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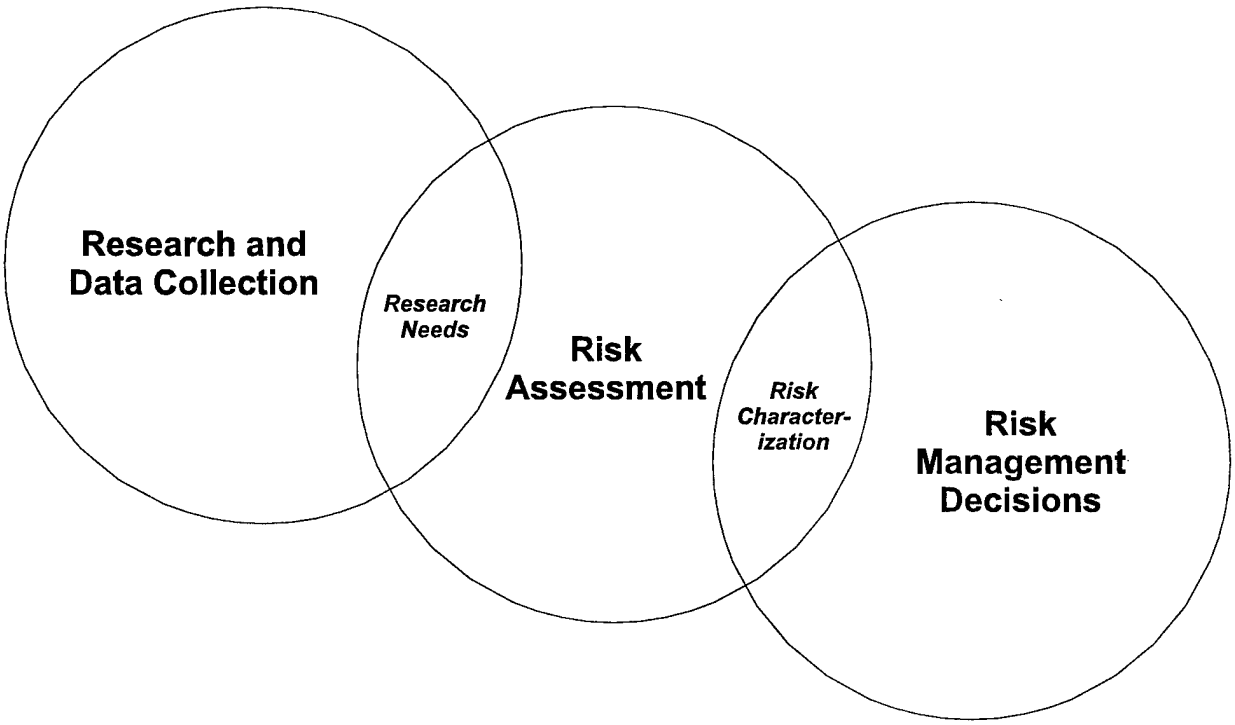
Human Health Risk Assessment Research Strategy

EXTERNAL REVIEW DRAFT
FEBRUARY 1998



U.S. Environmental Protection Agency
Office of Research and Development

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List of Abbreviations and Acronyms

ATSDR	Agency for Toxic Substances and Disease Registry
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
DBP	Disinfection by-product
DOE	Department of Energy
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administation
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
MCL	Maximum contaminant level
NAAQS	National Ambient Air Quality Standards
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute
NCTR	National Center for Toxicological Research
NHANES	National Health and Nutrition Assessment Surveys
NHAPS	National Human Activity Pattern Survey
NHEXAS	National Human Exposure Assessment Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute for Standards and Technology
NOAA	National Oceanic and Atmospheric Administration
NRC	National Research Council
ORD	Office of Research and Development
PAH	Polycyclic aromatic hydrocarbon
PBPK	Physiologically based pharmacokinetic
PCB	Polychlorinated biphenyl
PM	Particulate matter
RCT	Research Coordination Team
SAB	Science Advisory Board
SAR	Structure-activity relationship

List of Abbreviations and Acronyms
(cont'd)

STAR	Science to Achieve Results
TEF	Toxic equivalency factor
THERdbASE	Total Human Exposure Research Database and Advanced Simulation Environment
TSCA	Toxic Substances Control Act
VOC	Volatile organic compound

Executive Summary

Background

This document describes the direction in which the Office of Research and Development (ORD) human health risk assessment research program is expected to evolve over the next several years. The ORD research planning process involves a series of steps designed to identify, verify, and document research priorities. This research strategy represents a step in this process; it is both an elaboration of the description of ORD's human health risk assessment research program contained in the ORD Strategic Plan and an outline for development of the more specific laboratory/center implementation plans.

This document describes ORD's human health research program that addresses key uncertainties in human health risk assessment. This research strategy is an attempt to build consensus for a focused, integrated research agenda that will strengthen the scientific foundation for future risk assessments.

Strategic Research Directions

Based on an evaluation of the needs of the U.S. Environmental Protection Agency's (EPA's) regulatory and regional programs and consideration of recommendations made by external advisory groups, three key strategic objectives have been identified for core human health risk assessment research. These objectives, as listed below, will provide direction and focus for ORD human health risk assessment research for the next 5 to 10 years:

(1) *Reducing uncertainties in exposure measurements and measurement-derived models,*
(2) *Applying mechanistic information (to reduce uncertainties) in hazard characterization and dose-response assessment, and*
(3) *Characterizing and assessing variation in human exposure and susceptibility to disease*

Research directions for each of these objectives are provided, along with explanation of the process used to prioritize the objectives. Discussion is presented in the context of ORD's organization along the lines of the risk assessment paradigm.

Anticipated Results

Focusing human health risk assessment research on the strategic objectives identified in this document will lead to the development of specific research products identified for each research objective. The potential applications of these results are discussed within the document in terms of products and anticipated uses. In addition, the impacts that the overall research program and its individual components are expected to have on the quality of human health risk assessments are identified and discussed.

1

Introduction

1.1 Purpose: Achieving a Focused Research Agenda

The purpose of this research strategy is to present current and future directions for ORD's core research program in human health risk assessment. This research strategy represents the second step of a three-step research planning process. In the first step, ORD established, and published in the *1997 Update to ORD's Strategic Plan* (U.S. Environmental Protection Agency, 1997a), strategic research planning principles, ranking criteria, and six high-priority research areas that will receive special, expanded attention within the broad program of research it supports.

This document represents the second step. Essentially, this document expands the description of the core program (see box below) in human health risk assessment beyond the brief summary provided in ORD's Strategic Plan. During this second step, ORD will solicit and incorporate inputs from the broad EPA community (both scientists and policy makers) and the external scientific community on the most appropriate long-term research directions that will improve the scientific foundation for the conduct and interpretation of health-related problem-directed research (See research plans/strategies for these problem-directed areas in particulate matter, microbes/disinfection by product, endocrine disruptors, arsenic). In the final step of the research planning process, this document will be used by ORD's laboratories and centers to prepare detailed research project plans.

Thus, this document is both an elaboration of the core research program in human health risk assessment described in the ORD strategic plan (U.S. Environmental Protection Agency, 1997a) and a goal-oriented outline for the development of a more detailed laboratory/center implementation plans. The critical question that this document addresses is *What are the appropriate strategic directions for this core research program that will develop the fundamental methods, databases, and measurements to strengthen the scientific foundation for health risk assessments across EPA?* The relationship between the core and problem-driven components of ORD's human health research program is illustrated in Figure 1-1.

In focusing this document on strategic directions for a core research program in health risk assessment, ORD is adopting a recommendation of the National Research Council's Committee on Research Opportunities and Priorities for EPA. "Core research should seek better understanding of fundamental phenomena and generate broadly applicable research tools and information. These goals will not vary much over time, and thus core research priorities will stay relatively constant." Core research should include three basic objectives: "(1) Acquisition of systematic understanding about underlying environmental processes . . .; (2) Development of broadly applicable research tools, including better techniques for measuring physical, chemical, biological, social, and economic variables of interest; more accurate models of complex systems and their interactions; and new methods for analyzing, displaying, and using environmental information for science-based decision making; (3) Design, implementation, and maintenance of appropriate environmental monitoring programs, with evaluation, analysis, synthesis, and dissemination of the data and results to improve understanding of the status of and changes in environmental resources over time and to confirm that environmental policies are having the desired effect" (National Research Council, 1997).

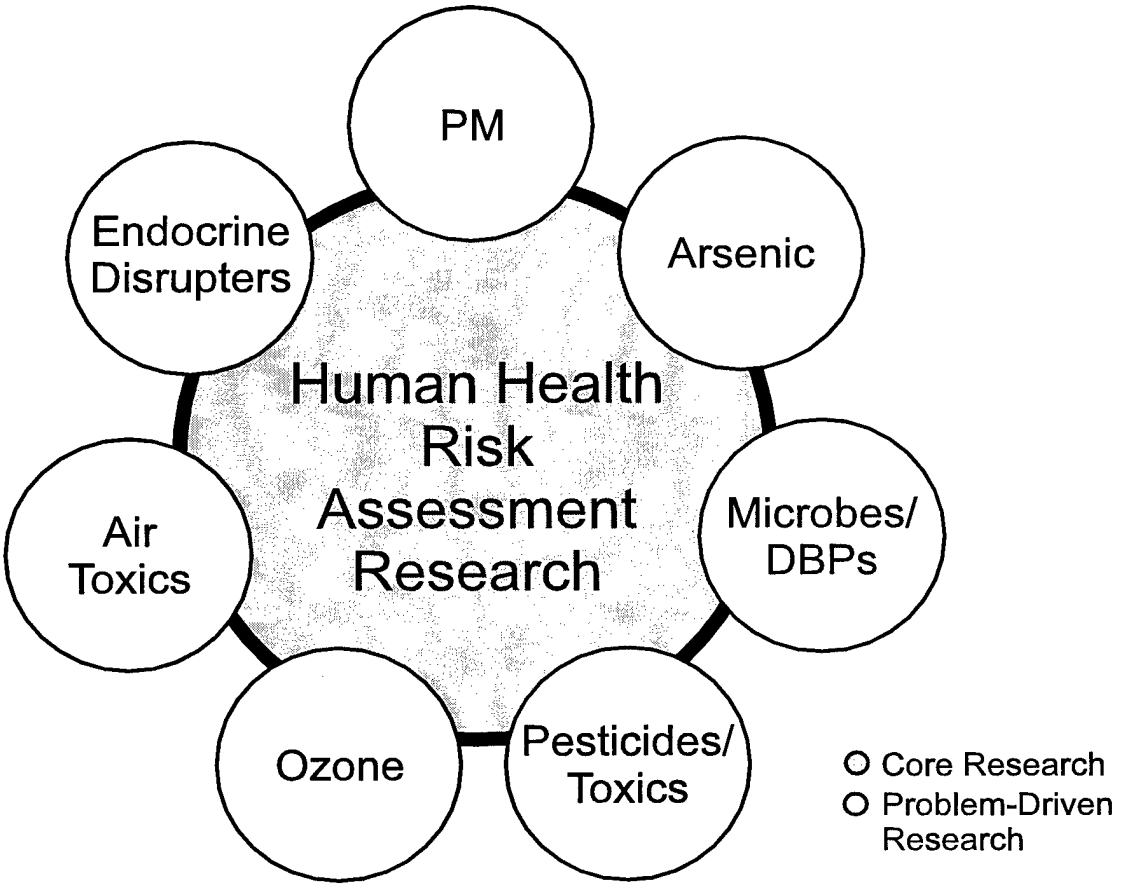

Figure 1-1. Relationship between core and problem-driven components of ORD's human health research program.

This strategy is not intended to be a technical document. Rather, it is targeted to an audience of senior scientific advisors, environmental policy and decision makers, and anyone with a strong interest in establishing research priorities and directions to strengthen the scientific foundation for EPA decision making.

1.2 Scope of the Research Problem

Human health risk assessment is a process that characterizes the potential adverse health effects resulting from exposure to environmental hazards (National Research Council, 1983). In 1983, the National Research Council described four primary steps of risk assessment that are qualitative or quantitative in nature. They are: (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization (Figure 1-2). Hazard identification describes the likelihood that an environmental agent can produce an adverse effect in humans under certain exposure conditions. Dose-response assessments quantitatively estimate the relationship between exposure and the health effect. Elements of exposure assessment include the identification and quantification of the population exposed, important routes of exposure, and estimations of magnitude, duration, and frequency of contact between an environmental agent and humans. The last step, risk characterization, integrates this information into a qualitative or quantitative estimate of the likelihood that a hazard posed by exposure to the agent would pose a human health risk (National Research Council, 1994). A risk characterization describes the assumptions and uncertainties associated with the risk estimate. Assumptions and uncertainties exist because of a lack of knowledge about the biological, chemical, and physical processes within and between exposure and effect. It may not be possible or practical to study the causal relationship for all the different health outcomes resulting from numerous exposure scenarios. Thus, use of assumptions and defaults becomes necessary in characterizing risk. Research that targets key assumptions can improve the scientific underpinning of the resulting risk assessment by reducing the inherent uncertainties.

In recent years, advances in the state of environmental science have illustrated that new risk assessment methods are needed to investigate complex environmental and human health issues that were not contemplated in early environmental legislation. These advances illustrate the importance of new risk management options for EPA, replacing, where appropriate, the "one-size-fits-all" approach to risk management with a more population-specific approach where

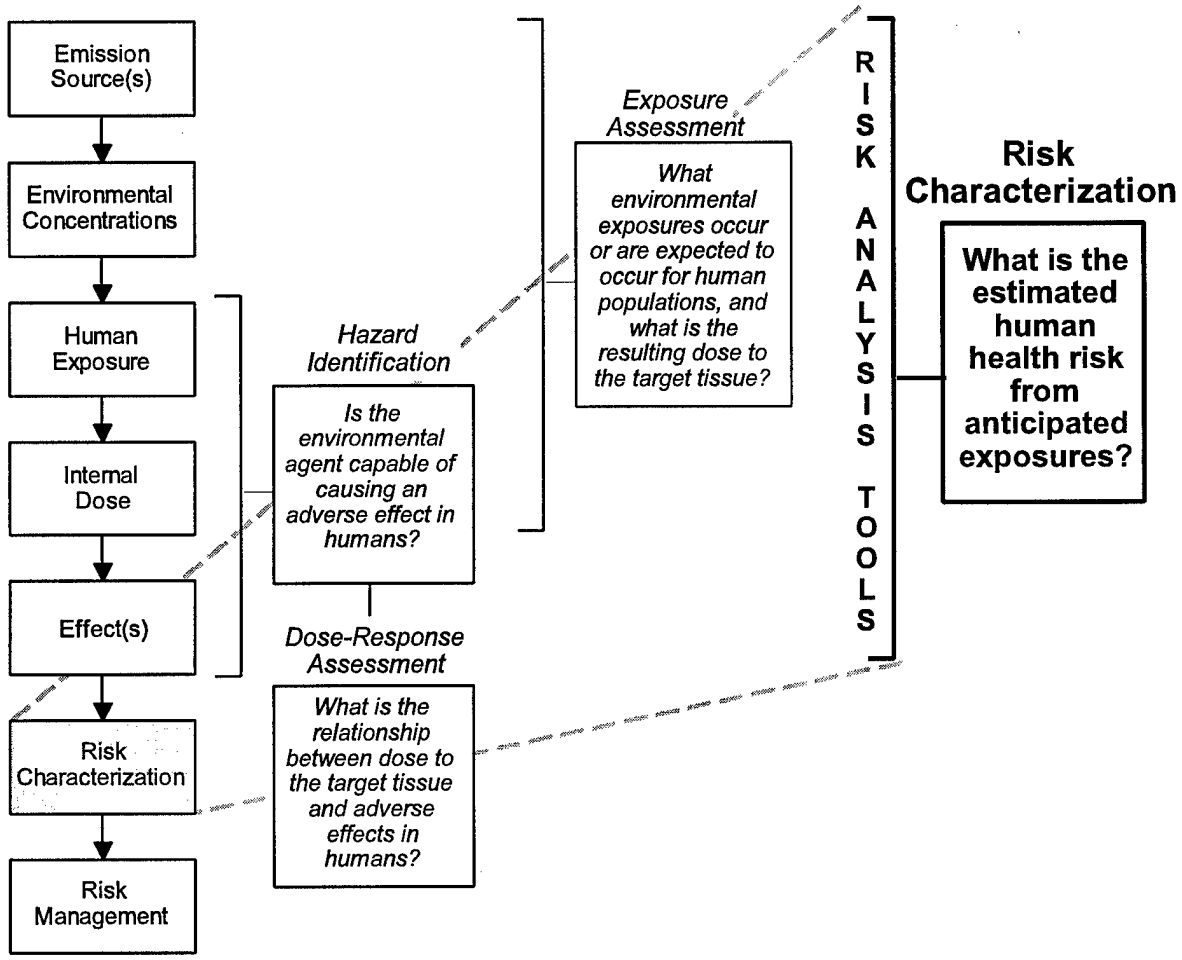

Figure 1-2. The elements of human health risk assessment.

risk management options are developed for infants and children, susceptible subpopulations, or the general population (see text box below).

Emerging Emphases in Human Health Risk Assessment and Management

Historic Approach	Emerging Emphases
General population	Sensitive subpopulation
Single source	Multiple sources
Single pollutant	Multiple pollutants
Single pathway	Multiple pathways
Single endpoint	Multiple endpoints
Central decision making	Community decision making
Command and control	Flexibility in achieving goals
Single stressor risk reduction	Holistic risk reduction

In recognition of these changes, EPA-wide guidance recently was provided "to take into account cumulative risk issues in scoping and planning major risk assessments and to consider a broader scope that integrates multiple sources, effects, pathways, stressors, and populations for cumulative risk analyses . . . " (U.S. Environmental Protection Agency, 1997b).

The need for additional research in human health risk assessment is both urgent and compelling (see Appendix A and the text box below). During the past 10 years, a number of national scientific advisory groups have identified significant deficiencies in EPA-wide risk assessment practices. These advisory groups also have developed specific recommendations to assist EPA in identifying critical scientific issues that must be remedied to strengthen human health risk assessment across EPA. However, the scope and number of scientific uncertainties that need to be addressed with research is substantial and disproportionately large in comparison to current EPA resources. In the words of the National Research Council, "Because EPA's task of protecting the environment and human health is so vast and difficult, and because resources to undertake the necessary research are very limited, choices will have to be made among many worthwhile projects" (National Research Council, 1997).

> "In the absence of reliable risk assessment, enormous sums of money that might be better spent elsewhere may be allocated to dealing with *perceived* risks. While it is essential to ensure public health and environmental integrity, limited resources reinforce the need to assess risks as accurately as possible . . . . Estimates have indicated that the cost of environmental regulations in the United States will total between $171 and $185 billion by the year 2000 (Carlin et al., 1991). Compliance with air pollution control regulations will cost an estimated $94 billion per year by the year 2000 (Carlin et al., 1991). Russell et al.(1991) estimated that cleaning up all the major hazardous waste sites would cost between $500 billion and $1 trillion over the next 30 years. The sums are enormous, and a convincing analysis must be provided to demonstrate that these expenditures are justified as the most cost-effective way to reduce risks to human health and to the environment" (National Research Council, 1997).

After considering recommendations from extramural advisory groups, as well as from senior scientists from across ORD and EPA's program and regional offices, *ORD has identified three strategic directions for its core human health risk assessment research during the next several years*. When adopted, these strategic directions will focus future ORD research in three areas that would have the broadest applicability for improving the scientific foundation for EPA risk assessments (see Appendix B):

(1) *reducing uncertainties in human exposure measurements and models;*

(2) *applying mechanistic models and data to reduce uncertainty in hazard characterization and dose-response assessment; and*

(3) *characterizing variability in human exposure and susceptibility to disease.*

The implications of these research problems for EPA health risk assessments are described briefly in the following sections and explored in more detail in Chapters 2 through 5 of this document.

1.2.1 Reducing Uncertainties in Human Exposure Measurements and Models

Risk assessors rarely have actual exposure information to assess environmental risks and usually are dependent on a variety of models and assumptions. In the rare case where actual exposure measurements have been made, there may remain a considerable lack of knowledge about the internal dose to humans. Frequently, human exposure is multichemical and multipathway in nature, but historic approaches to regulation have tended to focus on a single chemical and a single exposure pathway. Examples include evaluation of dietary exposure to a specific pesticide or outdoor inhalation exposure to VOC's.

There are many gaps in the knowledge of human exposure to environmental pollutants. Currently, because of lack of data, risk assessment default assumptions are made that there are no significant differences in time-activity patterns as a function of age, gender, socioeconomic status, or ethnic origin; and there are no significant differences in time-activity patterns of the population in relation to regional variability or rural, urban, or suburban place of residence. In reality, the amount of time spent in different microenvironments can vary significantly over a lifetime and can have a large impact on both the actual exposure and the risk assessment.

The pattern and frequency of exposure also affect the type of health effects produced. Short-term exposures of intense magnitude result in a different pattern of target tissue insult than does the same total dose delivered over a longer time period. Also, short-term exposures can occur at critical times during growth and development with far greater effect than if the exposures were to occur at other times.

1.2.2 Developing and Applying Mechanistic Models and Data To Reduce Uncertainties in Hazard Characterization and Dose-Response Assessment

Risk assessment often involves the extrapolation from observations obtained at exposures orders of magnitude greater than the environmental exposure for which estimates of risk are being made, as well as from test animals to humans. The uncertainties in such extrapolations are considerable and represent major problems facing the risk assessor.

Extrapolation from animal data to estimate human risks involves a variety of assumptions about interspecies differences between animals and humans.

Extrapolation from high to low dose from either animal or human data requires assumptions about the potential high-to-low dose difference in the shape of the dose-response curve. For carcinogens, EPA has taken the default approach that, in the absence of biological information to the contrary, a linear low-dose approach to risk estimation is to be used, despite recognition that the actual risk could be between the estimated risk and zero. For noncancer risks, EPA uses uncertainty factors to establish a dose below which adverse effects are not expected to occur. These estimates are generally conservative and are made with little if any knowledge of whether biological effects actually occur at such low doses. Research to investigate factors that affect the shape of the response curve at low doses will greatly improve both hazard characterization and dose-response assessment.

1.2.3 Characterizing Variability in Human Exposure and Susceptibility to Disease

The significance of variation in human susceptibility to disease has been recognized for many years. Similar variation is known to exist in response to environmental toxicants and may be related to factors such as age, preexisting disease, lifestyle, genetic background, gender and ethnicity (or some combination of these). For example, the developing nervous system of a child is especially sensitive to lead exposure and young children have behaviors (e.g., eating paint chips, hand-to-mouth activities) that increase their exposures to lead. Thus, adequately protecting children from the risks of lead (or other susceptible subpopulations from other chemicals) requires a fuller understanding of these factors. Such variation must be addressed to develop improved exposure, health, and risk assessments. However, currently available approaches are often crude (e.g., assuming a 10-fold uncertainty factor for susceptibility in

noncancer health assessments) or rarely used because of intense data requirements (e.g., exposure assessments of a specific vulnerable subpopulation such as children exposed to ozone).

As is obvious from this discussion, there is an immense set of possible combinations of risk factors and chemicals, effectively preventing a direct measurement of each set. The only effect approach is to carefully prioritize potential scenarios of high concern and conduct research to understand the fundamental principles. Such information can serve as the basis of models between measured and unmeasured scenarios or the basis of the design of problem-directed research. For example, a more complete understanding of activity patterns of children would allow estimation of factors that result in increased chemical contact and dose. Such historical knowledge led to concerns about children exercising outdoors when ozone levels are high and drove ozone-specific research to enable a quantitative assessment. As another example, a core goal is to identify the mechanisms of sensitivity of children to pesticides and to quantify the activity patterns of children. This information enables the design of separate problem-driven research on what specific pesticides children are most susceptible to and what activity patters increase their exposure to those specific pesticides. Even with the design and conduct of more studies on this issue, risk assessment models will still need to make assumptions. Hence, this core research on susceptibility must provide principles that can be translated to improved risk assessment models. This need was also recognized in the Food Quality Protection Act which required a protective factor for children.

1.3 Coordination with the Broader Environmental Research Community

The ORD has been a federal leader in human health risk assessment research for the past 15 years and sustains an in-house scientific capability in all the elements of human health risk assessment research. ORD scientists have fostered research coordination and collaboration in health risk assessment with their peers in other federal and state agencies (e.g., National Institute of Environmental Health Sciences [NIEHS], Centers for Disease Control and Prevention [CDC], Food and Drug Administration [FDA], National Oceanic and Atmospheric Administration [NOAA], National Cancer Institute [NCI], Agency for Toxic Substances and Disease Registry [ATSDR], NCTR, National Institute for Occupational Safety and Health [NIOSH], and Department of Energy [DOE] laboratories, and states, including California, Texas, and New Jersey), as well as in academic and private research organizations. In addition to peer

collaboration, a major portion of ORD's human health risk assessment research program has been sustained through cooperative agreements, grants, and interagency agreement with these organizations. Moreover, ORD has established a number of formal agreements with several of these agencies to sustain and improve current research coordination.

It is essential that future ORD research in human health risk assessment continue and expand on current interagency research collaboration and formal research agreements to ensure the broadest possible leverage of expertise to this complex research area. This is particularly important for the resource-intensive elements of risk assessment research (e.g, human exposure field studies) where current staffing levels are very limited. Currently, ORD's interagency coordination and collaboration in these areas is quite strong (see, for example, the text box about the National Human Exposure Assessment Survey [NHEXAS] at the end of Chapter 2).

1.4 Structure of This Document

The initial portion of this document includes an executive summary and introduction. The main body of the document includes three chapters that explain the strategic directions for future health risk assessment research and the research approaches and scientific contributions that ORD expects will result from these strategic directions. The sixth chapter discusses the improvements in the science of human health risk assessment that will result from these strategic directions. The final chapter contains the references cited in preceding chapters, followed by Appendixes A through D.

Within the main body of the document, the information presented in Chapters 2 through 5 begins with a *background* section, which describes the scientific elements of each component of the risk assessment paradigm and examples of current research supported by ORD. Subsequent sections of each chapter discuss the *strategic directions for future research* for each research area. This is accompanied by a discussion of the principal scientific problems or areas of uncertainty; the scientific questions that must be addressed to resolve the problems; and the research approach and scientific contributions (or products) that will respond to the questions as well as the contributions that this research will make to strengthen the scientific foundation for risk assessment.

Summary of Document Structure

Executive Summary

Chapter 1: Introduction and Identification of Broad Strategic Directions for Core Research

Chapters 2 through 4:
Research Area
- Background information
  - The scientific elements of the research area
  - Examples of current research in the area supported by ORD
- Strategic directions for future research
  - Principal scientific problems
  - Scientific questions or areas of uncertainty
  - Research approaches and scientific contributions or products

Chapter 5: Implications for reducing uncertainty in risk assessment

Chapter 6: References

Appendixes

2

Human Exposure Research

2.1 Background

Figure 2-1 presents a conceptual diagram of the scientific elements involved in human exposure research. This figure illustrates the relationships among sources of environmental contamination, transport and transformation, environmental characterization, and human exposure and dose. *Source characterization and source-attribution research* involve quantifying, in time and space, emission source characteristics in such a fashion that source-receptor relationships can be developed for single or multiple environmental contaminants. *Transport and transformation research* involves quantifying physical transport processes (from source to receptor), physical and chemical transformations, and biological processes. *Environmental characterization research* focuses on the physical structure of an environment and on determining ambient levels of chemical or biological contaminants in that environment. In the human exposure context, environments of concern include settings where short- or long-term exposures may be of concern (e.g, occupational, residential, and commuting environments). *Time-activity pattern research* develops temporal profiles of those environments in which humans are exposed to environmental contaminants during their daily activities, the duration of those exposures, and the human activities or behaviors that may affect the exposure.

Conceptually, *human exposure research* investigates the magnitude, duration, and frequency of contact between an environmental contaminant (or biological agent) and the human body (National Research Council, 1991; Duan and Ott, 1989).[1] *Total human exposure*

[1]A quantitative definition of exposure is more complex than this qualitative description implies. For example, an air pollution scientist may characterize human exposure as the magnitude and duration of the atmospheric contaminants at the interface with the human breathing zone. From the perspective of a health scientist, the concept of human exposure to atmospheric contaminants may refer to an aerosol within the lung at the interface between airway and alveoli that, because of interactions within the body, may possess a different chemical composition from that of the aerosol before it was inhaled. A different type of complexity is introduced when considering human exposure from multiple environmental pathways. For example, when considering an infant's exposure to lead inhaled from motor vehicle exhaust and ingested through dermal-oral or pica activities, calculating the resulting exposure requires that the pathway-specific exposures be expressed in comparable terms. In summary, a mathematical definition of human exposure depends critically on where the human-environmental boundary is located and on whether single-pathway or mutipathway exposures are being investigated.

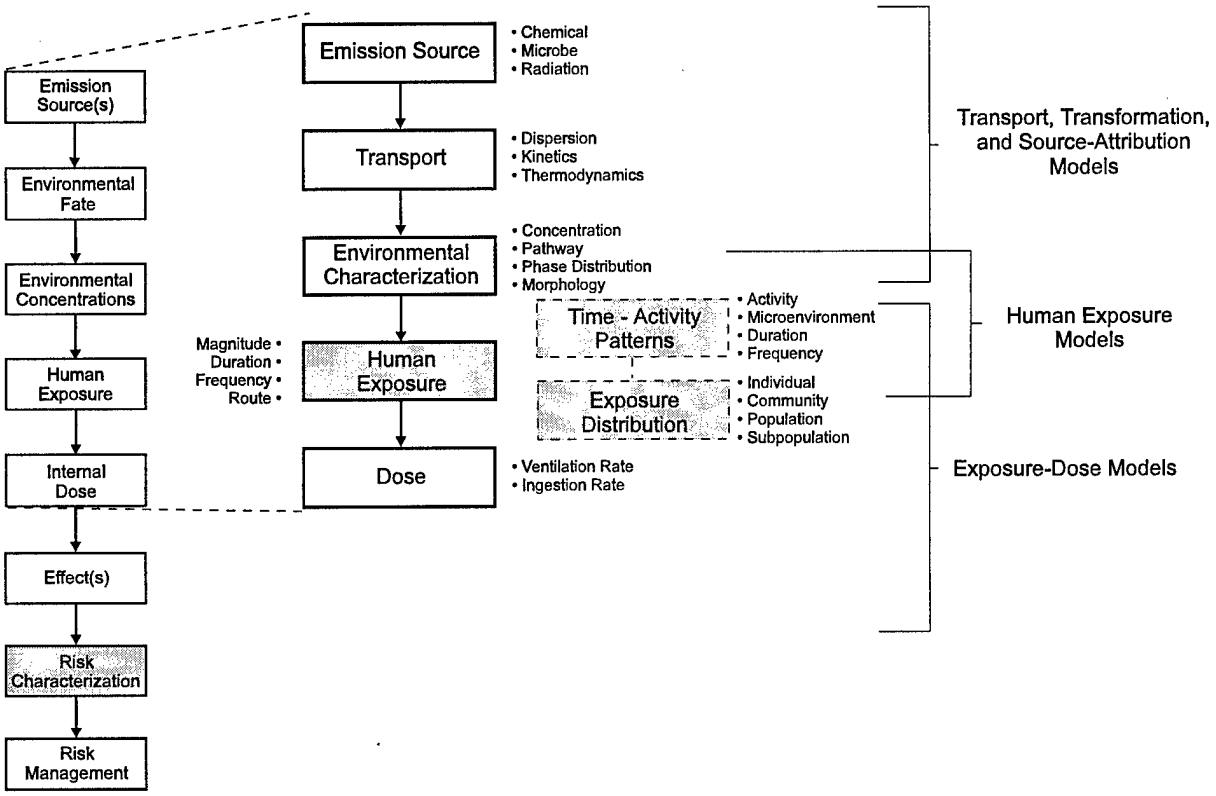

Figure 2-1. Scientific elements involved in human exposure research and exposure assessment.

integrates all relevant routes of exposure to a specific contaminant(s). For example, people are exposed to lead via inhalation, food, water, and hand-to-mouth behavior and evaluation of one route only would result in erroneous exposure assessment and ineffective risk management. This example also illustrates the importance of time-activity pattern research (e.g., what is the relationship between the hand-to-mouth activity of a young child and lead exposure). Even when total human exposure is known, dose must be understood to put the influence of different pathways into perspective. For example, suppose food concentrations of a chemical are high, but little is eaten, and little is absorbed compared to low concentrations of the same chemical in air with a high rate of absorption into the body from the lungs.

The scope of ORD's current human exposure research includes projects that seek to measure, evaluate, and model exposure-dose relationships illustrated in Figure 2-1 and to begin to link this knowledge to source and fate research (described elsewhere) with the ultimate goal of source-to-dose modeling.

ORD human exposure research in this area has been developed over the past 15 years through collaboration between ORD scientists conducting human exposure, environmental health, and risk assessment research with their peers in other federal agencies (e.g., NIEHS, CDC, FDA, NCI, NICHD, ATSDR, NIOSH, DOE) and in academic and other research organizations. Although ORD scientists participate in establishing strategic directions for EPA research, they are not responsible solely for conducting the research to accomplish the strategic goals. A major portion of ORD's human exposure research has been supported through cooperative agreement and grant assistance mechanisms. The focus of ORD's current human exposure research responds to the following four scientific questions.

(1) *What methods are needed to measure multipathway human exposure and to develop estimates of total exposure?*

(2) *What are the statistically representative time-activity patterns that affect microenvironmental exposure at different scales (e.g., population, subpopulation, national, regional)?*

(3) *What protocols are needed to develop measurement-based population distributions of multipathway human exposure and to communicate the results of these studies?*

(4) *What models and systems are needed to mathematically represent microenvironmental and population distributions of human exposure?*

Current human exposure research sponsored by ORD (in cooperation with grantees from academic and private research institutions, partnerships with other federal and state agencies, and scientists in its laboratories and centers) is summarized in Table 2-1. Current human exposure measurement research includes projects to develop and evaluate: (1) statistical and analytical chemistry measurement methods, (2) microenvironmental (including residential) exposure measurement databases, (3) pilot studies to develop population-scale multimedia exposure protocols, and (4) time-activity pattern databases. Current human exposure modeling research focuses on developing microenvironmental models and a framework for total human exposure modeling. Microenvironmental models are designed to predict single- or multipathway human exposure to contaminants in specific (e.g., residential, commuting, occupational) environments. Total human exposure models are designed to predict multipathway human exposure and the frequency distribution of exposures for a population or subpopulation, either from a probabilistic sample of human exposure and activity pattern measurements or from the integration of

Table 2-1. Overview of Current Human Exposure Research Sponsored by ORD

Scientific Questions and Research Focus	Research Approach	Research Products	Future Emphasis
What protocols are needed to develop measurement-derived exposure databases at different scales?	Develop, demonstrate, and evaluate protocols for single and multipathway exposure measurement studies. ORD research focuses on development of protocols for community-scale and regional-scale population distributions. Examples include NHEXAS, the Pesticide Residential Exposure Research Guidelines, and the investigation of pesticide exposures in children.	Reduced uncertainty in quantifying population distributions of human exposure; guidelines for environmental health and human exposure investigations by EPA offices, states, and industry Guidelines for human exposure and environmental health investigations for EPA offices and states	Future emphasis will be on multipathway protocols for exposure surveillance. Future research activities are anticipated to be sustained at current levels.
	Develop, demonstrate, and evaluate protocols for single and multimedia residential exposure studies that incorporate source-pathway-exposure investigations.	Reduced uncertainty in characterizing residential exposures and the relationships between indoor and outdoor sources	Future research activity is anticipated to increase.
What methods are needed to measure multipathway human exposure and total exposure?	Develop, demonstrate, and evaluate methods for measuring dermal, oral, and dietary exposure. Improving the accuracy of exposure estimates for infants and children is one focus of ORD research in this area.	Reduced uncertainty in estimating multipathway and total human exposure for infants and children	In general, future research activity is expected to decrease for methods development.
	Develop, demonstrate, and evaluate single- and multimedia methods for measuring mixtures and phase-distributed compounds. ORD research focuses on aerosols, metals, VOCs, semivolatile organic compounds, and microbiological contaminants.	Reduced uncertainty in measuring mixtures and interpreting multipathway exposures for these compounds	In general, future research activity is expected to decrease for methods development.
	Develop, demonstrate, and evaluate low-cost indicators of multimedia exposure. ORD research focuses on immunoassay, biosensor, and blood-breath techniques.	Low-cost measurement methods and near-real-time sensor technology	Future research in development of low-cost methods will be sustained at current levels.
What are the statistically representative time-activity patterns that affect exposure at different scales?	Develop, demonstrate, and evaluate statistical instruments for identifying time-activity patterns for populations and population subgroups. ORD research focuses on children and farmworkers.	Reduced uncertainty in human exposure models that incorporate time-activity pattern data	Future research activity is anticipated to be sustained at current levels.
What are the statistically representative time-activity patterns that affect exposure at different scales?	Research to develop, demonstrate, and evaluate time-activity pattern data and a database system to incorporate both exposure measurement and time-activity pattern data. ORD research focuses on NHAPS and on THERdbASE.	Reduced uncertainty in time-activity pattern profiles; databases for construction of time-activity pattern profiles, simulation of exposure distributions, and evaluation of exposure mitigation and risk management options	Future research activity in this area is expected to be sustained at current levels.

Table 2-1 (cont'd). Overview of Current Human Exposure Research Sponsored by ORD

Scientific Questions and Research Focus	Research Approach	Research Outputs	Future Emphasis
What models and systems are needed to mathematically represent microenvironmental and population distributions of human exposure?	Research to develop, demonstrate, and evaluate measurement-based models that represent personal and microenvironmental exposures, exposure-source relationships, and the physical and chemical factors that affect exposure magnitude, duration, frequency, and variability. ORD research focuses on developing models that can reduce uncertainty in risk assessment. Exposure measurement data from NHEXAS and pesticide exposure studies will be used in this research.	Reduced uncertainty in both microenvironmental models and models based on population distributions of exposure Development of prospective and retrospective exposure models that are evaluated with measurement data Reduced uncertainty in risk assessment models	Future research activity in this area is expected to increase and to focus on both single and multipathway models that represent exposure in different microenvironments.
	Research to develop, demonstrate, and evaluate measurement-based models that represent exposure-biomarker-dose relationships and the physical and chemical factors that affect potential and absorbed dose.	Reduced uncertainty in exposure-PBPK models	Future research activity in this area is expected to increase.
	Research to develop, demonstrate, and evaluate measurement databases for baseline comparisons to interpret exposure data and exposure mitigation options with study participants, their communities, and governments.	Baseline data for interpreting future exposure studies at community to regional scales New approaches for design and interpretation of exposure and biomarker databases	Future research activity in this area is expected to increase.
What are the important biomarkers of exposure and effect?	Research to develop and evaluate biomarkers of exposure and effect to priority pollutants and for multiple endpoints, including cancer, respiratory toxicity, neurotoxicity, immunotoxicity, and developmental and reproductive toxicity. ORD research is focused on DNA adducts of products of incomplete combustion, PAHs, and drinking water disinfection by-products (DBPs); biochemical markers for model neurotoxicants; and cellular markers for reproductive toxicants, dioxins, and PCBs.	Improved exposure and dose-response assessment: qualitative and quantitative characterization of target tissue exposure	Research activities to address this objective are anticipated to increase.

microenvironmental models and time-activity pattern data to predict daily exposure profiles or population exposure distributions.

2.2 Strategic Directions for Research To Reduce Uncertainties in Exposure-Dose Measurements and Models

2.2.1 Problem Statement

In 1995, EPA's Science Advisory Board (SAB) completed a report that reviewed the state of exposure assessment science, identified constraints on exposure and risk assessment within EPA, and formulated recommendations for strengthening the scientific foundation for exposure and risk assessment through future research (U.S. Environmental Protection Agency, 1995a). Significant concerns about the lack of exposure measurements, databases, and models across EPA are prominent among the findings and recommendations in this report. The implications for exposure and risk assessment posed by these deficiencies are summarized in Table 2-2. The SAB report acknowledged the capability and relevance of ORD's current research for addressing these agency-wide problems. However, it also concluded that a substantial and long-term future research effort to improve exposure measurements and to develop exposure databases and models would be required to remedy these scientific deficiencies. Relevant findings from this and other national advisory panels are summarized in Appendix A.

In addition to this SAB study, the National Research Council (NRC; 1994) completed a report on science in risk assessment that made wide-ranging recommendations to improve EPA's risk assessment procedures. The report identifies the need for research into variability in human exposure and the extent to which this contributes to variability in susceptibility to disease prominently among its recommendations because of the substantial scientific uncertainty in this area. Variability and susceptibility are related also to age, lifestyle, genetic background, gender, and ethnicity (see also Chapter 3)—at individual-to-population-scales. The NRC panel concluded that the amount of variation could have a significant effect on current estimates of individual exposure and risk and, depending on the homogeneity of the population from which exposure and risk are determined, on the estimation of population risk as well.

This chapter integrates discussions about exposure research for the general population and susceptible subpopulations because susceptibility (from the exposure perspective) is investigated

Table 2-2. Scientific Constraints and Uncertainties on Exposure and Risk Assessment in EPA (U.S. Environmental Protection Agency, 1995a)

Scientific Components of Exposure Assessment	Examples of Constraints and Scientific Uncertainties
Environmental and Exposure Measurements	1. There are virtually no measurement studies or protocols that characterize multipathway exposures either at microenvironmental or population scales. 2. EPA typically measures pollutant emissions without determining actual human exposures or biological markers of exposure and effect. 3. Although EPA supports costly ambient monitoring networks to implement regulations that protect the public or environmental health, these networks do not measure exposure or biological markers of exposure and effect. 4. When EPA conducts exposure and risk assessments, sources of emissions and dispersion models typically are used in place of actual exposure data. Despite evidence that determining less-than-lifetime exposures is essential to defining relationships between acute exposure, dose, and response, EPA's assumptions about emission sources and their associated ambient concentrations fix them as constants during a 70-year human lifetime. 5. When EPA conducts environmental measurement studies for screening or exposure assessment, the studies rarely investigate the multiple environmental pathways that are essential for a scientifically valid estimate of total human exposure. 6. Typically, EPA's exposure and risk assessments are conducted on a pollutant-by-pollutant basis without regard to the nature of pollutants during actual exposures. 7. Despite evidence that people spend 50 to 80% of their time in residential environments, EPA exposure and risk assessments typically assume that residential exposures are equivalent to outdoor ambient concentrations of pollutants and are not affected by either the building or indoor sources of pollution. 8. Methods of adequate sensitivity and accuracy that are inexpensive enough for broad use in multimedia exposure measurements are often not available.
Exposure Modeling, Databases, Time-Activity Patterns, and Susceptible Subpopulations	1. There are virtually no databases of human time-activity pattern data at regional, population, or subpopulation scales. 2. EPA exposure and risk assessments typically assume that an individual's time-activity patterns are invariant over a lifetime. 3. EPA exposure and risk assessments typically assume no difference in time-activity patterns across a population as a function of region, residential location (urban versus rural), gender, age, socioeconomic status, or ethnic origin. 4. EPA exposure and risk assessments typically do not identify characteristics of susceptible subpopulations (including time-activity pattern behavior or acute exposure information) related to elevated exposures or effects. 5. EPA exposure and risk assessments typically ignore residential time-activity pattern data related to indoor and residential exposures. 6. There are virtually no measurement-derived databases of multipathway human exposure. 7. EPA exposure and risk assessment models rarely, if ever, are validated with actual human exposure measurements. 8. EPA exposure and risk assessments assume statistical distributions of population exposures that are not validated and do not include information about highly exposed individuals or susceptible subpopulations. 9. There are no protocols for communicating exposure, risk, and mitigation information to residents in communities or regions. 10. There are virtually no multipathway human exposure models that represent relationships between exposure and dose. 11. There are virtually no multipathway human exposure models that represent prospective or retrospective relationships between pollutant sources, pathways, environmental concentrations, exposures, and dose. 12. EPA rarely achieves the integration of models and measurements required by the scientific method for investigation of actual human exposures.
Pollutant- or Media-Specific Issues	1. The distribution of exposure to common pollutants such as particulate matter (PM), microbes, DBPs pesticides, and other toxics in susceptible subpopulations is not known. 2. Whether populations are exposed to sufficient concentrations of endocrine disrupters to cause adverse effects cannot be estimated. 3. In some significant instances (e.g., microbes, pollutants in drinking water, pesticides, PM), adequate analytic methods do not exist.

through studies of time-activity pattern-exposure-dose. Thus, one typical research project serves both.

2.2.2 Scientific Questions

The scientific uncertainties posed by these limitations in exposure and risk assessment can be represented within a framework for future research that is composed of the following three fundamental and related scientific questions.

(1) *What are the pathway-specific measures of human exposure for contaminants of concern?*

(2) *What are the behavioral and time-activity determinants of human exposure for populations and susceptible subpopulations?*

(3) *What are the mathematical relationships among contaminant sources, environmental fate processes, pathway-specific environmental concentrations of contaminants, total human exposure, and dose for average and susceptible subpopulations?*

This framework for future research acknowledges the importance of direct measures of exposure, activity pattern data, and biological indicators of exposure and of the integration of measurements and modeling. Creating these measurements requires the development, evaluation, and application of appropriate methods. In addition, research to develop and apply statistical techniques and time-activity questionnaires that represent the distribution of exposures across subpopulations (e.g., infants, children) is essential for the development of scientifically valid models of exposure and dose.

2.2.3 Research Approaches, Products, and Uses

The three scientific questions highlighted in the previous section provide the strategic framework to define future research approaches and products required to improve the scientific foundation for exposure and risk assessment. These future research approaches, products, and outcomes are summarized in Table 2-3 and described briefly in the discussion in the rest of this section. *As Table 2-3 indicates, ORD will direct its human exposure research program to respond to the most critical deficiencies and constraints in EPA-wide exposure and risk assessment practices.* This will be accomplished by increasing ORD's research emphasis on (1) developing, demonstrating, and evaluating protocols for measurements of actual human exposure; (2) developing human time-activity pattern data and on interpreting and extending this

Table 2-3. Future Approaches and Products for Human Exposure Research Sponsored by ORD

Scientific Uncertainties/Future Focus	Research Approach	Research Products	Risk Assessment
What are the pathway-specific measures of human exposure for contaminants of concern?	Develop and demonstrate and evaluate methods that reduce uncertainty or costs in measuring multipathway exposures. Develop, demonstrate, and evaluate protocols and databases to characterize microenvironmental exposure. Develop and demonstrate protocols and databases for measuring, and communicating the results of population distributions for multipathway and total exposure.	Validated methods for measuring pathway-specific and multipathway exposure. Validated "next generation", low-cost methods for measuring human exposure. Validated residential and microenvironmental measurement protocols and databases. Validated protocols for determining and communicating the result of multipathway population exposure distributions at community-to-regional scales.	New exposure methods to reduce uncertainty in determining multimedia and total exposures. Enhanced ability to design and conduct exposure measurement studies. New exposure measurement databases to evaluate existing exposure models, to determine the reasonableness of exposure assessments, and to develop more accurate models. Enhanced ability to communicate results of exposure studies.
What are the behavioral and time-activity determinants of human exposure for populations and susceptible subpopulations?	Develop, demonstrate, and evaluate a national human activity pattern database. Determine relationships between time-activity patterns and exposures at various scales. Investigate relationships between exposure and factors that may affect susceptibility. Apply time-activity pattern data to investigate exposures for population subgroups that may have increased susceptibility.	A national human activity pattern database. Linked activity pattern/exposure modeling databases that permit statistical analysis of relationships between time-activity patterns and exposure. An evaluation of time-activity pattern and exposure data to identify susceptible subpopulations.	Enhanced ability to apply and interpret statistically representative time-activity pattern profiles. Reduced uncertainty in models, exposure assessments, and risk assessments that rely on time-activity data. Enhanced ability to characterize subpopulations and to identify differential exposures for subpopulations and regions where variability plays a significant role for exposure and risk assessment.
What are the mathematical relationships among contaminant sources, environmental fate, pathway-specific environmental concentrations of contaminants, and total human exposure?	Develop, demonstrate, and evaluate microenvironmental exposure models. Develop, demonstrate, and evaluate multipathway and total human exposure models. Develop, demonstrate, and evaluate models that represent prospective and retrospective relationships among sources, pathway-specific environmental concentrations, total exposure, and dose.	Validated models that represent multipathway residential and microenvironmental exposure. Validated models that represent population distributions of total human exposure at community-to-regional scales. Validated prospective and retrospective exposure models.	New measurement-derived exposure models to reduce uncertainty in exposure and risk assessments. Enhanced ability to apply exposure models to investigate designs for future exposure measurement studies for microenvironments, and populations at community-to-regional scales. Reduced uncertainty in characterizing exposure-dose relationships and in risk assessments.

data to increase the understanding of exposure; and (3) developing exposure models and on evaluating these models with measurement-derived databases.

Future exposure research shall emphasize developing and evaluating protocols and databases of exposure measurements for the general population and for susceptible subpopulations. Despite the importance of direct measurements of exposure, current exposure assessments in single- and muliple-media continue to be hampered by a significant lack of exposure measurement databases. A survey of exposure-related databases in the United States (Sexton et al., 1992) has identified only a relatively small number that report *actual measures* of exposure or dose and virtually none that collect measures of exposure across all relevant environmental pathways.

Although there is a large body of environmental and occupational measurement data for airborne pollutants (especially for the criteria air pollutants, volatile organic compounds (VOCs), and some inorganic constituents of aerosols such as acidity and sulfates), few exposure databases exist to characterize airborne or multimedia human exposure in residential environments (where humans spend the majority of their time) or the relative residential/ambient outdoor contributions to these exposures. This is because research has shown that the air pathway alone may not be the most important route of exposure for some aerosol constituents (such as polycyclic aromatic hydrocarbons [PAHs]) and that the personal aerosol cloud in the human breathing zone contains contaminants that did not originate from conventional stationary air pollutant sources. Future multimedia exposure measurement studies are needed also to characterize exposure to other semivolatile organic compounds, particularly pesticides.

In some cases, protocols for conducting future human exposure measurement studies of subpopulations will evolve from current research sponsored by ORD in partnership with other federal agencies and internationally recognized academic leaders. For example, ORD pilot studies to evaluate protocols for residential exposure measurements, population-scale exposure measurements, and exposure communication and mitigation procedures currently are being developed or evaluated.

Research has clearly demonstrated that the persons who are most at risk are members of susceptible subpopulations (e.g., the elderly, the infirm, the poor, the very young, those who engage in frequent strenuous physical activity, those who are highly exposed occupationally). In the context of residential exposure, infants and children may represent one of the largest and

most susceptible subpopulations, both in terms of their potential for exposure to environmental contaminants and the likelihood of adverse responses to these exposures. Their behavioral patterns may result in greater exposures to contaminants in the environments where they live and play; their small body size may increase their dose, and their developing organ systems may put them at greater risk from these exposures relative to adults. For example, infants and children may consume greater amounts of some foods and may ingest greater amounts of some contaminants (from dermal-oral mouthing of lead or pesticide residue in household dust or of lead from soil) than do older children and adults. Thus, measurements (particularly for metals and persistent organic pollutants) shall be made in food, water, and other beverages; indoor, outdoor, and other microenvironmental air; and interior and exterior dust and soil. Activity pattern determinations, dermal-oral patterns of activity and ingestion, and biomarker measurements shall be made to allow calculation of potential contaminant dose and actual dose. Studies now are being completed that will furnish survey, sampling, analysis, and interpretation methods for childrens' total exposure to several organic pollutants, including PAH, pesticides such as DDT, chlordane, chlorpyrifos, and 2,4-D; phthalate esters; phenols, especially bisphenol-A (a potential endocrine disrupter); and polychlorinated biphenols (PCBs). Children are also likely to be at increased risk from outdoor exposure because they typically exercise more outdoors, thereby increasing their dose of air pollutants.

In addition to these methodological shortcomings for characterizing susceptible subpopulations, research will develop methods to characterize microenvironmental and population exposures. *However, future exposure methods research shall be justified within the context of human health risk assessment*, for example, when current methods for high-priority contaminants do not include adequate detection limits, accuracy, or precision, or when current methods are so costly as to effectively preclude their use.

Future exposure methods shall be developed to measure multipathway exposures (particularly for biological fluids and in dermal and dietary routes of exposure) to semivolatile compounds such as PAHs and pesticides and their metabolites. Methods are needed also to measure human exposure to microbial pathogens in drinking water (see microbe/DBP research plan). Potential urinary biomarkers of exposure have been identified for several PAHs, pesticides (e.g., chlorpyrifos, pentachlorophenol, DDT), and other organic pollutants that are persistent in the environment and may be bioaccumulated. However, they will be validated and

biomarkers for other high-priority persistent pollutants will be identified and their measurement methods developed or improved. Potential biomarkers will be examined and validated in other easily obtained biological excreta such as breath sweat, saliva, or sebum. Screening methods that have low limits of detection and high sensitivity will be necessary to estimate exposures from sampling such media. These methods are likely to include enzyme-linked immunosorbent assays (ELISA). Improved low-cost sampling methods, such as dermal wipes, will be tested for application to persistent organic contaminants. Rapid, low-cost screening techniques shall be developed, evaluated, and used to determine whether simple screening methods (e.g., immuno-chemical methods, such as immunoassay-based tests) can identify those situations where high exposures are likely and warrant further investigation. Rapid, generic extraction methods such as supercritical fluid extraction shall be improved for use as screening tools.

Future exposure research shall emphasize developing and evaluating databases for behavioral and time-activity determinants of human exposure for susceptible subpopulations. Significant uncertainties exist about how variations in time-activity patterns and behaviors contribute to variations in human exposure and susceptibility to disease. Two major types of variability that contribute to this uncertainty are (1) exposure profiles (magnitude, duration, and frequency) and (2) sensitivity to toxic insults (i.e., responsiveness to a given dose, such as that of a person with asthma being more responsive to some air pollutants than is a person with healthy lungs. Exposure and sensitivity are related also to age, lifestyle, genetic background, gender, ethnicity, socioeconomic status, and preexisting disease. Until recently, the time-activity pattern information required to investigate these issues had limited spatial, geographic, and demographic coverage. However, with the recent completion of the National Human Activity Pattern Survey (NHAPS) supported by ORD, national time-activity pattern data is being compiled by categories such as gender, age, spatial location, occupation, socioeconomic status, race, day of the week, and years of education (Nelson et al., 1994).

This database will be evaluated in the future to identify relationships between time-activity patterns and high-end exposure for the general population, as well as for population subgroups and regions. These investigations will enable future research to develop more accurate exposure models and to identify and characterize population subgroups (e.g., infants, children, the elderly, ethnic groups) more accurately and will contribute to exposure models. Such time-activity pattern data will also be used to improve survey methodology. For example, a standard

residential exposure questionnaire will be developed to obtain more detailed time-activity data for all age groups and for underrepresented subpopulations such as those who are not fluent in English. Automated passive collection devices that record events and microenvironmental locations on a real-time basis will be refined and field tested.

Future exposure research shall emphasize developing, demonstrating, and evaluating mathematical models that represent relationships between environmental contaminants and multipathway human exposure and dose. Currently, the science of total human exposure modeling is in its infancy. Although mathematical formulations for total exposure models have been developed (Georgopoulos et al., 1997), no total exposure model has been demonstrated and evaluated using field exposure measurements.[2] Research support must be provided to achieve this objective and to link total exposure models with dose models (i.e., physiologically based pharmacokinetic (PBPK) models), as well as with models that predict source-environmental concentration relationships (i.e., prospective and retrospective total human exposure models). In developing the pathway-specific components of total exposure models, dietary and dermal exposure pathways require particular emphasis because of their current higher degree of uncertainty. Future dietary exposure models under development will be able to utilize food consumption data, dietary behavior characteristics (e.g., characteristics related to regional and ethnic influences), chemical residue data, and microbial contamination data. Future dermal exposure models will be able to incorporate dermal contact and transfer data, data on skin permeability to adsorption or absorption for various contaminants, and dermal-oral transfer and ingestion data. In addition to this research, computational research will focus on developing a modular multipathway modeling system that can incorporate measurement databases; time-activity pattern data; demographic data; and contaminant emission, transport, and transformation processes.

In directing ORD resources to accomplish these future research objectives, some elements of ORD's current human exposure research program will be sustained at current levels, some will be increased compared to current levels, and some will be decreased. ORD expects to decrease support for basic source characterization and source attribution research, transport and

[2]With the possible exception of Ott et al. (1988).

transformation research, and environmental characterization research. It is anticipated that future research in these areas will be supported by other components of ORD's research program.

ORD also expects to decrease significantly its current support for exposure measurement methods research after ongoing projects to develop multimedia methods for dietary exposure, dermal exposure, biological markers, and semivolatile organic compounds are complete. Methods will focus on resolving measurement-related uncertainties for contaminant exposures where health risks are considered to be highly uncertain but of substantial concern and on developing the next generation of low-cost and rapid-response methods (e.g., biological markers of exposure, biosensors).

ORD will continue to support research to investigate relationships between human exposure and time-activity patterns, and will increase future efforts to investigate subpopulations. Future research will focus initially on analysis and dissemination of the survey results from the NHAPS.

ORD will change the focus of the exposure research it conducts and sponsors to emphasize the integration of measurement and modeling disciplines that have, in many instances, developed historically as independent scientific functions. This exposure section addresses two components of this strategy concurrently, namely exposures and susceptibility because the research must be concurrent. For example, in evaluating population distributions of exposure, several subpopulations must be considered and it is expected that they would have a range in susceptibility. Also, for exposure, susceptibility is often defined by the extent of exposure, one group versus another, again requiring concurrent comparisons. A close research relationship between all parts of the risk assessment process in required for success. However, a significant level of coordination is required to understand the exposure-dose-response relationship. In this chapter, dose is primarily considered in close relationship to exposure, as in development of models that predict the dose to the target with certain multipathway exposures; such research is dependent significantly on the pharmocokinetic research described in Chapter 3, which is conducted in close relationship to effects. Biomarkers research is also a continuum. This chapter focuses on exposure biomarkers (e.g., blood or breath levels of a chemical); Chapter 3 focuses on effects biomarkers (e.g., DNA adducts, endpoint markers). Of course, often biomarkers are indicators of exposure, effects, and/or susceptibility, leading to the need for close coordination of such research.

An Example of Strategic Partnerships for Human Exposure Research and Exposure and Risk Assessment Development in ORD: The National Human Exposure Assessment Survey

The National Human Exposure Assessment Survey (NHEXAS) is perhaps the most ambitious study ever undertaken to examine a wide range of environmental pollutants and chemicals that humans are exposed to in daily life. Whereas previous studies have focused on exposure to one chemical through one environmental pathway, the goal of this study is to better understand the complete picture of human exposure to toxic chemicals, by looking at humans' many exposures to all types of toxic chemicals through all routes of exposure. Based on their experience with previous single- and multipathway exposure studies in the United States and with the World Health Organization, ORD research scientists developed the initial concept and design for this survey and coordinated this major research effort with colleagues in the FDA, CDC, and the National Institute for Standards and Technology (NIST). NHEXAS studies are being conducted in three different regions of the United States:

(1) a study in Arizona is being conducted by the University of Arizona, Battelle Memorial Institute, and the Illinois Institute of Technology;
(2) a study in Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin is being conducted by the Research Triangle Institute and the Environmental Occupational Health Sciences Institute of Rutgers University; and
(3) a study in Maryland is being conducted by Harvard University, Emory University, Johns Hopkins University, and WESTAT.

Scientists from ORD, FDA, CDC, and NIST are collaborating members of the research teams in each of these studies.

During the course of these studies, researchers work with participants to measure the level of chemicals in the air they breathe, in the foods and beverages they consume (including drinking water), and in the soil and dust around their homes. Chemicals being analyzed include VOCs in air and water, metals such as lead and mercury, and pesticides in food and soils. Researchers also are measuring chemicals in participants' blood and urine samples. Participants complete questionnaires to help identify possible sources of chemical exposure. At the conclusion of the study, each participant will receive a report on the results of exposure and biological measurements, with an explanation of the findings' significance. Confidentiality of participants is strictly protected, although they are free to inform others if they choose.

Data collected during these studies are expected to enable the human heath risk assessment research community to accomplish the following scientific goals.

- *Improve estimates of total human exposure to chemicals and identify population subgroups that are highly exposed to environmental chemicals.*
- *Provide a baseline of the normal range of human exposure to chemicals in the general population, to allow comparisons with specific studies on particular exposure routes.*
- *Relate identifiable pollution sources to the actual exposures that people experience and compare short-term exposures to longer term exposures.*
- *Ultimately, enable researchers to improve the accuracy of human exposure assessment models and of human health risk assessments.*

Sample collection for the studies began in mid-1995 and is expected to be completed by late 1997. Sample analyses are expected to be completed by early 1998. After statistical analysis and summary, significant findings from each of the studies are expected to be peer reviewed and published in 1998, with databases becoming publicly available in 1999.

ORD expects that current and future resources for human health risk assessment research will not be adequate to support large-scale population exposure studies (i.e., a regional- or national-scale population exposure or surveillance study such as that contemplated as the long-term goal for the NHEXAS program). However, recognizing the importance of population-

scale exposure research to reducing uncertainty in risk assessment and to the development of total human exposure models, ORD will continue efforts to build a broad partnership and support to achieve this objective. This partnership will include other federal agencies with intramural and extramural research programs directly related to human health risk assessment (e.g., NIEHS, CDC, FDA) and scientific experts from academic and private research institutions.

3

Dose and Effects Research

3.1 Background

Figure 3-1 illustrates the scientific components of dose estimation and health effects research that lay the framework for this section of the proposed strategy. Figure 3-1 illustrates the scientific elements involved in dose estimation research. Dose estimation serves as the link between exposure and effects. That portion of the environmental contaminant that is transferred into the body surfaces (i.e, by inhalation, dermal contact, or ingestion) is known as the *applied dose*. The applied dose ultimately is absorbed, leading to a *dose at a target organ* that causes the effect of concern at that site. Investigation of dose and biological markers of exposure and effects (e.g., DNA adducts, cholinesterase inhibition) represents the point of transition between *exposure assessment* and *effects assessment*. Exposure biomarkers demonstrate that exposure to a given agent has occurred, whereas effects biomarkers identify an effect of a particular type that has occurred. Also at this transition point, quantitative relationships between exposure, absorption rate, distribution, metabolism, and elimination rate are represented mathematically by *PBPK models*. There is clearly a continuum between exposure-dose-response and between biomarkers of exposure, effects and susceptibility. Those aspects closely aligned with exposure are contained within Chapter 2 (Exposure). Those more related to effects are given here. In practice, there is collaboration between the ORD researchers in these areas.

The assessment of effects includes both *hazard characterization* and *dose-response evaluations*. ORD's hazard characterization research involves the development of methods that demonstrate a qualitative relationship between exposure and effect. Dose-response research then characterizes this relationship to link exposure-dose with incidence and severity of effect, considering mechanisms and factors that may affect dose- response relationships. This information is then used to develop quantitative models for estimating risk. In this chapter, the term dose-response is used because it is the NAS terminology and the ultimate goal. In most cases, the exposure-response is the object of study and assessments.

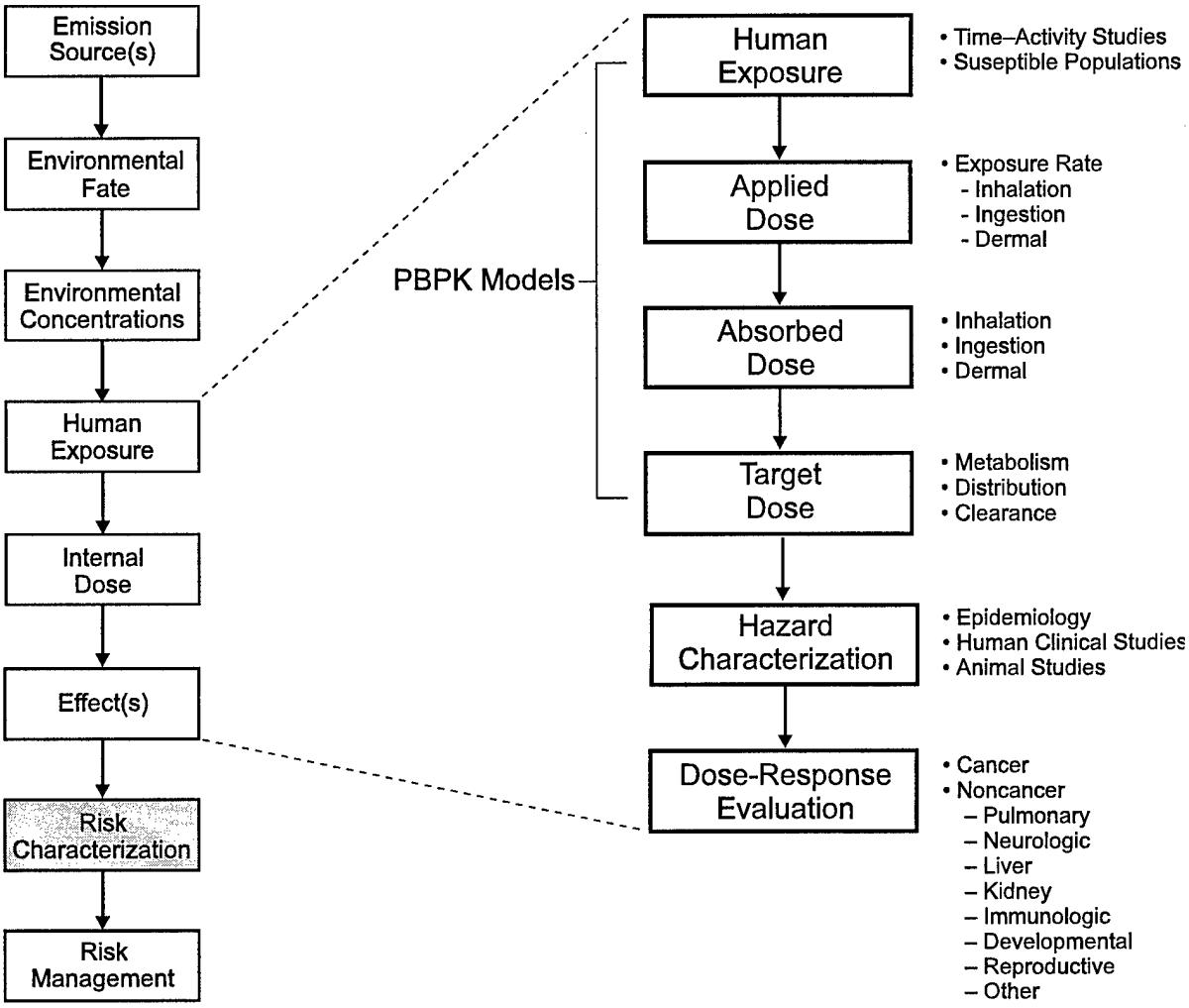

Figure 3-1. Scientific elements in dose estimation research.

Traditionally, EPA has taken different quantitative approaches of risk assessment for cancer and noncancer effects. In cancer dose-response assessment, the default assumption, in the absence of relevant biological evidence on mechanism of action, has been that increased risk varies linearly with dose, even at low doses. Thus, exposure to any dose would result in some increase in cancer risk. Under the proposed new cancer guidelines (U.S. EPA, 1996) a similar default assumption is retained; however, data on the mode-of-action of a chemical is emphasized, and such data will guide the process of risk estimation. Mode-of-action refers to the interaction of the chemical with specific targets or pathways. It is important to recognize that a given chemical may display more than one mode of action. For example, one of the targets of

carcinogens is the genes (DNA) that control cell growth; other targets are the biochemical processes that are involved in cell growth, cell growth regulation, cell signaling, and cell-to-cell communication. Still other targets of chemical carcinogens may include processes involved in cell toxicity and death, alterations in hormone levels, effects on receptors involved in cell growth, effects on enzymes that metabolize carcinogens, effects on the immune system, and effects on the cellular repair systems that allow cells to repair damage caused by carcinogens. Concomitant with the recognition of these facts has been the realization that the currently used, statistically based cancer risk assessment models (e.g., the linearized multistage model) are probably not appropriate for all types of chemical carcinogens. Despite the recognition of various targets and events in carcinogenesis, mechanistic information remains largely incomplete, and, for most direct DNA reactive carcinogens, the assumption of linearity will still apply.

For many noncancer toxicities, it is assumed that dose thresholds exist, that below a certain dose, no overt toxicity will be expressed. This assumption is based on the known capacity of the organism to detoxify the chemical or repair a certain amount of damage at the molecular, cellular, tissue, or organ level. In addition, multiple insults at the molecular or cellular level may be required, given that a population of cells often must be affected to produce an effect on the whole organism. Newer research, such as that on dioxins, has shown that the cancer-noncancer dichotomy, as reflected in the preceding discussion, may have limited relevance in a unified concept of health risk assessment.

3.1.1 Current ORD Research

ORD's current program concerning dose estimation research focuses on three scientific questions (also see Table 3-1).

(1) *How can estimations of deposition (for chemicals having portal-of-entry effects) or absorption (for chemicals having systemic effects) following inhalation, oral, or dermal exposures be improved?*

(2) *What are the critical factors affecting estimation of target tissue dose?*

(3) *What are the biomarkers of effects?*

Table 3-1. Overview of the Current Dose Estimation and Health Effects Research Program

Scientific Questions and Research Focus/Objective	Research Approach	Research Outputs/Products	Future Emphasis
How can models linking exposure scenario and target tissue dose be improved?	Develop and evaluate PBPK models to predict target dose and to elucidate factors affecting dose estimation. ORD research is focused on model compounds such as trichlorethylene, chloroform, carbon tetrachloride, dibromochloromethane, arsenic, acrylamide, PAHs, DBPs, and dioxins.	Improved dose-response assessment and research targeting: improved extrapolation and interpolation of data (cross-species, cross-route, cross-dose scenario, etc.) using PBPK models	Research activities to address this objective are anticipated to increase.
How can estimations of absorption for inhalation, oral, and dermal exposures be improved?	Research to identify and characterize factors affecting absorption, including physicochemical characteristics; exposure conditions, including dosing pattern and vehicle; and portal of entry factors, including contact location. ORD research is focused on VOCs, such as trichloroethylene and carbon tetrachloride; on respirable PM; on metals such as arsenic; on respiratory irritants such as ozone; and on dioxins and PCBs.	Reduced uncertainty in dose-response assessment: complete and consistent reference values for use in dose estimation and identification and characterization of the factors producing greatest uncertainty in estimation of absorption	Research activities to address this objective are anticipated to decrease.
What are the critical factors affecting estimation of target tissue dose?	Research on factors affecting distribution and tissue dose, including metabolism and clearance; tissue binding; blood flow and tissue volumes; tissue/blood partitioning; and co-pollutant exposures. ORD research is focused on human and rat physiological parameters, dioxin sequestration, arsenic metabolism, and pulmonary particle clearance.	Improved dose-response assessment: improved interspecies estimates of target dose and evaluation of the effects of dosing scenario on target dose	Research activities to address this objective are anticipated to be sustained at current levels.
How can models linking exposure scenario and target tissue dose be improved?	Develop and evaluate PBPK models to predict target dose and to elucidate factors affecting dose estimation. ORD research is focused on model compounds such as trichlorethylene, chloroform, carbon tetrachloride, dibromochloromethane, arsenic, acrylamide, PAHs, DBPs, and dioxins.	Improved dose-response assessment and research targeting: improved extrapolation and interpolation of data (cross-species, cross-route, cross-dose scenario, etc.) using PBPK models	Research activities to address this objective are anticipated to increase.

Table 3-1 (cont'd). Overview of the Current Dose Estimation and Health Effects Research Program

Scientific Questions and Research Focus/Objective	Research Approach	Research Outputs/Products	Future Emphasis
How can estimations of deposition and absorption for inhalation, oral, and dermal exposures be improved?	Research to identify and characterize factors affecting absorption, including physicochemical characteristics; exposure conditions, including dosing pattern and vehicle; and portal of entry factors, including contact location. ORD research is focused on VOCs, such as trichloroethylene and carbon tetrachloride; on metals such as arsenic; on respiratory irritants such as ozone; and on dioxins and PCBs.	Reduced uncertainty in dose-response assessment: complete and consistent reference values for use in dose estimation and identification and characterization of the factors producing greatest uncertainty in estimation of absorption	Research activities to address this objective are anticipated to decrease.
What are the critical factors affecting estimation of target tissue dose?	Research on factors affecting distribution and tissue dose, including metabolism and clearance; tissue binding; blood flow and tissue volumes; tissue/blood partitioning; and co-pollutant exposures. ORD research is focused on human and rat physiological parameters, dioxin sequestration, arsenic metabolism, and pulmonary particle clearance.	Improved dose-response assessment: improved interspecies estimates of target dose and evaluation of the effects of dosing scenario on target dose	Research activities to address this objective are anticipated to be sustained at current levels.
Improve hazard characterization	Develop and evaluate new toxicological test methods to identify and characterize the hazards posed by environmental exposure to chemicals (i.e., pesticides, industrial chemicals), coupled with research to improve the interpretation of toxicological data. Includes research to elucidate underlying mechanisms of pollutant toxicity and the repair or adaptation of damaged tissues using animal models and human studies, as well as computational chemistry/SAR. ORD research emphasizes neurotoxicity, developmental and reproductive toxicity, pulmonary toxicity, immunotoxicity, and cancer.	New and refined test methods. Impaired methods of data interpretation.	Research activities to address this objective are anticipated to be sustained.

Table 3-1 (cont'd). Overview of the Current Dose Estimation and Health Effects Research Program

Scientific Questions and Research Focus/Objective	Research Approach	Research Outputs/Products	Future Emphasis
Improve biological basis for dose-response assessment	Research to elucidate underlying mechanisms of pollutant toxicity and the repair or adaptation of damaged tissues using animal models and human studies, as well as computational chemistry/SAR. ORD research focuses on reproductive and developmental toxicity, cancer, neurotoxicity, pulmonary toxicity, immunotoxicity, and hepatic and renal toxicity. Model compounds (e.g., chemicals for which existing data provide a strong basis for study) are employed in hypothesis-driven research. Solvents, metals, PM and other air pollutants, dioxins, mercury, and drinking water DBP are being studied.	Improved near-term understanding of the level of confidence to associate with existing methods for dose-response assessment In the longer term, evaluation of the potential for biological models to estimate dose response based on mechanistic understanding	Research activities to address this objective are anticipated to increase.
Improve empirical methods for dose-response assessment	Research to support development of empirical methods, such as the benchmark dose model and the categorical regression approach. ORD research focuses on evaluation of these methods for developmental, pulmonary, immunological, and neurotoxicological endpoints.	Improved near-term methods for risk assessors to estimate dose response from existing data	Research activities to address this objective are anticipated to decrease.

[a]FIFRA = Federal Insecticide, Fungicide, and Rodenticide Act.
[b]TSCA = Toxic Substances Control Act.

To address these questions, ORD conducts research that identifies and characterizes various factors that may affect deposition and absorption, such as the physicochemical characteristics of the pollutant and the exposure conditions, including exposure patterns and portal of entry. Research also has been conducted on the factors that affect the distribution, metabolism, clearance, and other dynamics, such as tissue binding, that help to estimate target-tissue dose. Both the research on absorption characteristics and target tissue dose estimation have helped to reduce the uncertainty in dose-response assessment through the development of reference values and through improved methods for characterizing interspecies extrapolation of dose and effect. Specific areas of emphasis include research on trichloroethylene and other volatiles; PM; and inorganics, such as arsenic, ozone, dioxins, and PCBs. The intent is to improve the qualitative and quantitative characterization of target tissue exposure for endpoints such as respiratory, developmental, neuro-, immuno-, and reproductive toxicity, as well as cancer. Biomarkers research has been initiated for products of incomplete combustion, PAHs, DBPs, dioxins, arsenic, PCBs and pesticides.

Current ORD health effects research includes investigations on improved methods of hazard characterization and on biologically based and empirical dose-response models (Table 3-1). This research area seeks to develop an improved scientific basis for risk assessment by developing new toxicological test methods to identify and characterize hazards, and to define underlying mechanisms of toxicity and carcinogenicity to facilitate methods and model development and validation. The goals are to elucidate the critical physiologic and mechanistic factors that contribute to health effects in laboratory animals and humans; to determine the effects of varying route, dose, dose-rate, duration, and cumulative dose on health outcomes; and to develop data for and to evaluate biologically based dose-response models for application in human health risk assessments. The overall scientific approach is to conduct and link laboratory studies and model development activities to understand and describe the mechanisms of toxicity and methods to estimate toxic response to target tissue concentrations. The continued development of biologically and physiologically based dose-response models will support dose extrapolation to humans and will refine risk assessments through consideration of mechanism-of-action. Results of this research will support the development of empirical methods such as the benchmark dose and categorical regression approaches to health assessment.

The following sections identify research needed to reduce significant scientific uncertainties in dose and effects research. The following areas will be the focus of this research.

3.2 Dose Estimation Research

3.2.1 Uncertainties in Mechanistic Data for Hazard Characterization and Dose-Response Assessment

3.2.1.1 Problem Statement

For quantitative noncancer health assessments, EPA typically estimates the daily exposure from a particular route of exposure that is not anticipated to cause significant adverse effects over a lifetime. In many cases, data are available only from studies in laboratory animals and may not be available for the route or pattern of exposure of interest. Under these conditions, risk assessors must determine whether available data can be extrapolated to the route, species, and exposure conditions being assessed. In general, the lack of data, difficulty in data interpretation, and underutilization of existing data because of insufficient models and statistical reliability reduce the validity of extrapolations used to estimate target dose. Although the current research program has focused on characterizing absorption, distribution, and clearance, there remains a need to continue research to improve the knowledge of absorption characteristics, the potential for portal-of-entry effects, the potential for first-pass metabolic effects to modulate target dose, and the influence of exposure pattern on target tissue dose and response for acute, intermittent, and longer-term exposures.

3.2.1.2 Scientific Questions

The scientific question that provides the strategic direction to define the research products and their use in risk assessment (i.e., to improve the application of mechanistic data for hazard characterization), exposure-dose-response research, and risk assessment is (see Table 3-2):

How can dose estimation across species and exposure scenarios be improved?

(A related question concerning variability in response to toxicity is addressed partially in Chapters 2 and 4.)

The concentration of a pollutant to which a human is exposed is often not the same as the dose (i.e., the amount of pollutant delivered to the target organ). A number of mechanisms,

Table 3-2. Future Directions in Dose Estimation and Human Health Effects Research To Improve Human Health Risk Assessment

Scientific Questions and Research Focus	Research Approach/Tasks	Research Products	Use in Risk Assessment
How can we improve the accuracy of dose estimation across species, exposure routes, and scenarios?	Develop, validate, and apply new biological markers of exposure and effect to reflect exposure-dose-response relationships. Develop better PBPK models for dose estimation.	PBPK models for classes of compounds to estimate blood and tissue concentration and time course. Validated biomarkers of exposure and effect for use in dose response estimation.	Reach reliance on assumptions and route-to-route extrapolations.
How can mechanistic information be used to improve the ability to detect hazards?	Develop screening methods to set testing priorities Develop cost-effective methods for toxicity data collection	Validated screening protocols using, for example, in vivo, in vitro, and SAR methods New and revised standard toxicity testing protocols	To identify and rank existing pesticides and industrial chemicals in terms of potential toxicity To screen new chemicals as they enter the regulatory system and to assess relative toxicity To develop EPA test guidelines To support regulatory activities (e.g., TSCA test rules and consent agreements, FIFRA data call-ins)
How can toxicity data be better interpreted to predict and define hazards?	Develop improved methods for data interpretation; for example, identify biomarkers of exposure and effect and validate the use of biomarkers in human populations; focus on hazards resulting from less-than-lifetime exposures	Guidance document on interpretation of toxicity data	For incorporation into risk assessment guidelines

Table 3-2 (cont'd). Future Directions in Dose Estimation and Human Health Effects Research To Improve Human Health Risk Assessment

How can uncertainty in extrapolations (e.g., from high doses in animals to environmental exposures in humans) be reduced?	Develop quantitative models for predicting tissue and organism response to target tissue dose (i.e., biologically based dose-response models) Develop improved empirical dose-response models (i.e., benchmark dose models)	Models for predicting toxicity from chemical exposures that can be modified and applied in chemical-specific risk assessments Validated benchmark dose models and guidelines for applications	To provide critical examples of development and use of mechanistic models and to evaluate the potential of these models for replacing default approaches for cancer and noncancer risk assessment To provide a state-of-the-science basis for replacing default, primarily empirical risk assessment approaches To improve reference dose/reference concentration procedures and thereby improve the basis for risk management decisions
What are the factors influencing human susceptibility to disease? How do they influence human health risk assessment?	Determine biomarkers of susceptibility within the human population Determine the magnitude of contribution of susceptibility factors to human health risk assessment	Methods for detection of susceptible individuals Models for predicting the distribution of susceptible individuals within the human population	Application of biomarkers in risk assessment

many poorly understood, affect the transport of the pollutant through the portal of entry (e.g., the lung for air pollutants, the digestive tract for pollutants in drinking water and food) to the target organs. Also, the physical and chemical status of the pollutant within the body is affected by a number of mechanisms, physicochemical and metabolic, that can alter the disposition of the pollutant and, ultimately, the dose of the active agent to the target organs.

In risk assessment, however, the exposure concentration of a pollutant often is used as a surrogate for the dose because data on the dose of the active agent to the target organs are not available. Research to improve target dose data, including methods and models, is needed to reduce uncertainties associated with extrapolation from one route of exposure to another; from high to low exposure; from one species to another; and among exposure scenarios of varying magnitude, duration and frequency. One important aspect of this research is the development of biological markers for exposure and the quantitative linkage of these markers with markers of effect. Improved quantitative PBPK models to relate actual exposures to target tissue dose in humans under a variety of exposure conditions are needed to provide more accurate "dose" input for dose-response assessment.

3.2.1.3 Research Approach, Products, and Uses

Table 3-2 identifies the research tasks and products that respond to the scientific question mentioned above, and it also describes the products of this research that are related to improvements in the scientific foundation for risk assessment. Given the substantial criticism associated with current EPA practices for estimating cancer risks (e.g., linear extrapolation) and noncancer risks (application of uncertainty factors to a NOAEL/LOAEL), an area of increased emphasis will be obtaining fundamental pharmacokinetic and mechanistic data and tools for application in deriving more biologically defensible risk assessments. The pharmacokinetic data and models will serve as the linchpin for linking exposure and effects. Pharmacokinetic research will address issues related to route-to-route and cross-species extrapolation and identification of markers of actual target tissue dose. The mechanistic data will allow for clarification of the relevance of animal models (cross-species extrapolation) and the validation of biomarkers of toxic effects that may serve as early indicators of effects and be used as the basis for low-dose extrapolation.

3.3 Effects Research

3.3.1 Problem Statement

Characterization of hazard potential and extrapolation of dose-response data from animals to humans is fraught with uncertainty. The interpretation of animal toxicological data with regard to interspecies hazard and selection of a dose-response model that fit experimental data well may result in estimates that can span several orders of magnitude at environmental exposure levels. The uncertainties stem from fundamental gaps in knowledge regarding interspecies and intraspecies extrapolation, variability in susceptibility and response, and the shape of the dose-response curve at environmentally relevant doses. Default assumptions are used in the face of these uncertainties and knowledge gaps. Research is needed to define and reduce the uncertainties, minimizing the need for default assumptions and providing a stronger mechanistic basis for human health risk assessment.

3.3.2 Scientific Questions

Three scientific questions provide the strategic focus to define the research required to improve the accuracy of hazard characterization, exposure-dose-response research, and risk assessment.

(1) *How can mechanistic information be used to improve the ability to detect hazards?*

(2) *How can the methods to interpret human health effects data be impaired?*

(3) *How can uncertainty in extrapolations (e.g., from high doses in animals to environmental exposures in humans) be reduced?*

3.3.3 Research Approach, Products, and Uses

The above questions provide the strategic framework to define the human health effects research approaches and associated research products required to improve the scientific foundation for risk assessment. These approaches, products, and their anticipated benefits to improving risk assessment are summarized in Table 3-2. Research emphasis should include development of more selective and valid tests for mechanistically based hazard identification and characterization; enhancement of empirical approaches for dose-response assessment, using mechanistic information to move beyond benchmark and no-observed-adverse-effect-level approaches for cancer and noncancer risk assessments; performing research to improve the

understanding of receptor-mediated mechanisms; and focusing on health effects associated with less-than-lifetime exposures. The following sections are intended to amplify the specific research directions.

3.3.3.1 Development of More Selective and Valid Tests for Mechanistically Based Hazard Characterization

Improved tests for hazard characterization will be developed to assess the potential effects of chemicals on various health endpoints. For example, use of "transgenic mice" allows for the investigation of the influence of selective gene expression/nonexpression on the effect of a chemical. Similarly, more relevant in vitro models will be built by expressing human receptors in cell reporter assays. Such test systems may be validated using conventional test methods for which a greater degree of mechanistic understanding or database is available. Development of biomarkers will also enhance the identification of hazards.

Other new approaches, such as computational chemistry and structure-activity relationships (SAR), will improve the ability to conduct hazard identification on a large number of compounds for which there is little or no health effects information. These new approaches also will make the use of bioassays more cost-effective by improving the capacity to choose the most relevant bioassays to be performed. Computational chemistry and SAR approaches will complement ongoing experimental studies, involving hazard identification and mechanisms-of-action for important pollutant classes. These efforts will yield insights into underlying reaction mechanisms associated with chemical toxicity (e.g., computed energies to evaluate and compare plausible reaction pathways for metabolic activation), thus aiding in the design of research issues and approaches. SAR modeling also will be used to guide experimental studies into productive new areas, directing the application of assays to fill data gaps for SAR analysis and, in some cases, to providing a basis for extrapolation to untested chemicals. ORD will use this research information to support the process of guideline development, especially for emerging areas of health risk assessment (e.g., health risks associated with short-term exposures, such as pulmonary, neuro-, and immunotoxicity and complex mixtures).

3.3.3.2 Enhance Empirical Approaches for Dose-Response Assessment

Although the benchmark dose and other empirical approaches are seen as improvements over traditional (i.e., reference dose) noncancer risk assessment approaches through the use of more dose-response data, these approaches do not fully incorporate mechanism-of-action data. The continued development of biologically and physiologically based dose-response models will support animal-to-human extrapolation to humans and to refine risk assessments based on mechanism-of-action. The results of research on biological mechanisms and toxicokinetics will improve the quantitative estimation of human risk posed by environmental chemicals (including multiple chemical sensitivity) that have been described only empirically. Evaluation of the applications and limitations of these methods and the characterization of their strengths and weaknesses for risk assessment are essential.

3.3.3.3 Focus on Receptor-Mediated Mechanisms

The reassessment of health risks posed by dioxin found that compounds acting through the same receptor were additive in causing effects, whereas nonadditive interactions occurred when multiple mechanisms were involved. Thus, ORD will conduct additional research to assess the role of receptor-mediated mechanisms in toxicological effects produced by other compounds. An important focus in this research concerns how toxicants can interfere with critical cellular pathways (e.g., signal transduction pathways and receptors involved in cell growth). Computational chemistry/SAR studies will be used in conjunction with laboratory studies to identify key features of such receptors, to study receptor-mediated mechanisms of action, and to model the interaction of environmental chemicals with receptors.

More work also is needed to understand the effects of receptor mediation on the dose response of toxic chemicals and mixtures. A structure-activity-based toxic equivalency factor (TEF) approach has been applied to mixtures of dioxin-like compounds. Future research will examine the utility of the TEF methodology to predict biochemical and toxicological responses of environmentally relevant mixtures of dioxin-like chemicals in animal models.

Finally, receptor-mediated toxicity will be studied in humans as a function of genetic background and age. ORD will incorporate information on receptor-mediated mechanisms and toxicokinetics, as well as information obtained from human studies (e.g., receptor

polymorphisms, isoforms, levels, cross talk) into dose-response models that are relevant to specific segments of the human population.

3.3.3.4 Focus on Health Effects Associated with Less-Than-Lifetime Exposures

Noncancer-related toxic endpoints such as developmental, pulmonary, neuro-, and immunotoxicity may result from less-than-lifetime exposure scenarios. In neurotoxicology, animal-to-human extrapolation research focuses on developing animal models of neurotoxic effects that can be more precisely extrapolated to humans. Two effects that are particularly difficult to extrapolate from animals to humans are cognitive dysfunction and sensory alterations. Thus, research in neurotoxicology, will focus on developing and validating animal models of these endpoints that also can be measured in humans.

Research will also seek to improve key default assumption. For example, results of neurological and pulmonary toxicity research concerning the relationship between duration and concentration of exposure have suggested that dose rate is more critical for estimating effects than is cumulative exposure for some short-term and intermittent exposures (unless chemicals are persistent and bioaccumulative). Thus, research will characterize the relationships between dose rate (or dose metric) and toxicity and repair/compensation from short-term intermittent exposures to environmental chemicals.

ORD also seeks to improve the following quantitative models to further characterize and predict effects in humans: animal-to-human extrapolation models, models to evaluate the variability of exposure scenarios and the impact on time when predicting effects of pollutants on humans, and pharmacokinetic models in which physiological parameters (e.g., CO and CO_2 levels, other blood gases) can be taken into account when assessing effects of pollutants on humans. Another default assumption concerns cancer. It is presumed that cancer results from lifetime exposure to an agent. Research is needed to determine the time course for the development of cancer. In summary, ORD will pursue research on the effects of short-duration exposure and on relationships between exposure level and exposure duration. This research will be used to develop assessment methods, dose-response models, and guidance for assessing effects from less-than-lifetime exposures.

3.4 Characterizing and Assessing Variation in Human Susceptibility to Disease

3.4.1 Problem Statement

Uncertainties regarding human variation in susceptibility and response to environmental pollutants support the need for increased research on multidisciplinary endpoints to identify the factors that affect human susceptibility, the magnitude and distribution of these factors in the human population (see also Chapter 2), and the quantitative relationship between these factors and increased risk among specific subpopulations. Epidemiology, human clinical studies, animal toxicology studies, and in vitro assays are important methods to identify and assess factors that may contribute to observed variability in susceptibility. These factors, including age, lifestyle, genetic background, gender, and ethnicity, will be studied to determine how they contribute to human health risk.

3.4.2 Scientific Questions

Two scientific questions provide the strategic focus for future research needed to characterize variation in human susceptibility for exposure-dose-response research and risk assessment (see also Table 3-2):

(1) *How can hazards be better defined/predicted, dose-response extrapolation be improved, and variation related to human susceptibility be further characterized?*

(2) *How can risk assessments from varying exposure scenarios be improved?*

3.4.3 Research Approach, Products, and Uses

ORD's research will improve understanding how differences in susceptibility contribute to dose-response models representing various human subpopulations (e.g., infants and children, women, the elderly, individuals with preexisting diseases, and different races and ethnic groups). Particular emphasis will be placed on embryos/fetuses, infants, and children as a vulnerable population. This emphasis is consistent with the EPA Administrator's directive to consider risks that environmental pollutants pose to infants and children and with the national commitment to ensure a healthy future for children. The research proposed here, compliments the research directions outlined in the draft Research Strategy, being developed for childrens health

protection. Research will also be conducted to determine the conditions under which there are age-dependent quantitative and qualitative differences in responsiveness to pesticides.

Investigations on the toxicokinetics of susceptibility factors, on underlying mechanisms of increased sensitivity, and on disease-related physiological parameters will help to identify the critical genetic and biological biomarkers of susceptibility. As an example, research will be performed on chronic low-dose effects at the molecular and cellular levels that may result in the induction of genetic polymorphisms in the human germ line.

In adult volunteers, clinical investigations using carefully controlled exposures and dietary interventions can provide a wealth of data on the potential influence of specific polymorphisms on the likelihood of an adverse response to an environmental agent. In a clinical setting, exposure and dose-response relationships can be characterized for individuals with, for example, chronic pulmonary disease (e.g., asthma, bronchitis, chronic obstructive pulmonary disease [COPD]), cardiovascular disease, acute respiratory disease (e.g., upper respiratory infections), or multiple chemical sensitivity. In addition, potential susceptibilities associated with gender, age, or race can be studied.

Research will focus also on the underlying biological mechanisms responsible for individual susceptibility to pollutants. In particular, the mechanism by which different pollutants cause injury to cells in the respiratory tract will be studied. Cells and fluids from the upper and lower respiratory tract will be analyzed for biochemical and molecular responses of induced in vivo or in vitro (e.g., signal transduction systems and transcription factors involved in the responses of the cells to pollutant exposure). Again, new transgenic and knockout mouse models offer the possibility to directly examine the genetic regulatory mechanisms that influence these toxicological responses, thus directing the researcher to new hypotheses regarding possible mechanisms of action of environmental chemicals. Among the pulmonary toxicology models being studied in experimental animals are COPD, pulmonary and systemic hypertension, asthma and reactive airway diseases, degenerative heart disease, and pulmonary fibrosis. Appropriate animal strains and species assessments need to be determined for comparison to responses observed in humans.

Using a combined mechanistic approach of clinical and toxicological investigation, it will be possible to identify, select, and apply critical human biomarkers for the characterization of susceptible subpopulations in conjunction with epidemiologic field studies. These field studies

will provide the validation in the field of health effects that is seen in the laboratory and clinic. With sufficiently sensitive biomarkers, early changes can be detected, thereby improving EPA's ability to prevent effects. Public health programs of newborn screening could have major benefits in identifying susceptible individuals so that exposures to agents to which these infants are highly susceptible can be reduced or avoided.

4

Risk Assessment and Characterization Research

4.1 Background

Figure 4-1 highlights the primary elements of ORD's current program in risk assessment: development of risk assessment methodology, risk assessments of chemicals that demonstrate new approaches, and guidance and training. EPA's risk assessment research utilizes not only the results of research conducted by ORD, but health and exposure research conducted outside EPA (e.g., National Institutes of Health, universities, etc.) as well. The current ORD risk assessment program is summarized in Table 4-1. Current research in risk assessment include the following.

- *Methodology*
  - Methodologies for quantitative assessment (e.g., benchmark dose approach for noncancer endpoints, biological models for cancer dose-response assessment)
- *Prototype Assessments*
  - Assessments of contaminants and sites of national significance that demonstrate new approaches to risk assessment and that respond to contentious or sensitive issues
- *Guidance and Training*
  - Health and exposure risk assessment guidelines that incorporate the most recent and relevant scientific information (see text box)
  - Training and consultation in risk assessment (e.g., training on the various guidelines, consultation to EPA regions, and programs on various risk assessment problems)
  - Guidance on selected topics of interest, such as the relevance of rat kidney tumors to humans, the relevance of thyroid tumors produced at high chemical exposures in animals to the human situation, and Monte Carlo approaches to the use of information on exposure distribution
  - Risk information databases (e.g., the Exposure Factors Handbook currently available on CD with search capabilities, which provides information on exposure parameter distributions of interest to the risk assessor, such as fish consumption rates, respiratory rates, daily volume of drinking water consumed, etc.)

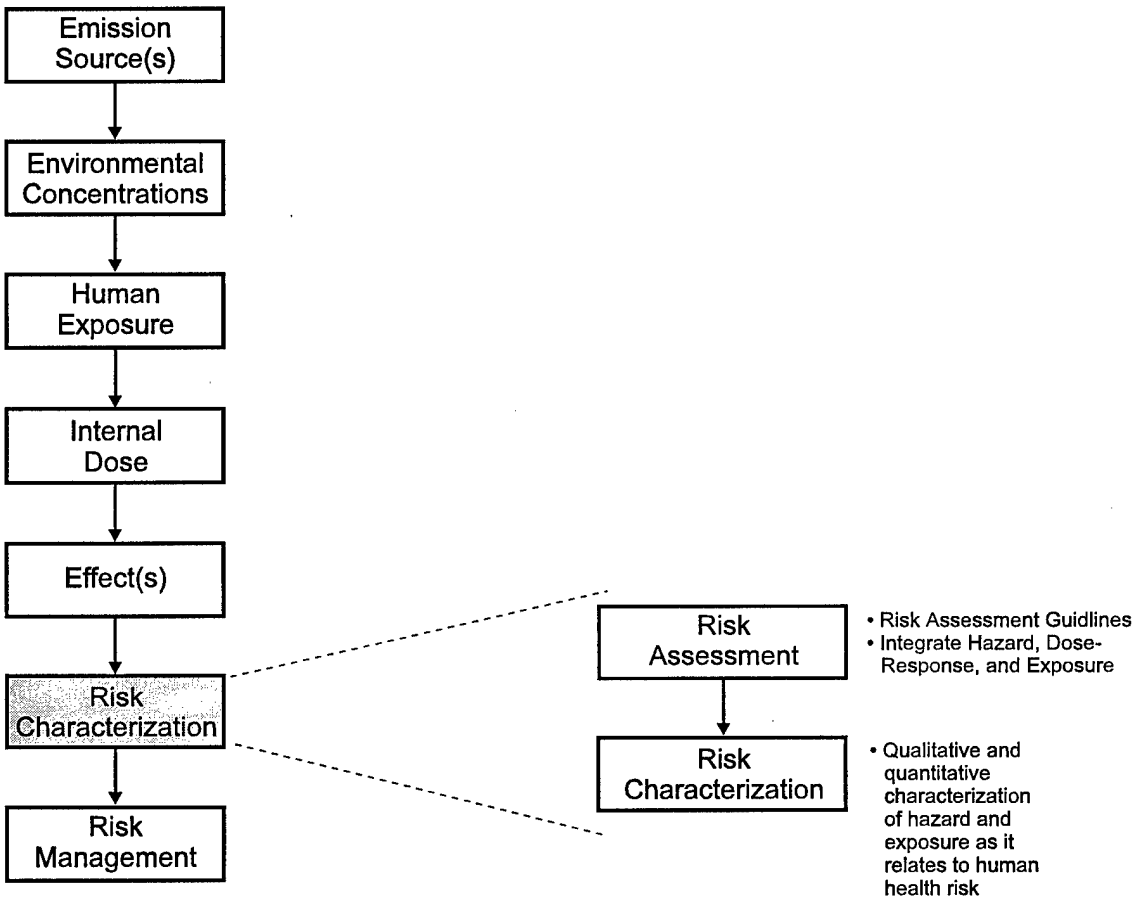

Figure 4-1. Scientific elements in risk assessment and characterization research.

- Risk information expert systems (e.g., Risk Assistant, which is an interactive software program guiding the risk assessor through various choices on a risk assessment problem)

4.2 Strategic Directions

4.2.1 Problem Statement

Inherent in all risk assessment guidance and methodology are uncertainties and gaps in scientific knowledge. Many of these gaps and uncertainties likely will continue for years to come, but health risk assessment, because of public health considerations, cannot wait for complete information. The challenge to the risk assessor is to develop approaches and default options (i.e., policy judgments to accommodate uncertainties and gaps in scientific knowledge) that make maximum use of existing information.

Table 4-1. Overview of ORD's Current Health Risk Assessment Research Program

Research Objectives	Research Approach	Research Products	Future Emphasis
Develop risk assessment methodology	Quantitative models for dose-response assessment Dermal exposure methodology Uncertainty analysis for reference concentrations Improved methodology for multipathway and multichemical exposure assessment	Provide new methods to address risk assessment questions	Research activities in this area are anticipated to increase.
Conduct prototype risk assessments	Selection for risk assessment of chemicals of high visibility to EPA or for which new data has become available that allows a demonstration of new risk assessment approaches	Provide assessment of the chemical under study and provide advanced methods of assessment that may have applicability to other chemicals	Research activities in this area are expected to continue at a level similar to that of the past.
Develop risk assessment guidance and databases and provide risk assessment consultation and training	Risk assessment guidelines Guidance documents on topics of interest, such as rat kidney tumors, Monte Carlo approaches, etc. Risk assessment databases (e.g., Exposure Factors Handbook, MIXTOX Data Base, Integrated Risk Information System, etc.) Risk assessment training Consultative advice to regions and programs Expert system software (e.g., Risk Assistant)	Provide an improved framework for systematic risk analysis and guidance on difficult risk assessment issues Provide information on parameters of interest to the risk assessor Improved knowledge and capability for risk assessors in the regions and programs	Research activities on risk assessment databases are expected to increase; other areas are expected to continue at a level similar to that of the past, with the exception of expert systems, which is expected to decrease.

EPA has developed the following health risk assessment guidelines:

- Carcinogen Risk Assessment (1996) (Proposed)
- Reproductive Toxicity (1996)
- Neurotoxicity (1995) (Proposed)
- Exposure Assessment (1992)
- Developmental Toxicity (1991)
- Health Assessment of Chemical Mixtures (1986) (Currently being revised for proposal in FY 1998)
- Mutagenicity (1986)

These and other guidelines are revised as new information and understanding becomes available. The Carcinogen Risk Assessment Guidelines are a good example of the changes and developments that have occurred in risk assessment thinking over the years. The first Carcinogen Risk Assessment Guidelines in 1976 introduced some basic ideas: risk assessment versus risk management and hazard identification versus dose-response assessment. The second iteration of the guidelines in 1986 incorporated the thinking of NRC's 1983 *Risk Assessment in the Federal Government: Managing the Process* (the Red Book) and the Office of Science and Technology Policy's 1985 *Scientific Principles of Carcinogenesis*. The 1986 guidelines provided guidance on classification for hazard identification, approaches to dose-response assessment, and an outline of what should be covered in risk characterization. The currently proposed guidance on carcinogen risk assessment places an emphasis on using all the relevant biological information in the assessment. It eliminates a matrix approach to hazard identification, expands and simplifies the discussion on dose-response assessment, and expands the guidance on risk characterization.

4.2.2 Risk Assessment Questions

Although there are many gaps and uncertainties that exist in human health risk assessment, the areas of primary concern chosen by ORD for this strategy are the three areas articulated in Chapter 1. The risk assessment questions that arise as a result are presented below.

- *What are the distributions of chemical exposure for children, adults, and selected vulnerable populations, the exposure pathways and activity patterns associated with these distributions, and the relationships and trends associated with such data?*
- *What and how should biological information, including information on short-term exposures, be incorporated into qualitative and quantitative risk assessments?*
- *What are the factors that affect variation in exposure and variation in human susceptibility to disease from environmental pollutants, how are such factors distributed in the population, and how can they be incorporated into human health risk assessments?*

4.2.3 Risk Assessment Approach, Products, and Uses

The approaches that will be taken in response to the questions identified above, the products of the research, and the anticipated uses are summarized in Table 4-2. Additional detail is provided below.

4.2.3.1 Biological Measures of Exposure and Their Relationship to Human Activity Patterns, Media, and Pathways

NHEXAS will provide information on biological assays (e.g., urine, blood, hair, nails, and other biomarkers) for chemical exposures, human activity patterns, exposure by different media (e.g., air, food, water, soil), and pathways (e.g., ingestion, inhalation, dermal absorption). Analysis of these data in the coming years is expected to provide the basis for exposure assessment guidance major pathways. Guidance also expected to be developed as a result of the NHEXAS analyses are recommendations on more accurate and cost-effective methods of measuring exposures (e.g., utility of cross-sectional survey data such as 24-h dietary recall, 4-day duplicate diet, and 24-h personal air sample; types of dust sampling methods such as wipe, vacuum, or deposition).

The primary database for developing such guidance at least in the near term, is expected to be NHEXAS. Data from currently available and future National Health and Nutrition Assessment Surveys (NHANES), administered by the U.S. Department of Health and Human Services, and other surveys are expected to figure more prominently in the assessment work in this area in the next 5 to 10 years.

4.2.3.2 Use of Biological Information in Risk Assessment

There has been a rapid increase in the understanding of the underlying biological basis of toxicological reactions to compounds, and emerging techniques promise to fuel continued progress. Thus, an important direction in health risk assessment is to incorporate the results of research on biological mechanisms and toxicokinetics into the quantitative description of human risk posed by environmental chemicals and to reduce reliance on toxicological endpoints. Research on mechanisms is particularly important given that EPA's revised guidelines for carcinogen risk assessment pay considerable attention to the use of mechanistic models and data

Table 4-2. Future Research Directions To Improve Human Health Risk Assessment

Risk Assessment Questions	Approach in Response to Question	Products	Uses
What is the baseline multichemical exposure distribution for children, adults, and selected vulnerable populations; the exposure pathways and activity patterns associated with these distributions; and the relationships and trends associated with such data?	Analysis of large databases on exposure (e.g., NHEXAS, NHANES, Department of Agriculture Marketbasket, FDA Total Diet Study, North American Free Trade Agreement (NAFTA), total exposure assessment monitoring studies pesticides and particulate exposure, NHAPS, etc.)	Report on population exposure to chemicals and the factors affecting the distribution Improvements in the Exposure Factor Handbook Update Exposure Assessment Guidelines and Health Assessment of Chemical Mixtures Guidelines	Improved probabilistic exposure assessment methods derived from *field* measurements of exposure
What and how should biological information, including information on short-term exposures, be incorporated into qualitative and quantitative risk assessments?	Analysis of scientific literature	Revisions to risk assessment guidelines Prototype assessments for chemicals for which biological information can improve the assessment Report on current knowledge concerning acute-to-chronic extrapolations Report on the use of mechanistic information in low-dose risk assessments for cancer and noncancer endpoints	Improved use of all relevant biological information in risk assessment
What are the factors in human susceptibility to disease from environmental pollutants? How are such factors distributed in the population, and how can they be incorporated into carcinogen and noncarcinogen risk assessments?	Analysis of scientific literature, census data, large databases on distribution of potential human susceptibility factors (e.g., NHANES, Harvard Nurses Study, etc.)	Report on the extent of exposures to susceptible populations to identify for follow-up study those groups at increased risk Methods and guidance on how variation in susceptibility and exposure should be factored into risk assessments	Assessments that evaluate the risk to susceptible subpopulations, as well as to the general population

in both hazard characterization and dose-response assessment (U.S. Environmental Protection Agency, 1996).

The pollutant exposure scenarios that EPA must assess reflect a continuum from acute (e.g., accidental releases and spills) or intermittent bursts of exposures (e.g., during pesticide application) to longer durations of exposure (e.g., via drinking water) that are still less than lifetime exposures. Adverse health effects can be elicited in some cases after only a few periods of exposure; in others, longer term exposure is required. Understanding the biological processes involved is critical to understanding the dose-rate phenomenon. ORD will use research data on the effects of short-term exposure and on relationships between exposure level and exposure duration to develop guidance for assessing risk from less-than-lifetime exposures. For example, ORD currently is developing a standard method to assess risk from short-term exposures with regard to inhaled substances (i.e., Acute Risk Assessment Methodology for Inhaled Chemicals). This document will include dose-response models and dosimetric considerations that readily address models for acute exposures. The sort of work being done for inhaled chemicals will be extended to other routes of exposure.

4.2.3.3 Variation in Human Susceptibility

Interindividual variation in susceptibility currently is not considered in EPA's cancer risk assessments and is addressed only in default fashion in its noncancer assessments (the variation across the population is assumed to be 10-fold). A factor of 10 may be inadequate to protect certain subgroups and may be too conservative in other situations. An important strategic direction for ORD is to develop assessments, guidance, and dose-response models that incorporate data from different subgroups (e.g., young and old, women and men, healthy and diseased individuals, different races, different ethnic groups, different genetic profiles) and from the variability in exposure profiles.

More specifically, risk assessment guidelines will be improved, based on research that

- validates or improves the default assumption that, on average, the general population has the same susceptibility to that of humans in the relevant epidemiologic studies, the most sensitive rodents tested, or both;
- assesses the need for presenting age-specific risk estimates and integrated lifetime risk estimates; and

- estimates the interindividual variability in the parameters of biologically based dose-response models.

5

Science Directions for Human Health Risk Assessment Research

The preceding chapters each focused on separate components of the research needs and activities affecting health risk assessment but did not provide integrated perspective on the total ORD research strategy. The purpose of this chapter is to paint a comprehensive picture of how ORD is focusing the human health risk assessment research program on the highest priority needs and to describe the approaches and results anticipated as the research is conducted.

Table 5-1 links the three overarching priorities identified in Section 1 to selected questions that focus the research program. Approaches to address the key questions, which were described in the previous chapters, result in products such as those listed in this table. Finally, the research products and scientific capabilities resulting from ORD's program are applied through improved methods, models, and data used by clients; through improved risk assessment guidelines for clients; and through improved training and consultation to clients. Through these applications, improved risk assessments for more confident risk management are the end result, as is improved targeting of research and collection and synthesis of exposure- and health-related data and models. Clients are becoming more numerous as EPA seeks to empower the public with usable information. Historically, clients were primarily EPA program and regional offices. While they still are primary clients; states, local governments, tribes, and the public are more involved in environmental decision making which is founded on scientifically sound risk assessments.

As discussed in Section 1.1, the methodological research and measurement data obtained through ORD's core research in human health risk assessment research program is complemented by research results obtained through more problem-specific research (see Figure 1-1). Further, the application of the more generic methods, models, and data generated through this research program results in improved problem-specific risk assessments and improved targeting of future research efforts.

Table 5-1. Summary of Priorities in Human Health Research

Key Priorities	ORD Emphasis	Example Products	Applications
Reducing uncertainties in exposure measurements and measurement-derived models	What are the pathway-specific measures of total human exposure in microenvironments (including residences) and populations? What are the mathematical relationships between sources of contaminants, fate pathway-specific environmental concentrations, total human exposures, and dose-estimation?	Validated residential and other microenvironmental exposure measurement protocols Validated protocols for determining human exposures at community-to-regional scales A national human activity database Multipathway exposure models incorporating new measurement and activity patterns data Validated source-dose models incorporating multipathway transport and transformation processes Report on population exposure to contaminants and the factors affecting the distribution of exposures	New exposure methods to reduce uncertainty in determining total human exposure Enhanced ability to design and conduct future exposure measurement studies Improvements in Exposure Factors Handbook Update to Exposure Assessment Guidelines and Health Assessment of Chemical Mixtures Guidelines Training and consultation support to risk assessors New measurement-derived exposure databases and models to reduce uncertainty for future exposure and risk assessments Prototype risk assessments to demonstrate application of advanced data and methods
Applying mechanistic models and data in hazard characterization and dose-response assessment	How can the accuracy of dose estimation across species and exposure routes and scenarios be improved? How can the ability to detect hazards be improved? How can toxicity data to predict and define hazards be improved? How can uncertainties in extrapolations (e.g., from high doses in animals to environmental exposures in humans) be reduced?	PBPK models for classes of compounds to estimate blood and tissue concentration and time course Validated biomarkers for use in dose-response estimation Quantitative models for predicting toxicity resulting from chemical exposures, which can be modified and applied in chemical-specific risk assessments Validated benchmark dose models and guidelines for applications New and refined test methods	Incorporation in updates to endpoint-specific risk assessment guidelines (e.g., cancer, developmental, reproductive, neurological) New and revised standard toxicity testing protocols Validated screening protocols using, for example, in vivo, in vitro, and SAR methods Guidance documents on interpretation of toxicity data Prototype risk assessments to demonstrate application and evaluation of mechanistic data

Table 5-1 (cont'd). Summary of Priorities in Human Health Research

Key Priorities	ORD Emphasis	Example Products	Applications
Characterizing and assessing variation in human exposure and human susceptibility to disease	What are the behavioral and time-activity determinants of human exposure and for exposures to susceptible subpopulations (e.g., infants, children, different socioeconomic status, preexisting disease)? How can hazards be better defined/predicted, dose-response extrapolation be improved, and variation related to human susceptibility be characterized?	Measurement data on multipathway exposure (including less-than-lifetime) and time-activity patterns for highly exposed and susceptible populations Report on conditions under which there are age-dependent quantitative and qualitative differences in responsiveness to pesticides Identification of critical genetic and biological markers of susceptibility Reports on enhanced susceptibility of individuals with pre-existing disease conditions (e.g., COPD, asthma, CVD) to environmental agents and biological mechanisms responsible for enhanced responsiveness	Incorporation into endpoint-specific guidelines for risk assessment More accurate identification and characterization of highly exposed subpopulations, where variability plays a significant role for exposure and risk assessment Completion of prototype risk assessments to demonstrate incorporation of new data on human variability in exposure and response

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Appendix A:

Recommendations for Strengthening Human Health Risk Assessment in EPA

During the past 5 years, a number of scientific, advisory, and legislative groups have evaluated challenges to and strategic directions for strengthening human health risk assessment research within EPA. A synopsis of relevant recommendations is presented below.

In 1997, The Presidential/Congressional Commission on Risk Assessment and Risk Management recommended a new framework for risk assessment and risk management. It stressed that "Failure to account for multiple and cumulative exposures is one of the primary flaws of current risk assessment and risk management. Whenever possible, measurements should be obtained to support or validate any generic values in exposure assessment, to check modeling results or to provide more realistic estimates of exposure than can be obtained with models."

During 1995, in Beyond the Horizon: *Using Foresight to Protect the Environmental Future* (U.S. Environmental Protection Agency, 1995c), EPA's SAB recommended that "the Agency should place equal emphasis (with the cancer endpoint) on noncancer human health risks; EPA should broaden its human health research and regulatory focus to include respiratory, cardiovascular, immunologic, neurologic, and reproductive endpoints . . . ; EPA should continue broadening its approach to human health risk assessment by explicitly considering risks to susceptible populations . . . ;" and that "new dose-response models (for the noncancer endpoints) should be considered."

In 1995, in *Human Exposure Assessment: A Guide to Risk Ranking, Risk Reduction, and Research Planning* (U.S. Environmental Protection Agency, 1995a), EPA's SAB concluded that exposure and risk assessment are hampered by persistent and "severe limitations in the currently available exposure measurement techniques, by severe limitations of the currently available databases containing exposure and exposure-relevant data, by reliance on numerous assumptions which have been proven incorrect or are not supported by common experience and/or direct observations, and by the current fragmentation and lack of coherence of available models for different media, pathways, chemicals . . . ." The report recommended that EPA undertake an extensive exposure research program, as well as a more integrated exposure, effects, and risk assessment research program, to ameliorate these deficiencies.

During 1994, in *Science, Judgment, and Risk Assessment*, (National Research Council, 1994) NRC made more than 70 recommendations regarding risk assessment and risk assessment research, including recommendations for continued research to improve cancer guidelines, risk

characterization and communication, noncancer risks, uncertainty analysis, and interindividual susceptibility to chemicals.

In 1993, the U.S. Congress's Office of Technology Assessment report, *Researching Health Risks* (Office of Technology Assessment, 1993), identified several areas that hold promise for improving risk assessment: research into new methods for toxicity studies, biomedical and molecular epidemiology, mechanistically based effects and dose-response extrapolation methods, improved methods for measuring or estimating human exposures, mechanistic studies of the actions of toxic substances, attention to methods evaluation and validation, and techniques for characterizing and communicating risks and information management.

Also in 1993, NRC issued a report, *Pesticides in the Diets of Infants and Children* (National Research Council, 1993), which recommended that EPA place increased emphasis on understanding the relationship between health effects and dietary exposures and residues in food eaten by children, multiple pollutants with common toxic effect, and total exposure estimates that include dietary ingestion and also account for all nondietary intake (e.g., air, dirt, indoor surfaces, lawns).

Appendix B:

ORD Research Strategies, Priorities, and Plans

Introduction

Figure B-1 illustrates the procedures that ORD follows to determine its strategic directions and research priorities, to translate these priorities into detailed research plans, and to implement these plans through its extramural Science to Achieve Results (STAR) program and its intramural program of laboratory research. As this figure indicates, there are three steps which are essential to these procedures.

In the first step, ORD establishes its overarching strategic directions, together with its strategic research planning principles and ranking criteria, and identifies a number of high-priority research areas that will receive special, expanded attention within the broad program of research it supports. This information is discussed in detail in the *ORD Strategic Plan* and the *1997 Update to ORD's Strategic Plan* (U.S. Environmental Protection Agency, 1997a). The high-priority research areas that ORD has identified include:

- core research in methods, models, and approaches to advance the science of risk assessment or risk management (i.e., research to improve human health risk assessment, research to improve ecological health assessment, and pollution prevention research); and
- research targeted at specific problems for which EPA has legislative or regulatory responsibility (e.g., safe drinking water, high-priority air pollutants) and at emerging scientific problems (e.g., endocrine disrupters).

In the second step, ORD prepares more detailed descriptions of its *core* and *problem-directed* research strategies. This is accomplished by considering the most important scientific questions or issues that must be addressed, as well as the scientific projects and accomplishments that will be needed to resolve the questions or issues. ORD then solicits the widest possible scientific review (e.g., from the EPA scientific community including program and regional offices, and the extramural community of national scientific experts) on the appropriateness of these strategic directions.

After integrating the recommendations from this review, ORD completes the third step of the research planning process by developing a detailed research plan to provide guidance on implementing future research projects. Typically, these detailed research plans are prepared by ORD's laboratories and centers (ORD's center responsible for the STAR program develops research plans that result in requests for assistance). The plans discuss how research will be

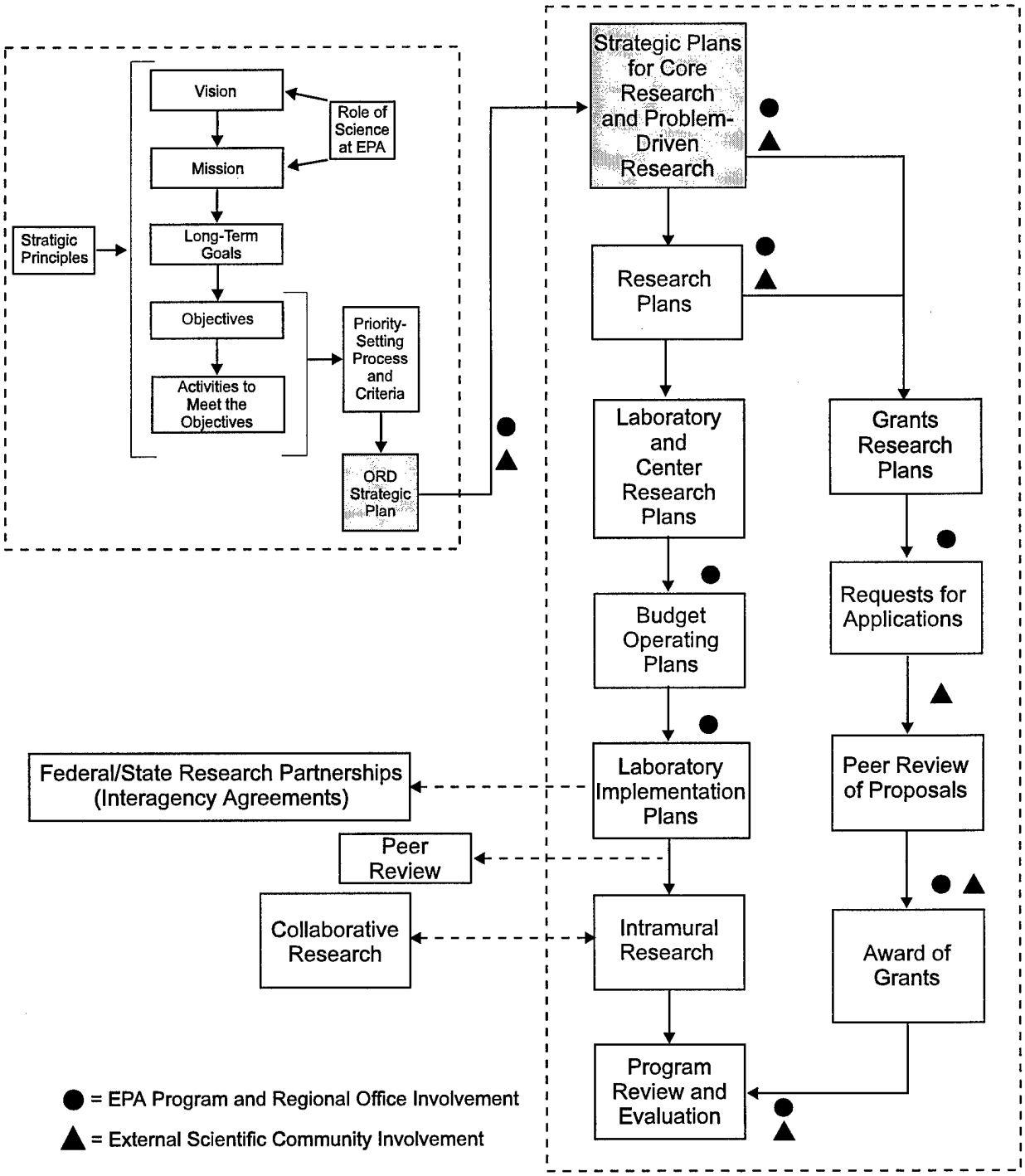


Figure B-1. Implementing ORD's strategic plan.

implemented, identify expected outcomes or scientific contributions, and explain provisions for accountability.

Establishing a Partnership To Identify and Focus EPA's Diverse Needs for Science and Research

Perhaps the most challenging aspect of this process is creating a consolidated research agenda that meets the needs of ORD's diverse clients. The magnitude of this challenge was illustrated in 1995 when ORD conducted a 4-month assessment to document research needs and priorities identified by all parts of EPA. This assessment identified literally thousands of needs—far more than could be accommodated through years of effort by ORD's entire staff and research budget. The review also indicated that, while ORD's research priorities generally respond well to the highest priority scientific problems identified by *individual* EPA client offices, it was very difficult to fashion an agency-wide agreement on a single, consolidated research agenda that would strengthen the scientific foundation for *all* of EPA's programs. This difficulty stems in part from EPA's science and research requirements and also from the substantial differences in legislative and regulatory mandates that EPA's program offices and regions are responsible for implementing. Recognizing the importance of this challenge, ORD has created an objective and inclusive research planning process which is described below.

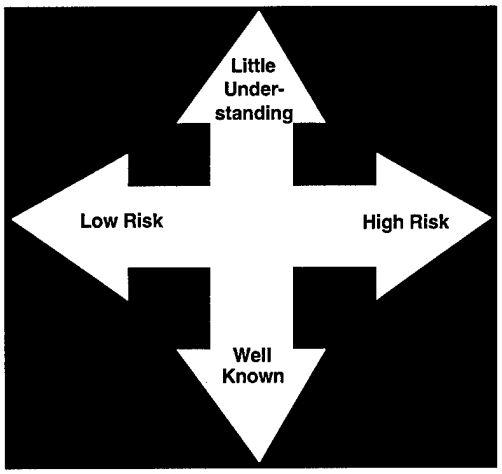
- This process engages all parts of EPA in helping to identify and describe potential research priorities. Members of the Research Coordination Teams (RCTs) (which consist of senior representatives from ORD's national laboratories and centers as well as from EPA's program and regional offices), the Research Coordination Council (which consists of the assistant administrators, regional administrators, or their designated senior representatives), and the Science Council (which consists of the associate directors from each ORD laboratory and center) each identify important and relevant environmental research needs for consideration. In addition, ORD solicits recommendations from EPA's extramural scientific advisors (e.g., SAB, NRC) about strategic scientific directions and priorities for ORD's research.
- The process empowers the EPA-wide representatives on the RCTs to narrow the pool of potential research needs by identifying those that are considered essential to strengthen EPA's scientific foundation and to enable it to respond to legislative mandates and regulatory issues. Subsequently, the RCTs define the components of these essential research needs by identifying the scientific questions or issues that must be addressed to reduce uncertainty in each element of the risk assessment or risk management paradigm. This step results in a series of research activities that correspond to identified scientific questions and research needs.

- This planning process enlists the expertise of the RCTs and the Research Coordination Council to recommend a consolidated research agenda. These two groups evaluate and rank research activities through the application of a series of risk assessment, methods/models, and risk management criteria. These criteria (Figure B-2) are designed to identify the most pressing problems; assess the potential for each research area to support effective risk assessment, risk management, or risk reduction; and ascertain research areas where ORD's scientific capability can make a significant contribution.

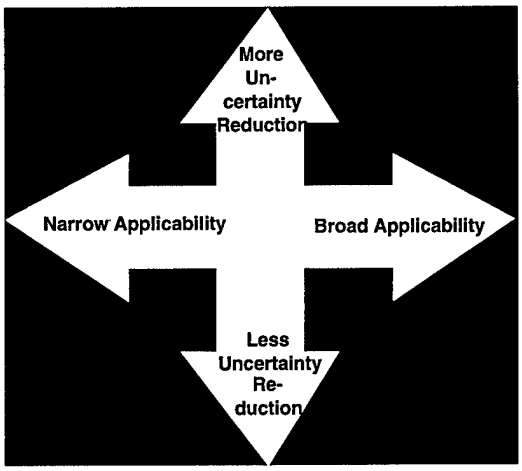
An Example of the Priority-Setting Process: Establishing Research Priorities for Human Health Risk Assessment

Before evaluating the significance and potential priority for research in human health risk assessment, ORD's RCTs considered recommendations from several sources. For this particular research area, the recommendations from scientists in program offices and regions, in ORD laboratories, and on extramural advisory boards *all* underscored the fundamental need for more scientifically defensible methods, measurement databases, models, and risk assessment protocols. Based on this clear consensus, the research coordination teams used the *methods and models criteria* (Figure B-2) to evaluate the significance of the research needs for human health risk assessment. Based on this evaluation, ORD's RCTs ranked the need for future research in this area as one of the highest. When these 31 research project areas were disaggregated into their constituent future research activities, all human health risk assessment research activities ranked in the highest priority tier of potential future research. The methods and models criteria considered the potential applicability of health risk assessment research, the potential contribution that future research would make to improving the science, and the size or extent of the community that would use or benefit from the research. Application of these criteria indicated the following.

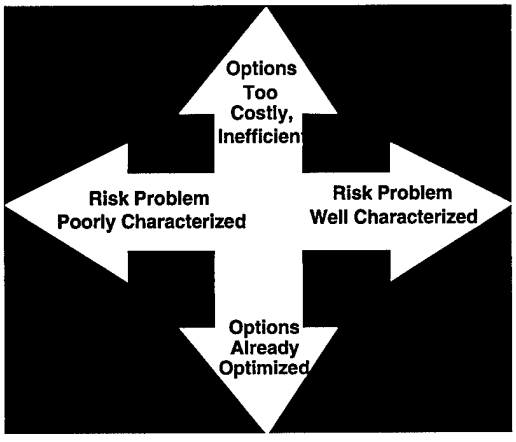
(1) *Core research in human health risk assessment would have broad applicability.* One of the reasons for the broad applicability of this research is that virtually all of EPA's major legislative mandates (those which require EPA to promulgate regulations to protect the public health from environmental contaminants) require EPA to develop human health risk assessments. These include the Clean Air Act, the Safe Drinking Water Act, the



Setting Priorities for Effects, Exposure, and Assessment Research



Setting Priorities for Methods and Models Research



Setting Priorities for Risk Management Research

Figure B-2. Criteria for setting research priorities.

Source: Adaped from Paul Slovic, *Risk Perception.*

Clean Water Act, TSCA, FIFRA, the Resources Conservation and Recovery Act, the Superfund Amendments Reauthorization Act, and the Food Quality Protection Act. In addition, in 1988, Congress enacted legislation that mandated EPA to undertake research to improve health risk assessment.

(2) *Core research in human health risk assessment would reduce significantly the uncertainties for EPA-wide risk assessment and risk management.* These research outputs would reduce significant uncertainties in the ability to quantify, model, and assess human exposures, exposure-dose-response relationships, and risk from environmental contaminants at community-to-regional geographic scales. Moreover, the research outputs would provide the first measurement-derived models for multipathway risk assessment and risk management decisions. In the absence of improved risk assessment and risk management methods, models, and measurement databases, ". . . enormous sums of money that might be better spent elsewhere may be allocated to dealing with *perceived* risks. While it is essential to ensure public health and environmental integrity, limited resources reinforce the need to assess risks as accurately as possible . . . . Estimates have indicated that the cost of environmental regulations in the United States will total between $171 and $185 billion by the year 2000 (Carlin et al., 1991). Compliance with air pollution control regulations will cost an estimated $94 billion per year by the year 2000 (Carlin et al., 1991). Russell et al. (1991) estimated that cleaning up all the major hazardous waste sites would cost between $500 billion and $1 trillion over the next 30 years. The sums are enormous, and a convincing analysis must be provided to demonstrate that these expenditures are justified as the most cost-effective way to reduce risks to human health and to the environment" (National Research Council, 1997).

(3) *Core research in human health risk assessment would benefit and be used by a large and diverse constituency.* During the 1995 base review of all ORD research and client office needs, research in human health risk assessment was identified as one of the most important research needs across all EPA regional and program offices. When considered from the broader national perspective, the 1993 study of health risk assessment conducted by the Office of Technology Assessment (1993) demonstrated that the benefits of research in this area would extend substantially beyond EPA's research, regulatory, and regional offices. In addition to EPA and other federal agencies, the "user community" would include states,

the private sector, academic research organizations, Congress, and international environmental health organizations.

Developing a Focused Research Agenda

In summary, once ORD has identified its broad strategic directions, two subsequent levels of planning are essential to the development of a focused research agenda. Typically, each step is accompanied by the development, review, and publication of an ORD document.

Research strategies frame the scientific questions associated with these research areas, and explain the direction, priorities, and outcomes of future research programs required to respond to these questions. All parts of EPA are involved through ORD's research coordination teams in helping define and describe research strategies. These strategies then undergo an external scientific peer review. Thus, research strategy documents present research goals that have been reviewed by the broad EPA community, by the extramural research community, and by scientists in ORD laboratories.

Within ORD's national laboratories and centers, the strategy provides senior scientists and research managers with a "blueprint" for designing and implementing research programs for a 5- to 10-year time frame. In addition, the research strategy enables ORD staff to relate their individual research projects to ORD's strategic goals. For ORD's many stakeholders (e.g., EPA's program offices, regional offices, academia, other government agencies, the public), a research strategy identifies the future directions, priorities, and scientific outcomes that can be used to measure the focus and progress of environmental research.

This "blueprint" is used to develop more detailed and narrowly focused *laboratory/center implementation plans* within ORD's national laboratories and centers that describe in detail the research projects, outcomes, and outputs that will be produced to accomplish the strategic goals or outcomes. Table B-1 lists and briefly describes the research strategies and plans that ORD is preparing during 1997 and 1998.

Table B-1. ORD Research Plans and Strategies

Title	Short Synopsis of Document's Focus
Microbes/Drinking Water Disinfection	The continued occurrence of waterborne disease outbreaks demonstrates that drinking water contaminated with bacteria, viruses, and parasites still poses a serious health risk when treatment is inadequate. A large number of DBPs have been identified that result from the disinfection of drinking water source waters. These DBPs have the potential to cause adverse health effects in the exposed public. The key areas of research will focus on assessing the health effects from exposure of waterborne pathogens and DBPs; the assessment of the potential exposures of pathogens and DBPs in various U.S. populations, especially in susceptible populations; assessing the risks from pathogen and DBP exposures and comparing the trade-offs between risks; and determining cost-effective technologies to treat source waters to achieve low-pathogen and DBP concentrations in final consumer drinking water.
Particulate Matter	The overarching mission of EPA's PM research program is to provide an improved scientific basis for future regulatory decisions concerning public health risks posed by airborne particles (emphasizing fine particle [$PM_{2.5}$] risks). The areas of PM health effects research that need to be addressed to effect these decisions and implementation activities are threefold: (1) development of a more complete interpretation of the PM epidemiologic data; (2) an understanding of the biological mechanisms of PM to explain the observed effects, the reported independence of effects from particle composition, and the lack of an obvious threshold for effects (i.e., every exposure concentration may cause an effect in some individuals in the population); and (3) an understanding of the composition, size, physical properties, and sources of PM that may cause health effects.
Arsenic in Drinking Water	The current arsenic drinking water maximum contaminant level (MCL) is 50 µg/L and was set in 1942 by the Public Health Service. This MCL is not based on health risk assessments as MCLs now are. The key areas of research will focus on the development of cost-effective arsenic control technologies for small drinking water systems; development and validation of analytical methods to speciate arsenic in water, soils, foods, and biological tissues; assessment and risk characterization of human and animal studies for arsenic exposures; and effects research on cancer and noncancer health effects, mechanisms of action, and human susceptibility.
Endocrine Disrupters	At present, the hypothesis that endocrine disrupting chemicals are causing adverse health in wildlife and humans remains simply an intriguing hypothesis. Most of the knowledge and concerns to date have risen from situations with relatively high-level exposure to persistent organic pollutants or therapeutic use of pharmacological agents. For proper regulatory action to occur, the understanding of the potential scope of endocrine disruption in humans and wildlife must be increased to include defining the range of health effects, critical life stages, sensitive species, and exposures relevant to alterations in endocrine function, and developing risk management options to reduce or prevent additional adverse effects in populations.
EMAP	This program develops the science of measuring ecosystem health and of monitoring the condition and trends of natural resources at the regional scale. Using the Committee on Environment and Natural Resources National Monitoring Framework and interagency workgroups as guides, EMAP supports complementary intramural and extramural (STAR) research programs to develop more cost-effective ecological indicators and to design multiple-tier monitoring methods capable of detecting trends and associating ecological impacts with likely stressors. The indicators and monitoring designs intended to support state-, regional-, and national-level environmental report cards encompass multiple stressors and many resource classes such as estuaries, streams, lakes, wetlands, forests, and grasslands.

Table B-1 (cont'd). ORD Research Plans and Strategies

Title	Short Synopsis of Document's Focus
Human Health Risk Assessment	Virtually all environmental legislation enacted by Congress requires EPA to conduct human health risk assessments to ensure a strong scientific foundation for decisions about the need for environmental regulations to protect human health and welfare. In recent years, increasingly complex environmental and human health issues have challenged EPA to develop more sophisticated regulations. At the same time, however, national scientific advisory panels have voiced increasingly strong concerns about the scientific adequacy of EPA's human health risk assessments. Responding to these concerns, ORD has developed a human health risk assessment research program that integrates the expertise of scientists in human exposure, dose-response, health effects, and risk assessment. This document describes the strategic directions and priority research objectives for this ORD research program during the next 10 years and explains how this strategy will respond to the key recommendations from EPA's scientific advisory panels. Specific research priorities discussed in the document include reducing uncertainties in exposure measurements and measurement-derived models, applying mechanistic models and data to reduce uncertainty in hazard identification and dose-response assessment, and characterizing and assessing variation in human exposure and susceptibility to disease.
Ecosystems Protection	In virtually every major environmental act, Congress has required EPA to protect human health as well as the environment. This document provides the strategic direction and priority research objectives for the ORD's Ecological Research Program. The goal of the program is to provide the scientific understanding required to measure, model, maintain, or restore, at multiple scales, the integrity and sustainability of ecosystems now and in the future. Fundamental research areas include monitoring, modeling, assessment, remediation, and restoration. Specific problems of importance discussed in the document include ecological research on ozone, acid deposition, ecocriteria, wet weather flow, pesticides, hazardous waste, global change, endocrine disrupters, ultraviolet-B radiation, contaminated sediments, exotic species, habitat alteration and restoration, and regional risk assessment.
Global Change	Based on the findings of the Intergovernmental Panel on Climate Change, guidance in ORD's strategic plan, and the priorities specified in *Our Changing Planet* (U.S. Global Change Research Program, 1997), ORD will strategically invest in global change research. ORD's Global Change Research Program will focus on ecological vulnerabilities of ecosystems to climate change, the implications for human health, and mitigation and adaptation approaches. The research conducted will provide policy makers with information on potential ecological and human health consequences of climate change and technical data needed to evaluate alternative GHG emission reduction and adaptation approaches.
Pollution Prevention	For pollution prevention to be a success, all stakeholders (e.g., regulators, industry, environmental groups) must have access to scientifically sound pollution prevention technologies and approaches. They must also be able to measure and objectively evaluate the viability and comparative environmental performance of these pollution prevention technologies and approaches. There is a lack of user-friendly tools and methods to compare pollution prevention solutions with each other and to end-of-the-pipe solutions, and there is also a lack of proven pollution prevention technologies and approaches for many pollutant sources in a number of economic sectors. Research is being undertaken in pollution prevention to address fundamental knowledge gaps in both of these areas.

Table B-1 (cont'd). ORD Research Plans and Strategies

Title	Short Synopsis of Document's Focus
Waste	The goal of the ORD Waste Research Strategy is to set forth an effective research program to understand and reduce human and ecological exposure to toxic materials released during waste management and to assess and remediate contamination that has occurred because of improper waste management. Focus is directed toward research on groundwater, soils, and the vadose zone at contaminated sites; active waste management facilities; and emissions from waste combustion facilities. Associated technical support activities to assist EPA program offices and regions and other stakeholders also are described.

Appendix C:

The Impact of Legislation and Regulation on Human Health Risk Assessment Research

The past 25 years have witnessed the enactment of a series of legislative mandates that require EPA to protect the public health and welfare from environmental contaminants. In the aggregate, this body of legislation mandates that EPA assume responsibility for conducting research, developing human health risk assessments, and establishing regulations and standards in all of the following areas.

- **Clean Air.** One section of the Clean Air Act mandates National Ambient Air Quality Standards (NAAQS) to protect the public health and welfare from criteria pollutants. State and federal air pollution programs are required to establish air pollution regulations that maintain air quality levels at or below the NAAQS levels. Other sections establish national standards for emissions of hazardous air pollutants from stationary and mobile sources that are hazardous to human health and require evaluation of public health risk from exposure to urban air toxics. The act authorizes EPA to conduct extensive research into the causes, effects, and extent of air pollution.
- **Drinking Water.** One section of the Safe Drinking Water Act establishes standards for drinking water quality known as maximum contaminant levels, which are based on human health endpoints. Recent changes to this legislation call for investigation of human exposure and health effects from drinking water contaminants such as disinfectant by-products, microbes, and endocrine disrupting compounds.
- **Clean Water.** The Clean Water Act requires EPA to develop ambient pollutant limits for surface waters and groundwater based, in part, on consideration of human health endpoints. Regulations for disposal of sludge are based on an assessment of health risks. The act authorizes EPA to conduct research on the harmful effects of water pollutants on human health and welfare.
- **Toxic Substances.** The Toxic Substances Control Act (TSCA) requires industry to submit exposure and health data that are used to determine whether to implement restrictions on the manufacture, use, or disposal of toxic chemicals. The act authorizes EPA to conduct research to develop techniques to screen and test for human health and ecological effects of chemical substances and mixtures.
- **Pesticides.** The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires the collection, review, and evaluation of toxicity and other health-related data to assess the effects

of pesticide products. The act authorizes EPA to conduct research to ensure implementation of its provisions.

- **Hazardous Waste.** The Resource Conservation and Recovery Act requires the evaluation of toxicity and other health-related data to determine which wastes are considered to be hazardous. Regulations for facilities that accept waste are designed to protect the health of residents near disposal sites. The act authorizes EPA to conduct research on the adverse health and welfare effects of solid and hazardous wastes.
- **Superfund Waste Sites.** the Superfund Amendments Reauthorization Act requires emergency response and cleanup actions that are designed to protect the health of populations near waste sites. The act authorizes EPA to conduct research to detect, assess, and evaluate the effects of hazardous substances on human health.
- **Food Quality.** The recently enacted Food Quality Protection Act of 1996 requires consideration of food consumption patterns, pesticide residues, human exposure and effects data, data on susceptible subpopulations, analysis of cumulative risk, potential effects from endocrine disrupters, and risk communication techniques, all with an emphasis on protecting infants and children.

In promulgating regulations that implement the numerous provisions of this legislation, EPA employs the human health risk assessment paradigm wherever it is scientifically relevant and authorized by statute to do so. Collectively, however, the scientific burden imposed on the human health risk assessment community by this legislation is significant, and it provides no "lowest common denominator" for human health risk assessment or regulatory decision making across EPA.

A related challenge for human health risk assessment is that, with limited exceptions (e.g., the Food Quality Protection Act of 1996), the body of legislation directs EPA to regulate one pollutant at a time, often from a single source and from one environmental pathway. The result inhibits EPA from considering human exposure to the same pollutant from different sources or environmental pathways, even where the cost or effectiveness of alternative risk management options may be significantly lower. This legislative focus on single sources, pollutants, and media has inhibited research to develop multimedia and multistressor risk assessment methods that are needed to investigate the complex environmental and human health issues present on community, regional, national, and international scales today. Another result of this

"one-size-fits-all" approach is that EPA has had very limited ability to develop risk management options that are flexible in their focus (e.g., on infants and children, cumulative risk, and specific geographic regions).

Within the past year, EPA has initiated a new policy that recognizes the importance of multimedia risk assessment, flexibility in developing risk management options, and community-to-regional-scale issues for its stakeholders. This policy directs each EPA program to invest a portion of its resources in community-to-international-scale environmental issues and affords an opportunity for ORD's human health research program to develop, demonstrate, and provide protocols to strengthen multimedia risk assessment methods, as well as to sponsor environmental health studies at community-to-international scales.