposed than others. Observed variability in human responses to environmental agents reflects differences in biological susceptibility and exposure. Variation in biological susceptibility depends on intrinsic factors (e.g., life stage, gender, genetic factors) and acquired factors (e.g., preexisting disease, nutrition, stress, licit and illicit drug use, cigarette smoking, alcohol use). Variation in exposure and

dose can be influenced by many of the same factors. In addition, factors such as occupation, location of residence, and activity patterns that place individuals in contact with environmental agents can cause variation in exposure. Information is needed on how various susceptibility and exposure factors alter responses to chemical exposures. ORD research on susceptible and highly exposed subpopulations will focus on three factors (i.e., life stage, genetic factors, and preexisting disease) that have been identified by a program office and the scientific community as having a high priority for risk assessment.

In addition to examining the role of each of the three factors separately, ORD will examine the interactions among these factors that may result in susceptibility greater than that caused by the presence of only one factor. For example, a child with autism or developmental delay might mouth hands and toys to a greater degree than the average child. The condition of autism might make the child a highly exposed individual within a group that is already prone to higher exposures. An early exposure might also affect the development of the immune system, which in turn, could make the individual more susceptible to development of cancer later in life. Genetic predisposition, such as lack of an enzyme that detoxifies a particular chemical, can make individual members of an already susceptible life stage even more susceptible.

While life stage, genetic predisposition, and preexisting disease provide a focus for the strategy, there are many complex interactions among risk factors that must be considered in any research program on susceptible and highly exposed subpopulations. Gender is not highlighted as a factor in this research strategy, but it is recognized that any study of the effect of life stage, genetic factors, or disease on response to environmental agents must understand how



differences between the sexes influence response to exposures. ORD recognizes that stressors associated with the physical and social environment of an individual can also increase susceptibility to environmental agents. In addition, factors such as socioeconomic status of individuals and communities, access to health care, nutrition, drug and alcohol use, and exposure to environmental tobacco smoke can alter the sensitivity to environmental agents. The influence of these factors on susceptibility and exposures associated with life stage, genetic predisposition, and disease will be considered in future implementation of the strategy.

ORD will identify and study those that are susceptible to disease that can be induced or exacerbated by environmental exposures. Disease endpoints that are included within the strategy include cancer; neurotoxicity; immune system effects; asthma and other respiratory effects; reproductive effects; and birth defects including death, malformation, and growth alteration. While the strategic focus is on life stage, genetic factors, and the effects of disease on responses to exposure, the interaction of these factors with intrinsic factors including gender and stressors in the physical and social environment will be an important consideration.

Other ORD research strategies which address susceptible and highly exposed subpopulations are the *Strategy for Research on Environmental Risks to Children* (U. S. EPA, 2000a) and the *Asthma Research Strategy* (U.S. EPA, 2001a). The influence of life stage on responsiveness to endocrine disruptors is also described in the *Research Plan for Endocrine Disruptors* (U.S. EPA, 1998).

### 2.3.1 Scientific Uncertainties

*Life Stage.* There are specific periods or windows of vulnerability during development, particularly during early gestation but also throughout pregnancy and early childhood through adolescence and old age, when toxicants might permanently alter the morphology and/or function of a system (Rodier, 1980; Bellinger, et al., 1987). Many specific adverse effects ranging from functional impairment to anatomical birth defects depend on an exposure at a specific stage of development. Children may also be more vulnerable to specific environmental pollutants because of differences in absorption, metabolism, and excretion (NRC, 1993). In addition, children's exposures to environmental pollutants are often different from those of adults because of different diets and different activities (e.g., playing on floors and in soil and mouthing of their hands, toys, and other objects) that can bring them into greater contact with environmental pollutants (Bearer, 1995). Because children consume proportionately more food and fluids, have a greater skin surface area relative to their body weight, and breathe more air per unit body weight than adults, they may receive greater exposure to environmental substances (NRC, 1993). These health threats to children are often difficult to recognize and assess because of a limited understanding of when and why children's exposures and responses are different from those of adults.

The effect of aging on response to environmental exposures is another area of uncertainty based on life stage. The elderly may respond to environmental exposures differently than younger adults. There may be an increased risk of cancer and degenerative diseases as a function of age. The prominence of these concerns is rapidly elevating with the largest birth cohort in the US, namely the "baby boomers," now becoming senior citizens. Many of these

individuals are living longer and the effect of previous exposures may be markedly magnified with aging. In 2002, EPA launched an Aging Initiative designed to study and prioritize the environmental health risks aging citizens face. As part of that initiative, EPA is in the process of creating a National Agenda on the Environment and the Aging. The intent of this agenda is to help identify research gaps and develop strategies that will help scientists better understand the environmental hazards affecting the health of older Americans. EPA has held listening sessions to solicit input from the public concerning the development of a research program on aging.

*Genetic factors.* There are a number of genetic factors that could predispose human subpopulations to adverse effects from exposure to pollutants, 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 such genetic differences significantly influence risk at realistic, low-dose exposures. Information on gene-pollutant interactions as a result of long-term exposure to environmentally relevant concentrations of pollutants is needed.

*Health status.* Preexisting diseases may influence an individual's 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 from exposure to several environmental agents including dioxin, ozone, and ultraviolet radiation. Research is needed to develop animal models of diseases having a high incidence in the human population and to determine the effects of the disease on the dose-response curves for high priority

environmental agents (e.g., air pollutants, pesticides).

### 2.3.2 Research Objectives

The *Human Health Research Strategy* provides a broad framework for ORD research in human variability. Issues specifically related to children's risk are also covered in more detail in the *Strategy for Research on Environmental Risks to Children* (U.S. EPA, 2000a), the *Strategic Plan for Endocrine Disruptors* (U.S. EPA, 1998) and the *Asthma Research Strategy* (U.S. EPA, 2001a). The following research objectives provide the framework for an integrated research program on variability in the human population:

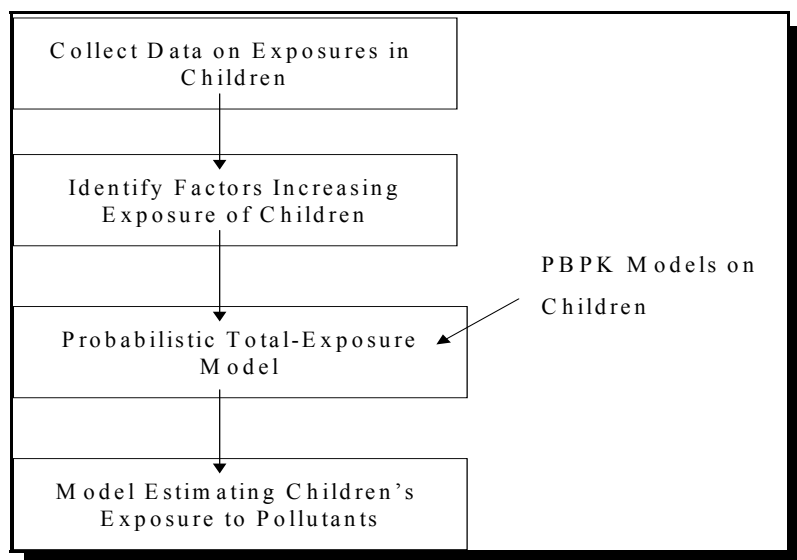
- Identify the key factors that contribute to variability in human exposure, including the distribution of human exposures and behavior associated with exposure to pollutants;
- Improve the accuracy of dose estimation in the general population;
- Identify the biological basis underlying differential responsiveness of sensitive subpopulations of humans to pollutant exposure; and
- Determine how exposure, dose and effect information can be incorporated into risk assessment methods to account for interindividual variability.

### 2.3.3 Research Approach

*Exposure Research.* Although an average person may not be exposed to an environmental agent at a level that would cause a health concern, a small percentage of the population may have significantly higher exposures because proximity to sources or activities increase likelihood of exposure. Therefore, exposure assessments should include distributions of exposures to allow identification and assessment of groups of people at risk from high-end

exposures. Exposure assessments should also account for the exposures of people who may be especially susceptible.

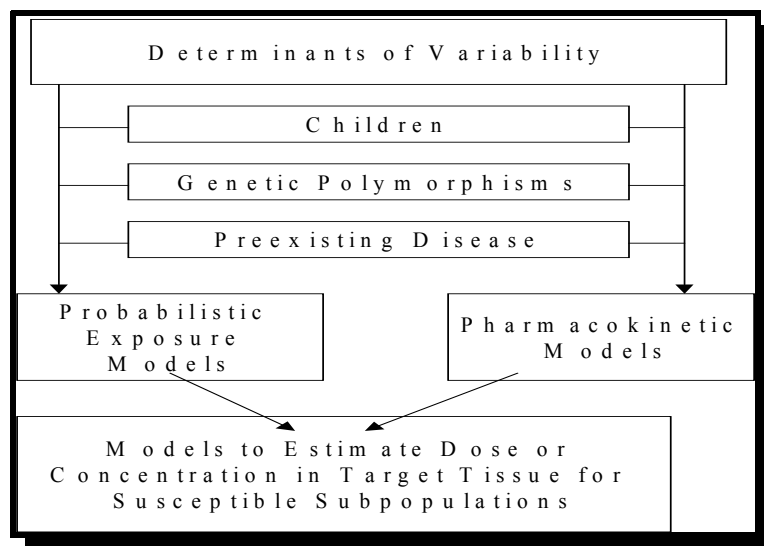
Initially, ORD's exposure research will focus primarily on children. The overall objective is to develop a broadly applicable probabilistic total-exposure model capable of linking to a PBPK model to estimate children's exposure (see schematic).



ORD will collect data on children's exposures and factors that influence exposure. These data will provide input to the development of a probabilistic model. Status and trends in children's exposure to environmental agents will also be characterized. Highly exposed subpopulations of children will be identified, and important sources and pathways of children's exposures will be delineated. Residential exposure factors for children will be characterized by age and gender for the national population, regional populations, highly exposed groups, and susceptible groups. Factors that will be characterized include activity patterns (time spent in a given activity and frequency of occurrence), soil and dust ingestion rates, factors reflecting transfer of environmental agents from objects and surfaces children commonly

touch, and factors related to ingestion of pollutant residues on surfaces. Future research will include the aging population.

*Dose Research.* Dose research in the area of susceptible subpopulations will focus on developing probabilistic exposure and pharmacokinetic models which estimate doses in susceptible subpopulations, including children and those with genetic polymorphisms or preexisting disease (see schematic below). This research will provide crucial information on the likelihood that a pollutant or its metabolites will be present at the target site, the concentrations in target tissues, and whether and how the dose varies between members of the general population and susceptible individuals. Measuring and modeling the effect of susceptibility factors on dose will help ORD design and conduct studies of the biological mechanisms on the cellular and molecular levels that lead to adverse effects. This will lead to a better understanding of the biological bases for differential sensitivity of susceptible subpopulations.



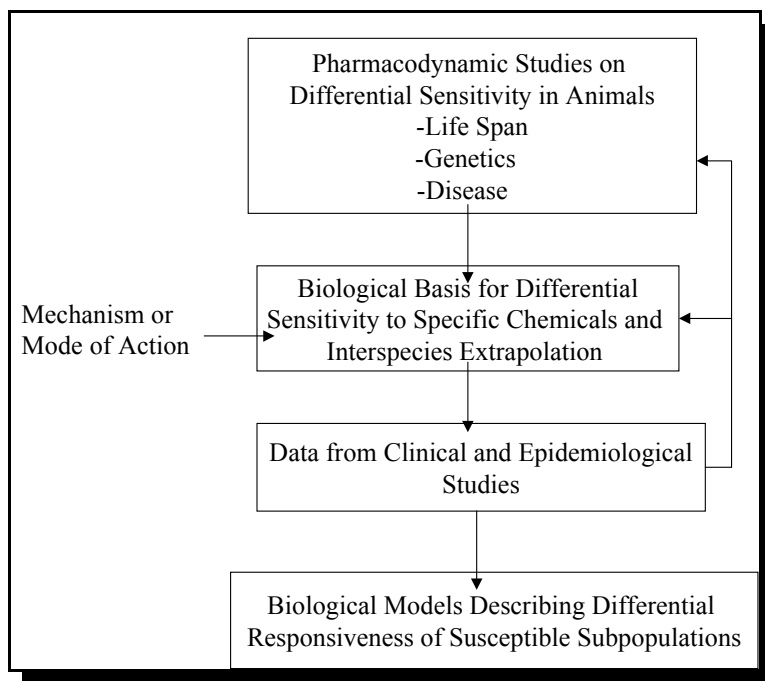
For the near term, ORD will continue its focus on children. Broadly applicable PBPK models and methods will be produced that allow better quantitative characterizations of dose to target tissue in developing organisms to replace default assumptions in children's risk assessments. Over the next two to three years, research on the influence of aging on pharmacokinetic parameters will increase.

The development and linkage of probabilistic exposure and pharmacokinetic models will provide valuable tools for analyzing and utilizing data describing variations in subpopulations for risk assessment. A key step will be to establish methods and approaches that can be applied to both animals and humans to aid in extrapolating from dose-response data collected in animals to humans.

*Effects Research.* The main hypothesis of the effects research on susceptible subpopulations is that differences among individuals (inter-individual) as well as the variability in an individual's responses over time (intra-individual) are due to biological variability. ORD's effects research on susceptible subpopulations will focus on developing biological models that describe the differential sensitivity of various subpopulations for risk assessment, especially the influence of life stage, genetic factors and preexisting disease on toxicological outcome or adverse health effect (see schematic).

Life Stage. There is now evidence that differential sensitivity of very young (early postnatal, children) and elderly individuals to certain pollutants may be related to pharmacokinetic factors. In conjunction with ORD's dose research program, the effects research program will develop longitudinal pharmacokinetic information for prototypic environmental agents from the prenatal and early postnatal period to senescence in

laboratory animals to determine how specific xenobiotic metabolizing enzymes change as a function of lifestage. Research will also determine how biological changes specific to some life stages (e.g., proliferative phase during development) can increase the risk of certain pollutants. Identification of such pharmacodynamic factors is crucial for the protection of susceptible subpopulations at different stages of development. As in the case of research on exposure, the initial emphasis will be on children. Research in this area will begin to focus on the elderly following the development of a national research agenda on aging. An objective of ORD's effects research will be to link life stage-related effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels



and to develop the first-generation of biologically based predictive models. Information from dose-response, pharmacokinetic, and mode-of-action studies in animals will be incorporated into models that more accurately predict children's risks.

Effects research currently focuses on the effects of pollutants on early stages of development. These endpoints include birth defects, reproductive, neurodevelopmental, immunological and endocrine disorders. As more is known about the effects of pollutants on infants and children, research efforts will begin to examine the influence of early exposure to pollutants on health status later in life. Multidisciplinary approaches will be developed in animal models to examine the effect of environmental pollutants on the aging process and to develop predictive models that can be incorporated into the risk assessment process.

While animal studies are useful in understanding mechanisms of toxicity and are frequently used to predict adverse effects in humans in the absence of human data, animals may not always be appropriate models for humans or for particular life stages. Extrapolation between animals and humans can be uncertain. Coordinating the development of animal models in ORD will be closely coordinated with human research.

Epidemiological studies will be crucial to understanding whether certain groups are more susceptible to environmental contaminants than others, and such studies will be conducted by all Laboratories and Centers in ORD. Hypothesis-based human epidemiological and clinical studies will be necessary to identify and confirm that adverse effects occur in humans, to identify risk factors, to develop dose-response relationships in humans, and to improve extrapolations from animal data to humans. Human studies will be conducted as needed for high-priority environmental agents and to assist in model development and validation.

In the Children's Health Act of 2000, Congress directed the National Institute of Child Health and Human Development to establish a consortium of federal agencies,

including EPA and the CDC, to design and implement a National Children's Study. This study will follow a cohort of children from as early in pregnancy as possible to adulthood to evaluate the effects of chronic and intermittent exposure on child health and human development. The goal is to enroll at least 100,000 children in the study. Exposure information will be collected for preconception exposures, at several times during pregnancy, and at several ages after birth; and outcome data will be collected during pregnancy, infancy, childhood, and beyond, perhaps focusing on developmental milestones of potential susceptibility in each of several age ranges. Biological specimens from the parents and children will be collected. Children will be followed at least through their primary school years and, preferably, into adulthood. ORD is participating in the planning and design of the study and developing and testing methods for data collection.

Genetic Differences. ORD's effects research on genetic influences will address the hypothesis that individuals harboring genetic polymorphisms in metabolic genes may have increased vulnerability to health effects following exposure to some pollutants. ORD research has shown, for example, that people who are phenotypic for rapid acetylation have higher levels of urinary mutagens following exposure to heterocyclic amines in food. The main scientific question for this research is whether such genetic differences significantly influence risk. This research will focus on the influence of genetic factors on long-term exposure to low levels of pollutants. The role of other genetic factors in susceptibility, such as differing rates of DNA repair and compensatory responses to toxic insult, will also be investigated.

Genotype can alter exposure and pharmacokinetic and pharmacodynamic factors. If individuals are genetically predisposed to

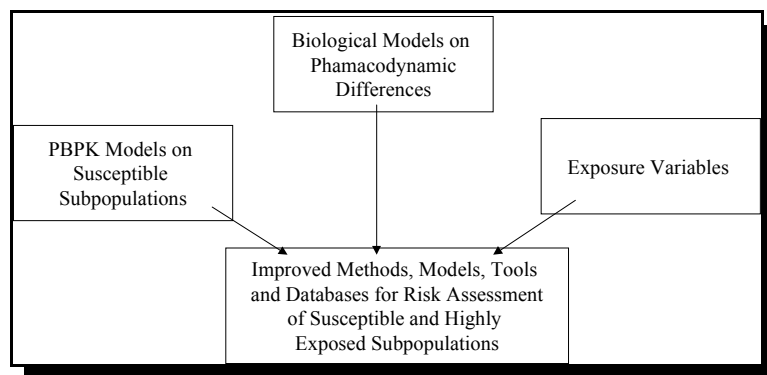
autism and if autism results in higher mouthing of objects and hands, then genetic factors could lead to higher exposures. Genotype can also alter transport proteins, clearance, metabolic profiles, and target organ sensitivity. Therefore, research will be conducted with the goals to develop exposure and pharmacokinetic and pharmacodynamic data and models with which to estimate dose and response in individuals with genetic polymorphisms. The use of these data in dose-response assessment will be similar to that described in the discussion of life stage.

Disease. 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. Preexisting dysfunction of a target organ may alter the type or severity of a chemically induced adverse effect on end organ function, such as the effect of air pollutants on lung function in individuals with asthma or the effect of exposure to a neurotoxicant on children with neurobehavioral dysfunction. In the near term, research will focus on the development of animal models of diseases having a high occurrence in the human population (e.g., asthma, bronchitis, hypertension) and on determining the effects of the disease on the dose-response curves of high priority environmental agents (e.g., air pollutants, pesticides). Mechanistic research will establish animal models that employ specific host traits that are characteristic of the disease and represent "risk factors" for increased sensitivity to chemicals. Once effects have been established using these animal models, studies will be conducted to extrapolate from animal data to human effects and across levels of biologic organization. Epidemiological studies will also be used to identify possible associations between exposure to a specific pollutant and manifestation of a disease. Such associa-

tions will then be tested in *in vitro* or *in vivo* animal models. Data derived from these studies can be used to assess the possible increased risk to pollutant exposure in individuals with preexisting disease. Research on health status will continue to focus on asthma and other respiratory diseases and air pollution; studies on other diseases and pollutant classes will be conducted as time and resources allow.

Effects research will be conducted with a goal to develop pharmacokinetic and pharmacodynamic data and models with which to estimate dose and response in individuals with a preexisting disease. ORD will examine the physiological and biological changes associated with common diseases and how these changes influence the pharmacokinetics and pharmacodynamics of environmental agents. This information will lead to improved models and methods for accounting for the effects of disease on individuals' responses to environmental agents.

*Risk Assessment Methods Research.* The results of ORD's research in exposure, dose, and effects, along with research supported by other government agencies and nongovernmental sponsors, will be used to develop improved methods, models, tools and databases for risk assessments of susceptible and highly exposed subpopulations (see schematic).



ORD will use pharmacodynamic data and PBPK models from research on effect and dose to develop better dose-response methodologies to account for susceptibilities of various life stages and to evaluate the adequacy of the current default uncertainty factor of 10 in accounting for human variability for noncancer health effects. ORD risk assessment methods research will also analyze data on exposure factors, human activity patterns, and environmental concentrations, including those generated by the exposure research program on pesticides and air pollutants, to quantify the important factors used in exposure assessment and to evaluate representativeness of the data based on factors such as life stage, genetics, and pre-existing disease. Databases on physiological and pharmacokinetic factors for various life stages will be developed to aid in development and implementation of PBPK models. Dose-response methodologies for specific life stages, accounting for differences between children and adults, will be developed. Distributions of exposure factors measured in ORD studies will be incorporated into the Exposure Factors Handbook (U.S. EPA, 1997b, 2000b). Finally, ORD will develop guidance for performing risk assessments for children, the elderly, and those with preexisting diseases and for taking into account genetic variation in risk assessment.

### 3. RESEARCH TO ENABLE EVALUATION OF PUBLIC HEALTH OUTCOMES FROM RISK MANAGEMENT ACTIONS

ORD's current Human Health Core Research Program began a new effort to evaluate the public health outcomes of EPA policies in 2001. The issue of "accountability," i.e., making sure that our research and pollution control programs produce measurable benefits in public health, is an important one. In order to better protect the country's air, water, and land resources, EPA 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 first goal of ORD's Strategic Plan, i.e., to support EPA's mission "to protect human health and to safeguard the natural environment—air, water, and land—upon which life depends." With the advent of the GPRA and calls for EPA to stress and demonstrate outcome-oriented goals and measures of success, research is needed to enable evaluation of actual public health outcomes from risk management (emission or exposure control) actions. Furthermore, in 2001, EPA announced an "Environmental Indicators Initiative" to improve the EPA's ability to report on the status of and trends in environmental conditions and their effect on human health and the nation's resources. ORD will work with the Office of Environmental Information to develop and publish a "State of the Environment Report" using available national level data and indicators to describe human health environmental conditions and human health concerns. Part of that report will identify data gaps and research needs and discuss opportunities for partnering with other research organizations in filling those gaps.

Estimating public health benefits of EPA regulatory decisions and rule-making or, in a more general sense, evaluating public health outcomes from risk management

actions will be a challenge. It will involve a number of disciplines grounded in both the physical and social sciences and increasingly must take into account the economic and behavioral aspects of human decision-making. The remainder of this chapter outlines the basic conceptual strategy of an emerging research program to evaluate the environmental public health consequences of EPA regulations, regulatory or non-regulatory programs, or other risk management activities. Both the precise methods to be used and the outcomes that will be studied have not yet been chosen.

Evaluating public health outcomes from risk management actions is clearly linked to assessing human health risks. EPA risk assessors and risk managers must consider the uncertainties associated with the risk assessment process, including the upper as well as the lower bounds of such uncertainty. Coupled with these uncertainties is the fact that EPA very often estimates the future benefits of public health outcomes in a politically charged environment. Depending on the desired human health protection endpoint, final decisions often rest with national and state policy makers and decision officials. These officials take scientific findings into account along with a number of other considerations that assist them in making more informed public policy decisions.

Generally, EPA has not prepared retrospective evaluations examining whether the intended benefits in protecting public health were realized once an EPA decision had been in place for a period of time. One exception to this was the decision to ban lead in gasoline and other products, the subsequent tracking of reduced blood-lead levels in children as a result of the ban, and



the epidemiological studies to confirm the linkage between elevated blood lead levels and reduced cognitive development in children. The confounding influences of various factors (e.g., age of exposure, duration of exposure, exposure to other pollutants alone or in complex mixtures) offer challenges at every turn in evaluating public health outcomes. As EPA develops and implements a research program advancing the evaluation of public health outcomes, either prospective or retrospective, participants and observers must recognize that the program will take years or perhaps decades to develop and fully implement. It will involve a number of organizations both within and outside of EPA working in partnership to collect and analyze data and then to use that data in methodologies and tools to objectively determine the effectiveness of risk management decisions on public health outcomes.

The Presidential Commission on Risk Assessment and Risk Management (1997) has supported the need for EPA to measure the effectiveness of public health interventions (see text box).

The Presidential Commission on Risk Assessment and Risk Management points out the need for progress in several scientific areas "...if we are to improve our ability to implement and measure the effectiveness of public health interventions. Specifically, we need to:

- (1) Link studies of exposure and studies of adverse health or ecological outcomes;
- (2) Determine regional differences in disease prevalence and disease incidence trends and risk factors;
- (3) Develop good baseline and surveillance information about incidence rates of diseases specifically linked to environmental causes; and
- (4) Identify the most important environmental causes of diseases." (page 47, Vol. 1)

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 led the Council of State and Territorial Epidemiologists, the CDC, the Agency for Toxic Substances and Disease Registry, and EPA to begin developing 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 of exposures to environmental pollutants such as polychlorinated biphenyls, metals, and pesticides.

Chapter 2 of the *Human Health Research Strategy* sets forth priorities for improving the science of human health risk assessment. These improvements will result in more effective and longer lasting risk management actions and will contribute to public health outcomes that can be achieved. Chapter 3 describes research enabling more informative and reliable evaluations of public health outcomes (e.g., improved estimates of actual reductions in risks to public health via exposure and effects data) from risk management actions. These two chapters taken together will provide the foundation for successful implementation of the *Human Health Research Strategy* in the years to come.

### 3.1 SCOPE AND DEFINITIONS

As discussed in Chapter 1, there are great similarities in information needs for risk assessment and risk management. This is because understanding the efficacy of an EPA decision requires a comparative analysis of risks before and after implementation of risk management actions (see Figure 3-1). At the same time, various risk management actions

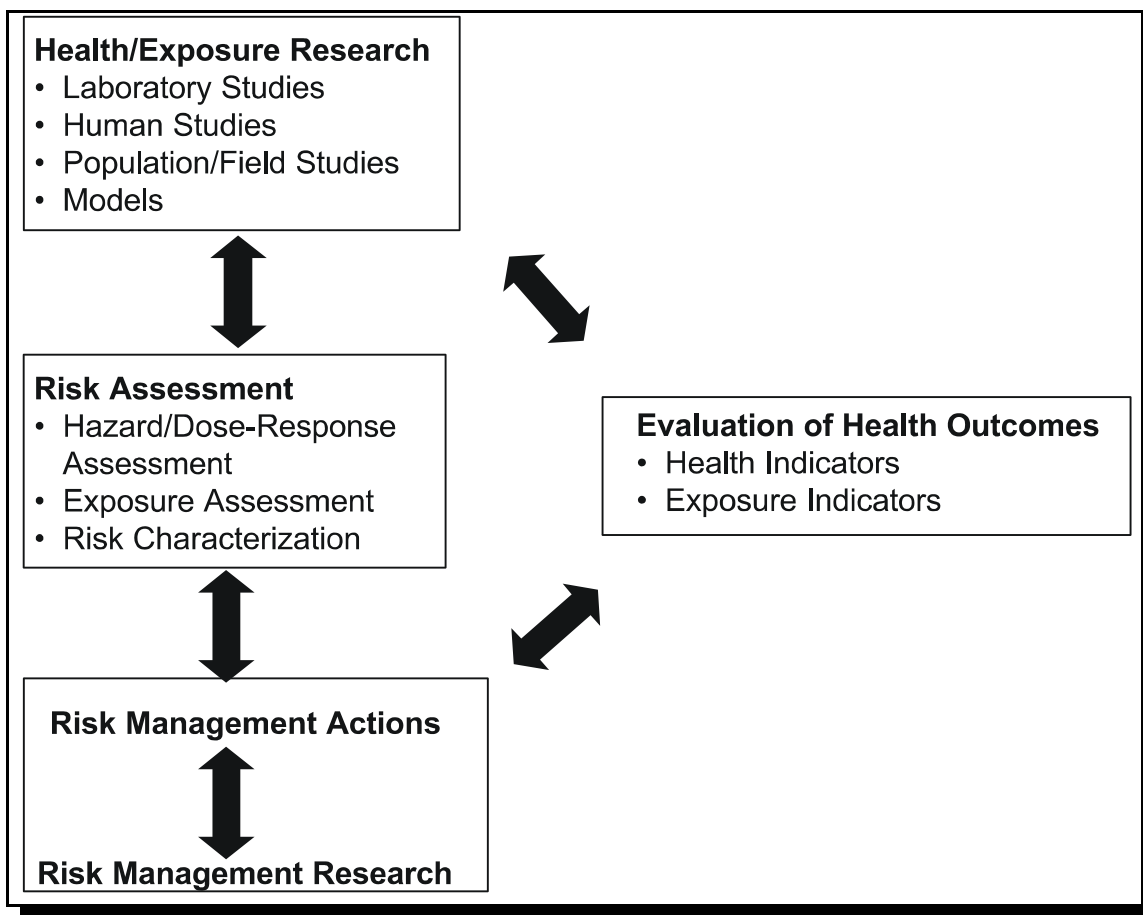


Figure 3-1. Role of analysis of health outcomes in the risk management decision process.

must be applied within the framework of maximum achievable risk reduction that is efficient, cost-effective, and long-lasting. Important issues need to be addressed that require research targeted at the most robust possible evaluation of public health outcomes from risk management actions.

This chapter stresses the identification of existing information and the creation of new information that can be used in evaluating public health outcomes from risk management decisions. Reflecting the close relationship between risk assessment and risk management, this public-health-outcomes research program is included in the *Human Health Research Strategy* for two reasons: (1) the need to link more closely risk assessment and risk management so as to improve human health risk assessments and (2) the need to improve the scientific basis for evaluating public health outcomes from risk management actions.

It is essential for the research described in this chapter to be based upon a common set of definitions. Haddix and others in their *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation* (1998) offer a set of useful definitions adopted for this research strategy (see text box).

**Definitions of Key Terms (Haddix et al., 1998)**

**Effectiveness:** The improvement in health outcome that a prevention strategy can produce in typical community-based settings (p.146).

**Efficacy:** The improvement in health outcome that a prevention strategy can produce in expert hands under ideal circumstances (p.146).

**Outcome Measure:** The final health consequence (e.g., cases prevented) on an intervention (p.149)

The remainder of this chapter discusses the scientific uncertainties underlying the evaluation of public health outcomes from risk management actions and describes the research approach used to meet the objectives of ORD's public-health-outcomes research program.

### 3.2 SCIENTIFIC UNCERTAINTIES

The basic philosophy behind the EPA's public health policies is that regulatory or other risk management actions are taken with the intent of preventing or reducing releases of pollutants of concern. This philosophy assumes that exposure prevention or reduction will lead to measurable reductions in specific human health effects. However, actual reductions in health effects will depend on the proportional relationships between the pollutant releases and health risks from a given source as well as whether the health risks are influenced by other sources and factors not being considered. The degree of certainty and directness of the links between source, exposure, and effect influence the validity of this assumption. Behavior of individuals and communities in reducing risk are additional important variables.

Unfortunately, in most cases, this linkage has a very poor quantitative scientific foundation; and health-protective default assumptions are generally used in cases of uncertainty or lack of information. If this linkage were better forged scientifically, the predictability of risk management action effectiveness would be more accurate. Even so, actual effects will need to be measured to evaluate whether the predictions (or the prediction approach) are correct. The optimal approach is to compare a health risk assessment before and after the risk management action has been employed. This is, however, a very complex and challenging undertaking because a systematic evaluation framework does not always exist given the

unethical nature of randomized controlled clinical trials in humans with toxic agents. Prospective assessments of risk often use multiple approaches with varying degrees of sensitivity, uncertainty, and reliability. Furthermore, even if prospective assessments were reliable, they may not be suitable for a retrospective analysis. For example, an epidemiological study with sufficient sensitivity for prospective risk assessment may not have the statistical power to detect the expected risk reductions in the size of the community affected. In addition, if the expected public health outcome is the lessening of a chronic effect (e.g., cancer), it may take many years to be detected with current risk assessment approaches that use cancer incidence as the outcome. Finally, some risk management actions create multiple and perhaps disparate benefits and possibly unintended consequences. This causes great difficulty in the analysis of management actions because the unintended effect has to be identified and evaluated.

**Long-Term Goal:** Provide the scientific understanding and tools to assist EPA and others for use in evaluating the effectiveness of public health interventions from risk management actions.

**Key Scientific Questions:** How can the most effective tools, systems, methods, and models be identified, discovered, or developed and integrated into a decision-making framework, to assist federal, state and local decision-makers in evaluating changes in public health as a result of risk management actions? What is the ability of this framework to quantify such changes accurately?

### 3.3 SCIENTIFIC OBJECTIVES

Two research objectives were developed based on the three research issues described below. The research questions were developed in accordance with the Long-Term Goal and Key Scientific Questions described in the text box on the previous page. The research questions serve as the foundation upon which to develop a coherent framework for an integrated research program and include the following:

- The kinds of policies, regulations, or actions that should be evaluated to determine the efficacy of risk management actions;
- The approaches available to address the effectiveness of risk management actions on public health; and
- The improvements needed to the approaches and the development of a useful framework for evaluating public health outcomes.

Admittedly, achieving the long-term goal and answering the key scientific and associated research questions will take considerable time and effort. ORD's three national Laboratories and two national Centers have agreed to work on this public-health-outcomes research program together; however, neither ORD nor EPA proposes to undertake this research alone. The research program described here will be a daunting undertaking and one that must rely on the contributions and collaboration with a number of different organizations. It will require feedback loops, engagement, and partnering with other organizations both within and outside EPA if it is to succeed.

In close collaboration with research partners, ORD's research will provide the scientific understanding and tools to assist EPA and others in evaluating public-health-outcomes resulting from risk management actions. The new public health outcomes

research program is designed to address the long-term goals and key scientific questions in a stepwise fashion from reductions in release, through reductions in exposure, to improvements in public health. It is not designed to be an expansion of the EPA's epidemiological research program; but will rely on collaborations with, and data and information from, other federal, state, and public health organizations. Ultimately, the tools, systems, methods, models, and the framework within which they operate should measure or reliably estimate changes in human health risks with a known level of precision and accuracy. This precision and accuracy should be sufficient to allow EPA to determine how its regulatory decisions and risk management actions contributed to those changes. Two specific objectives of ORD's research program emerge:

- Establish linkages between sources, environmental concentrations, exposure, effects, and effectiveness such that a change in a public health outcome consequent to a risk management action can be determined by measuring or modeling any one of these linked steps; and
- Improve tools, systems, methods, and models by which EPA and others can measure or predict changes in public health outcomes following risk management actions.

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 contained within problem-driven research programs (e.g., particulate matter, air toxics, hazardous waste; see Appendix A). Research on the effectiveness of public health outcomes will provide the linkages to these other related research programs.

General precedents indicate the feasibility and utility of meeting these two

objectives. For example, effectiveness evaluations have been conducted for diverse risk management actions (e.g., for pharmacologic therapy, vaccine efficacy, and smoking cessation). These evaluations are becoming more commonplace, and several groups have attempted to provide guidance for the conduct of such studies (Gold et al., 1995; Graham et al., 1998; Haddix et al., 1998).

### 3.4 RESEARCH APPROACH

In developing research program priorities and a deeper understanding of the relationships between risk management actions and public health outcomes, it will be necessary to select cases to study based on the suite of risk management actions that might be employed by the EPA. A decision on the appropriate number and scope of the case studies will be made after further deliberations in workshops and other fora both internal and external to EPA. Particular emphasis will be placed on policies, regulations, or actions attendant to risk management that EPA has developed, is developing, or may need to develop within the next 10 years. This type of approach will require close collaboration with EPA's Program and Regional Offices. Study sites and the selection of appropriate research approaches will vary depending upon the environmental exposures and effects of interest.

To ensure full coverage of the possible risk management alternatives, classes of risk management actions will be identified as the first step in the case study process. These classes of action include, but are not limited to, those that reduce exposure to pollutants currently in the environment, dispose of or redistribute substances currently in the environment, and those that license (or allow) new substances into the environment or allow levels of substances already in the environment to be increased. Coupled with these classes of risk management actions

will be an identification of their implications for evaluating public health outcomes.

Efforts to ascertain the effectiveness of risk management actions will depend on the selection of pertinent research approaches and appropriate indices of public health exposure and effects outcomes. An evaluation of the public health outcome of a risk management decision should answer two questions:

- Did the risk management action actually prevent, reduce, eliminate, or modify exposure to the pollutants of concern?
- Did this prevention, reduction, elimination, or modification result in disease prevention and improved public health?

Four approaches might be used to assess public health outcomes, including health outcome/effect studies, population exposure studies, field sampling of environmental media, and measuring changes in source emissions. Coupled with this will be the need to investigate and evaluate the performance of models used to estimate outcomes when measurement data may be inaccessible or too costly to collect except as a representative sample. These approaches are ordered in terms of their ability to determine human exposures and to link them with public health outcomes; however, this ordering does not mean that an approach listed before another approach is necessarily more feasible. Using these approaches effectively in evaluating public health outcomes from risk management actions will require linking them in the development of a framework or model. Each of these areas can be improved, in some cases as a result of the risk assessment research program discussed in Chapter 2. However, there are some special needs for evaluating regulatory efficacy for public health protection. Thus, a careful analysis and prioritization of the approaches *vis-a-vis*

the risk management action classes described above are essential.

Although the above approaches are listed discretely, perhaps the greatest challenge of the public-health-outcomes research program will be to elucidate the linkages among them. Ultimately, this will vastly increase the feasibility and accuracy of both prospective and retrospective risk 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 core research program described in Chapter 2, but additional models are likely to be required that incorporate the special needs of an retrospective assessment and more thoroughly link the approaches under consideration.

To assess the strengths and weaknesses of evaluations of public health outcomes from risk management actions, a logical first step will be to use existing approaches and to evaluate available databases that compile pollutant release information and environmental concentrations, health endpoints, or both. Appendix E lists some databases and other sources that contain information that could be used to correlate health endpoints with concentrations of pollutants. Such an exercise will likely identify priorities for future research. Better ways to measure changes in effects (or in indicators of effects, exposure, indicators of exposure, environmental concentrations, or source strength) are needed, together with programs to measure the effects before and after implementation of the EPA's decisions.

Risk management tools are needed that express the EPA's understanding of the cost-effectiveness and long-lasting nature of risk management actions and that convey that understanding to other regulatory offices, the regulated community, and the public. Finally, a framework to link models all the way from source to human health

effects provides more confidence in exposure-dose-response relationships through a thorough understanding of the critical processes within, and linkages between, each component of the human exposure-dose-response sequence.

### **3.5 RESEARCH IMPLEMENTATION**

The ultimate goal of ORD's new public-health-outcomes research program is to provide a set of fully developed frameworks and a suite of technical tools, systems, methods, and models that assist EPA and others in evaluating public health outcomes from risk management actions. The overall intention is to quantify environmental public health outcome trends that could (or should) change in response to risk management decisions (e.g., regulations, implementing emission control technologies) that affect the environmental exposures that are the primary risk factors in the causality of the outcome. The research program will require the full participation and active engagement of stakeholders at all levels, both internal and external to the EPA. It must leverage the research program with other public- and private-sector organizations involved in similar or compatible efforts since that is the only way it will succeed. The long-term goal to provide the scientific understanding and tools to assist EPA and others in evaluating the effectiveness of public health outcomes resulting from risk management actions is extremely ambitious and research in this area will proceed in a step-wise and incremental fashion as described below.

*Developmental phase.* This phase will provide a comprehensive state-of-the-science evaluation of currently available domestic and international tools, systems, and methods, along with frameworks that are being, or could be, used in evaluating public health outcomes from a variety of risk management actions. It will of necessity partner with EPA Program and

Regional Offices and will seek to engage organizations outside EPA that are positioned to engage in a public health outcomes research program.

*Investigation phase.* This phase will implement a detailed multiyear research plan for improving various tools, systems, and methods (existing and new) to evaluate public health outcomes from risk management actions. A preliminary compendium of tools, systems, and methods, along with selected framework(s), will be developed for the multiyear plan. Pilot investigations and studies on evaluations of health and exposure information will also be conducted, leading to further refinements of the frameworks.

*Delivery phase.* This phase will provide a set of fully developed frameworks and a suite of technical tools, systems, and methods for use by various stakeholders. This compendium will be closely coupled with illustrations and training on its use, along with case studies targeting decision-makers at multiple levels. As discussed above, a near-term objective of this research is to develop a framework and a multiyear plan for undertaking research on evaluating public health outcomes from risk management actions. Recommended next steps include the following:

- Conduct workshops, in consultation with federal, regional, state, and local decision-makers and other interested parties, to develop a comprehensive state-of-the-science evaluation and to identify the elements of a possible framework(s) for evaluating public health outcomes from risk management actions;
- Describe a set of specific cases/situations that are potential targets for case studies (including rationale) for evaluating public health outcomes from risk management actions;

- Through ORD's STAR program, issue a request for assistance for the development of statistical techniques using environmental and human health data in evaluating public health outcomes and conduct case studies to test these techniques;
- Assess state-of-the-science approaches for evaluating how human health is impacted by risk management actions;
- Identify the policies and regulations that would most likely benefit from the use of a framework and set of tools that evaluate public health outcomes from risk management actions;
- Understand how various decision-makers at the national, regional, state, and local levels currently use, or might use in the future, various frameworks and tools for evaluating public health outcomes from risk management actions; and
- Identify a set of environmental health indicators that can be used to evaluate the effectiveness of risk management actions on public health.

Components of the research program must address such factors as the likelihood for case studies to be informative and useful and the composition of research designs to achieve the desired long-term goals of the research program. It will be critical that pilot studies fill evidence gaps that provide cause and effect linkages between toxicants and environmental public health outcomes. Clearly, this new research program on the evaluation of public health outcomes of risk management activities is an undertaking too broad for EPA alone. While both the precise methods to be used and the outcomes which will be studied have not been decided, we expect much of the data, particularly on the public health side, will have to come from collaborations with our sister agencies such as the CDC. A multi-disciplinary approach to tying emissions, fate, transports of toxins; environmental

exposures; biomarkers of exposure; and early indicators of disease, as well as morbidity and mortality, requires the unification of many scientific disciplines. We expect broad teams of researchers, from several ORD laboratories and partners from other federal agencies will work together to carry out this research on a case-by-case basis.



#### 4. REFERENCES

- Bearer C. 1995. How are children different from adults? *Environ Health Perspect* 103 (Suppl. 6): 7-12.
- Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M.. 1987. Longitudinal analysis of prenatal and postnatal lead exposure and early cognitive development. *New Eng J Med* 316: 1037-1043.
- Centers for Disease Control and Prevention (CDC). 2001. *National Report on Human Exposure to Environmental Chemicals*. National Center for Environmental Health, CDC, Atlanta, GA
- Centers for Disease Control and Prevention (CDC). 2003. *Second National Report on Human Exposure to Environmental Chemicals*. National Center for Environmental Health, CDC, Atlanta, GA
- Food Quality Protection Act (FQPA). 1996. Federal Insecticide, Fungicide and Rodenticide (FIFRA) and Federal Food, Drug and Cosmetic Act (FFDCA) As Amended by the Food Quality Protection Act (FQPA) of August 31, 1996; U.S. EPA, OPP, document #730L97001, March 1997.
- Gold MR, Siegel JE, Russel LB, Weinstein MC. 1995. *Cost Effectiveness in Health and Medicine*. New York: Oxford University Press.
- Graham JD, Corso PS, Morris JM, Segui-Gomez M, Weinstein MC. 1998. Evaluating the cost-effectiveness of clinical and public health measures. *Ann Rev Public Health* 19: 125-152.
- Haddix AC, Teutsch SM, Shaffer PA. 1998. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation*. New York: Oxford University Press.
- International Programme on Chemical Safety (IPCS). 1999. IPCS Workshop on Developing a Conceptual Framework for Cancer Risk Assessment. 16-18 February, Lyon, France.
- National Research Council (NRC). 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press.
- National Research Council (NRC). 1993. *Pesticides in the Diets of Infants and Children*. Washington, DC: National Academy Press.
- National Research Council (NRC). 1994. *Science and Judgment in Risk Assessment*. Washington, DC: National Academy Press.
- National Research Council (NRC). 1997. *Building a Foundation for Sound Environmental Decisions*. Washington, DC: National Academy Press.
- Pew Environmental Health Commission. 2000. *America's Environmental Health Gap: Why the Country Needs a Nationwide Health Tracking Network*. Baltimore, MD.
- Presidential Commission on Risk Assessment and Risk Management. 1997. *Volume 1: Framework for Environmental Health Risk Management. Volume 2: Risk Assessment and Risk Management in Regulatory Decision-Making*.
- Rodier PM. 1980. Chronology of neuron development: animal studies and their clinical implications. *Dev Med Child Neurol* 22:525-545.
- Schlosser PM, Bogdanffy MS. 1999. Determining modes of action for biologically based risk assessments. *Regul Toxicol Pharmacol* 30:75-79.
- U.S. Environmental Protection Agency (U.S. EPA). 1986. *Guidelines for health risk assessment of chemical mixtures*. Federal Register 51:34014.
- U.S. Environmental Protection Agency (U.S. EPA). 1995. Science Advisory Board, Committee on Indoor Air Quality and Total Human Exposure. *Human Exposure Assessment: A Guide to Risk Ranking, Risk Reduction, and Research Planning*. U.S. EPA-SAB-IAQC-95-005.
- U.S. Environmental Protection Agency (U.S. EPA). 1996. *Proposed guidelines for carcinogen risk assessment*. Federal Register 61:56274-56322.
- U.S. Environmental Protection Agency (U.S. EPA). 1997a. *Update to ORD's Strategic Plan*. Office of Research and Development. Washington, DC.
- U.S. Environmental Protection Agency (U.S. EPA). 1997b. *Exposure Factors Handbook*. Office of Research and Development. Washington, DC. EPA/600/P-95/002Fa.
- U.S. Environmental Protection Agency (U.S. EPA). 1998. *Strategic Research Plan for Endocrine*

*Disruptors*. Office of Research and Development. Washington, DC. EPA/600/R-98-087.

U.S. Environmental Protection Agency (U.S. EPA). 1999a. *Guidelines for Carcinogen Risk Assessment*. Risk Assessment Forum. U.S. EPA, NCEA-F-0644.

U.S. Environmental Protection Agency (U.S. EPA). 1999b. *National Human Exposure Assessment Survey*. National Exposure Research Laboratory, National Center for Environmental Assessment, Office of Research and Development. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). 2000a. *Strategy for Research on Environmental Risks to Children*. Office of Research and Development. Washington, DC. EPA/600/R-00/068.

U.S. Environmental Protection Agency (U.S. EPA). 2000b. *Child-Specific Exposure Factors Handbook*. External Review Draft. Office of Research and Development. NCEA-W-0853

U.S. Environmental Protection Agency (U.S. EPA). 2000c. *Supplementary Guidance for Conducting Human Health Risk Assessment of Chemical Mixtures*. Risk Assessment Forum. EPA/630/R-00/002.

U.S. Environmental Protection Agency (U.S. EPA). 2001a. *Asthma Research Strategy*. Draft. Office of Research and Development. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). 2001b. *Strategic Plan for the Office of Research and Development*. Washington, DC.

## APPENDIX A

### ORD Research Plans and Strategies

<p><b>Final Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water (U.S. EPA, 1997)</b></p>	<p>This research plan describes ORD’s research to support EPA’s drinking water regulations concerning disinfectants, disinfection byproducts, and microbial pathogens. The research plan identifies key scientific and technical information gaps and provides guidance to both intramural and extramural research programs regarding priorities and sequencing of research.</p>
<p><b>Research Plan for Arsenic in Drinking Water (U.S. EPA, 1998a)</b></p>	<p>This research plan provides guidance to improve the scientific understanding of health risks associated with arsenic in drinking water and to support improved control technologies for water treatment.</p>
<p><b>Strategic Research Plan for Endocrine Disruptors (U.S. EPA, 1998b)</b></p>	<p>This research plan addresses research needs of biological effects for human health and wildlife and exposure assessment of endocrine disruptors. Integration of effects and exposure research is emphasized to provide a complete analysis of risk.</p>
<p><b>Airborne Particulate Matter Research Strategy (U.S. EPA, 1999)</b></p>	<p>This research strategy describes health, exposure, risk assessment, and management research on particulate matter to support EPA’s review and implementation of the National Ambient Air Quality Standards.</p>
<p><b>Strategy for Research on Environmental Risks to Children (U.S. EPA, 2000a)</b></p>	<p>This research strategy describes future directions and priorities of ORD’s program to reduce uncertainties in EPA risk assessments for children, leading to effective measures to prevent and/or reduce risk.</p>
<p><b>Mercury Research Strategy (U.S. EPA, 2000b)</b></p>	<p>This strategy presents the scientific questions and research goals and priorities for EPA’s research program on mercury.</p>
<p><b>Asthma Research Strategy (U.S. EPA, 2000c)</b></p>	<p>This strategy describes the research directions and priorities to improve the scientific understanding of environmental factors underlying increased risk for asthma and to develop more effective risk management control technologies to reduce and prevent asthma cases.</p>
<p><b>Air Toxics Research Strategy (U.S. EPA, 2000d)</b></p>	<p>This strategy presents research approaches and objectives to improve the scientific and technical knowledge base for the assessment and management of health risks from hazardous air pollutants.</p>

**Drinking Water Contaminants Candidate List (CCL) Research Plan (U.S. EPA, 2000e)**

This plan describes the research approach and process to provide improved scientific and technical bases for the assessment and management of drinking water contaminants that are on the CCL.

U.S. Environmental Protection Agency (U.S. EPA). 1997. *Final Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water*. Office of Research and Development. Washington, DC.

U.S. Environmental Protection Agency (U.S. EPA). 1998a. *Research Plan for Arsenic in Drinking Water*. Office of Research and Development. Washington, DC. EPA/600/R-98/042.

U.S. Environmental Protection Agency (U.S. EPA). 1998b. *Strategic Research Plan for Endocrine Disruptors*. Office of Research and Development. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). 1999. *Airborne Particulate Matter Research Strategy*. Office of Research and Development. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). 2000a. *Strategy for Research on Environmental Risks to Children*. Office of Research and Development. Washington, DC.

U.S. Environmental Protection Agency (U.S. EPA). 2000b. *Mercury Research Strategy*. Office of Research and Development. Washington, DC. EPA/600/R-00/073.

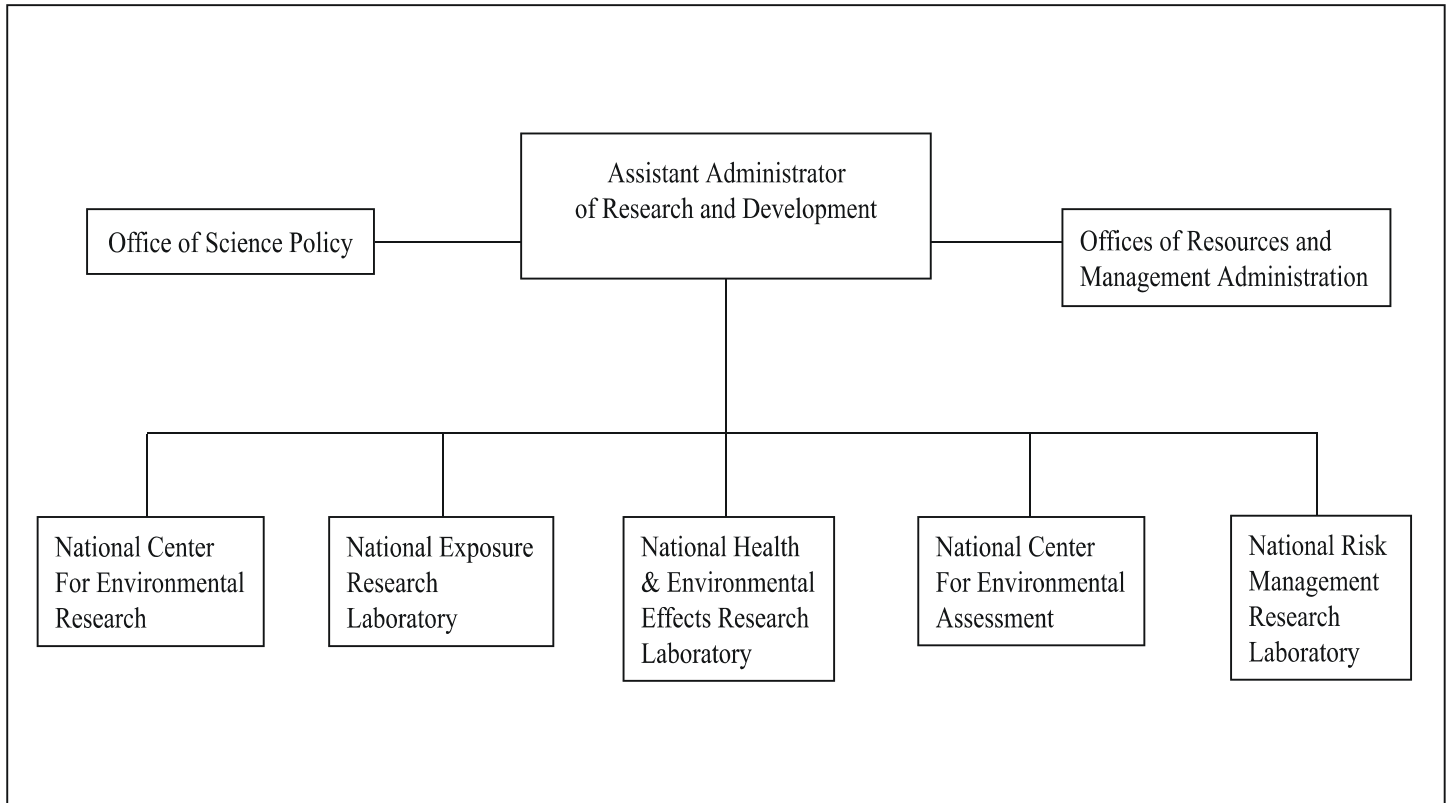
U.S. Environmental Protection Agency (U.S. EPA). 2000c. *Asthma Research Strategy*. Draft. Office of Research and Development. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). 2000d. *Air Toxics Research Strategy*. Draft. Office of Research and Development. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). 2000e. *Drinking Water Contaminants Candidate List (CCL) Research Plan*. Draft. Office of Research and Development. Research Triangle Park, NC.

**APPENDIX B**

**Organizational Chart  
EPA's Office of Research and Development**



## APPENDIX C

### Examples of Mechanistic Data Used in Risk Assessment

Pollutant	Supporting Research
<b>Aflatoxin B1</b>	Mechanistic studies showed that this compound forms DNA adducts and protein adducts, causing specific mutations in the p53 tumor suppressor gene. Because of this mechanistic information, formation of DNA adducts is now being used to assess cancer risk in human populations.
<b>Dioxin</b>	The understanding that essentially all the effects of dioxin are mediated via binding to the arylhydrocarbon (Ah) receptor provides the underpinning for the species extrapolation in the risk assessment of dioxin. The Ah receptor is highly conserved, present, and functional in nearly all vertebrates. The current consensus that dioxin is a known human carcinogen is based on clear animal data, limited human data, and the presence of a common mechanism of action.
<b>Dioxin</b>	The importance of PBPK models for risk assessment is illustrated by the identification of an inducible hepatic binding protein by dioxin, which results in dose-dependent sequestration of dioxin in multiple mammalian species, including humans. This information has allowed for a better understanding of the dose-dependent differences in the disposition of dioxin, which has led to the conclusion that body burden is the best dose metric for risk assessment of dioxin and related compounds. This approach allows for a direct comparison of animal and human data, which reduces the animal-to-human uncertainty in risk assessment.
<b>d-Limonene</b>	A number of chemicals (e.g., d-limonene) and chemical mixtures (e.g., unleaded gasoline) induce kidney tumors in male rats in cancer bioassays. Mechanistic studies have shown that kidney tumors in male rats are associated with an increase in the level of a specific protein, $\alpha_2\mu$ -globulin. Because this protein is not present in human male kidneys, risk assessors could predict that the cancer risk in humans for chemicals acting via an $\alpha_2\mu$ -globulin-mediated process will be low.
<b>Atrazine</b>	Research from ORD showed that the effects of atrazine on mammary gland and prostate development are associated with alterations in the hormone prolactin. This mechanistic information is currently being used to reevaluate the risk assessment for atrazine.

## APPENDIX D

### Agencies Having Research Programs Complementary to ORD

**The National Institute of Environmental Health Sciences (NIEHS)** achieves its mission through multidisciplinary biomedical research programs; prevention and intervention efforts; and communication strategies that encompass training, education, technology transfer, and community outreach. For example, the NIEHS program includes a trans-NIH effort to study effects of chemicals, including pesticides and other toxics, in children. EPA has collaborated with NIEHS in establishing Centers for Children's Environmental Health and Disease Prevention to define the environmental influences on asthma and other respiratory diseases, childhood learning, and growth and development. NIEHS and the National Institute of Allergy and Infectious Diseases (NIAID) are conducting the Inner-City Asthma Study, which is a prevention trial to develop an intervention strategy to reduce asthma morbidity in inner-city children and adolescents. The National Allergen Study, being conducted by NIEHS in collaboration with the Department of Housing and Urban Development (HUD), examines the relationship between allergens and lead and how allergen exposures differ as a function of geographic region, socioeconomic status, housing type, and ethnicity. NIEHS and the National Toxicology Program (NTP) are developing new technologies for high-throughput toxicity testing, and these agencies are responsible for one-third of all toxicity testing performed worldwide. Long-term collaborative efforts with NTP, particularly in the areas of carcinogenesis, reproductive/developmental toxicity, and neurotoxicity, are well established. NIEHS has established the National Center for Toxicogenomics (NCT) to coordinate an international research effort to develop the field of toxicogenomics. The NCT will provide a unified strategy, a

public database, and will develop the bioinformatics infrastructure to promote the development of the field of toxicogenomics. NIEHS will pay special attention to toxicogenomics as applied to the prevention of environmentally related diseases.

The **National Cancer Institute (NCI)** conducts population-based research on environmental and genetic causes of cancer and on the role of biological, chemical, and physical agents in the initiation, promotion, or inhibition of cancer and on the biological and health effects of exposure to radiation.

The **Centers for Disease Control and Prevention (CDC)**, through the National Center for Environmental Health (NCEH), studies health problems associated with human exposure to lead, radiation, air pollution, and other toxicants, as well as to hazards resulting from technological or natural disasters. These are mainly surveillance and epidemiological studies. NCEH is particularly interested in studies that benefit children, the elderly, and persons with disabilities. The National Center for Health Statistics (NCHS) of CDC is conducting the National Health and Nutrition Examination Survey (NHANES). NHANES is a national population-based survey and includes data on potentially sensitive subpopulations such as children and the elderly. EPA is participating in this survey with NCHS to collect information on children's exposure to pesticides and other environmental contaminants. CDC's *National Report on Human Exposure to Environmental Chemicals* provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring data collected through NHANES. The first national report provides information about levels of 27

chemicals, while the second report presents biomonitoring exposure data for 116 environmental chemicals for the U.S. population divided into age, gender, and race/ethnicity groups.

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

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



## APPENDIX E

### Examples of Health and Environmental Databases to Evaluate Public Health Outcomes From Risk Management Actions

Environmental Databases		
Source	Database Name	Contents
EPA/ORD	NHEXAS	Exposure data for Arizona, EPA Region V, and Baltimore
EPA	SDWIS/FED	Regulated pollutant concentration in drinking water
EPA	STORET	Surface water quality/biological monitoring
EPA/OAQPS	AIRS	Air pollutant concentrations at 4,000 sites; 9,000 point sources
EPA	ETS	Emissions from electric utilities
EPA	Center for Environmental Information and Statistics	Central source of environmental data/trends
EPA/OPPTS	TRI	Toxic compounds release inventory
EPA	CERCIS	Hazardous waste sites, assessment, and status
EPA	BASINS	Watershed pollutants (point and area source) and locations

<b>Health Effects Databases</b>		
EPA/ORD	IRIS	Hazard characterization and risk numbers for cancer and noncancer endpoints
NCI	SEER	Cancer incidence/prevalence by type and location
CDC	Behavioral Risk Factor Survey	Incidence of contagious diseases
Veterans Administration	VA databases	Major disease incidence and prevalence by location
National Center for Health Statistics	National Health Interview Survey	Prevalence and incidence data in populations
State Health Departments	Various	Disease incidence by location and time
Insurance Companies	Various	Disease and death incidence by location, time, and population
<b>Health and Environmental Databases</b>		
EPA, Region 3	Green Communities Initiative	Environmental health, economic, and societal indicators of impact of environmental regulation
ATSDR	Registries	Follow-up individual health outcomes on communities and populations exposed to specific environmental contaminants
	Hazardous Substances Emergency Event Surveillance System	Collects information on releases and victims



United States  
Environmental Protection  
Agency

Office of Research  
and Development (8104R)  
Washington, DC 20460

Official Business  
Penalty for Private Use  
\$300

EPA 600/R-02/050  
September 2003  
www.epa.gov

Please make all necessary changes on the below label,  
detach or copy, and return to the address in the upper  
left-hand corner.

If you do not wish to receive these reports CHECK HERE  ;  
detach, or copy this cover, and return to the address in the  
upper left-hand corner.

PRESORTED STANDARD  
POSTAGE & FEES PAID  
EPA  
PERMIT No. G-35



# HUMAN HEALTH RESEARCH STRATEGY



Recycled/Recyclable  
Printed with vegetable-based ink on  
paper that contains a minimum of  
50% post-consumer fiber content  
processed chlorine free