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Strategy for Research on Environmental Risks to Children

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STRATEGY FOR RESEARCH ON ENVIRONMENTAL RISKS TO CHILDREN

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

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

FOREWORD

The 1997 *Strategic Plan for the Office of Research and Development* (ORD) sets forth ORD's vision, mission, and long-term research goals. As part of this strategic process, ORD used the risk paradigm to identify EPA's top research priorities for the next several years. The ORD Strategic Plan serves as the foundation for the research strategies and research plans that ORD has developed, or is in the process of developing, to identify and describe individual high-priority research topics. One of these high-priority topics is to better understand environmental risks to children.

A team of scientists from ORD and other EPA offices, including the Office of Prevention, Pesticides and Toxic Substances; the Office of Water; and the Office of Children's Health Protection, prepared the *Strategy for Research on Environmental Risks to Children*. The ORD Science Council completed an internal review of the strategy in May 1999. Following revisions based on the Science Council review, the draft was reviewed by scientists outside EPA. The outcome of these reviews is a strategy that establishes EPA's long-term program goals and objectives for research in children's risk and documents the rationale for the chosen program direction.

The key scientific questions this strategy sets out to address are:

- What are the adverse effects from children's exposures to environmental agents that are qualitatively or quantitatively different from effects in similarly exposed adults? What are the near-term and delayed effects of childhood exposures? What are the characteristics of the environmental agents associated with these effects?

- What are the specific periods of development when exposure to environmental substances can cause adverse health effects?

- What are the best in vitro models and in vivo animal models for screening for and identifying hazards to children?

- To what environmental substances are children more highly exposed? How do exposures differ with age? What factors contribute to higher exposures?

- What are the relationships between exposures to children and adverse health effects observed in childhood or later? What factors in the child's environment can increase risks?

- How can laboratory and human data be used to predict responses to childhood exposures?

- What is the variation in exposure and susceptibility within members of the same age group, and what are the factors that contribute to this variation?

- What adverse effects from children's exposures to mixtures are quantitatively or qualitatively different from effects in similarly exposed adults?

- What are the uncertainties in estimating environmental risks to children and how can they be characterized in risk assessment? What are the most effective methods for communicating results, data, and risks to risk assessors, risk managers, and the public?

- What are the specific environmental agents and pathways of exposure where risk management research will be effective in addressing known risks to children? What are the most effective methods for reducing environmental risks to children?

To answer these questions, this strategy groups its research priorities into the following five areas: (1) development of data for risk assessment, (2) development of risk assessment methods and models, (3) experimental methods development, (4) risk management and risk communication, and (5) cross-cutting issues including variation in susceptibility and cumulative risk.

This research strategy is an important planning tool because it makes clear the rationale for, and the intended products of, EPA's research on children's environmental health and helps EPA effectively communicate its program to clients, stakeholders, and the public. This research strategy is also an important accountability tool, enabling EPA to clearly track progress toward achieving its research goals as required by the 1993 Government Performance and Results Act.

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The strategy was developed by a science team with representatives from ORD's laboratories and centers and from the Office of Prevention, Pesticides, and Toxic Substances (OPPTS); the Office of Water; and the Office of Children's Health Protection (OCHP). The following are the members of the science team:

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PEER REVIEW AND COMMENTS

An external peer review of the *Strategy for Research on Environmental Risks to Children* was organized by the Eastern Research Group (ERG). A peer review workshop was held on November 9 and 10, 1999, in Washington, DC.

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EPA Children's Health Protection Advisory Committee (Reigart, J.R. 2000. Letter to Carol M. Browner, Administrator, U.S. EPA, dated January 21, 2000, from J. Routt Reigart, M.D., Chair, Children's Health Protection Advisory Committee)

Andy Breslin, Physicians Committee for Responsible Medicine (Observer comment at Nov. 9-10, 1999, Peer Review Workshop)

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The cover of the strategy was designed by Stephen E. Wilson (ORD/NRMRL).

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ACRONYMS

AHS	Agricultural Health Study
ATSDR	Agency for Toxic Substance and Disease Registry
BBDR	Biologically based dose response modeling
CDC	Centers for Disease Control and Prevention
CHEHSIR	Children's Environmental Health and Safety Inventory of Research
DART	Developmental and Reproductive Toxicology Database
DNA	Deoxyribonucleic Acid
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GPRA	Government Performance and Results Act
HUD	U.S. Department of Housing and Urban Development
IEUBK	Integrated Exposure, Uptake, Biokinetic Model
IRIS	Integrated Risk Information System
ITC	Interagency Testing Committee
NAAQS	National Ambient Air Quality Standards
NAS	National Academy of Sciences
NCEA	National Center for Environmental Assessment (EPA/ORD)
NCER	National Center for Environmental Research (EPA/ORD)
NCEH	National Center for Environmental Health (CDC)
NCHS	National Center for Health Statistics (CDC)
NCI	National Cancer Institute
NERL	National Exposure Research Laboratory (EPA/ORD)
NHANES	National Health and Nutrition Examination Survey
NHEERL	National Health and Environmental Effects Research Laboratory (EPA/ORD)
NHEXAS	National Human Exposure Assessment Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIDCR	National Institute of Dental and Craniofacial Research
NICHD	National Institute for Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NRMRL	National Risk Management Research Laboratory (EPA/ORD)
NTP	National Toxicology Program
OCHP	Office of Children's Health Protection (EPA)
OPP	Office of Pesticide Programs (EPA/OPPTS)
OPPTS	Office of Prevention, Pesticides, and Toxic Substances (EPA)
ORD	Office of Research and Development (EPA)
OSWER	Office of Solid Waste and Emergency Response (EPA)
PBPK	Physiologically based pharmacokinetic modeling
PCB	Polychlorinated biphenyl
PM	Particulate matter
PM10	Particulate matter less than 10 ：m in diameter
RFA	Request for applications
RfC	Reference concentration
RfD	Reference dose
SDWA	Safe Drinking Water Act
STAR	EPA/ORD Science To Achieve Results extramural grants program
TSCA	Toxic Substances Control Act

GLOSSARY

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

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

Biological markers (biomarkers): Indicators signaling events in biological systems or samples. There are three classes of biomarkers–exposure, effect, and susceptibility. A **marker of exposure** is an exogenous substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism. A **marker of effect** is a measurable biochemical, physiological, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease. A **marker of susceptibility** is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic (NRC 2000).

Biologically based dose response (BBDR) model: A model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.

Cumulative risk: The combined risk from aggregate exposures to multiple agents or stressors.

Developmental toxicology: The study of adverse effects on the developing organism that might result from exposure (of either parent) prior to conception, during prenatal development, or from postnatal development to the time of sexual maturation.

Deoxyribonucleic Acid (DNA): A complex macromolecule that is composed of nucleic acids (adenine, guanine, cytosine, and thymine) and is found in cellular organisms. DNA carries all the genetic information necessary to determine the specific properties of an organism.

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

Dose-response assessment: The determination of the relationship between the magnitude of administered, applied, or internal dose and a specified biological response.

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

Exposure assessment: The determination or estimation of the magnitude, frequency, duration, and route of exposure.

Exposure pathway: The physical course an environmental agent takes from the source to the individual exposed.

Exposure route: The way an environmental agent enters an organism (e.g., by ingestion, inhalation, or dermal absorption).

Hazard identification: A description of the potential adverse health effects attributable to a specific environmental agent and the mechanisms by which agents exert their toxic effects.

Lowest observed adverse effect level (LOAEL): The lowest exposure at which there is a statistically or biologically significant increase in the frequency of an adverse effect when compared with a control group.

Mechanism of action: The complete sequence of biological events that must occur to produce the toxic effect.

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

No observed adverse effect level (NOAEL): The highest exposure at which there is no statistically or biologically significant increase in the frequency of an adverse effect when compared with a control group.

No observed effect level (NOEL): The highest exposure at which there is no statistically or biologically significant increase in the frequency of any effect, adverse or not, compared with a control group.

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

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

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

Physiologically based pharmacokinetic (PBPK) model: A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion.

Program Office: An EPA organizational unit that administers a major EPA program (Air and Radiation; Water; Prevention, Pesticides, and Toxic Substances; and Solid Waste and

Emergency Response)

Reference concentration (RfC): An estimate of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Reference dose (RfD): An estimate of a daily dose to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Risk: The probability of adverse effects resulting from exposure to an environmental agent.

Risk characterization: The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.

Risk assessment: The evaluation of scientific information on the hazardous properties of environmental agents and on the extent of human exposure to those agents. The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree.

Susceptibility: Increased likelihood of an adverse effect related to an individual's developmental stage.

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

Uncertainty Factor: One of several factors used to calculate an exposure level that will not cause toxicity from experimental data. Uncertainty factors are used to account for the variation in susceptibility among humans, the uncertainty in extrapolating from experimental animal data to humans, the uncertainty in extrapolating from data from studies in which agents are given for less than a lifetime, and other uncertainties such as using LOAEL data instead of NOAEL data.

OFFICE OF RESEARCH AND DEVELOPMENT STRATEGY FOR RESEARCH ON ENVIRONMENTAL RISKS TO CHILDREN

EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) is committed to promoting a safe and healthy environment for children by ensuring that all EPA regulations, standards, policies, and risk assessments consider special childhood vulnerabilities to environmental pollutants.

Windows of vulnerability exist during development, particularly during early gestation, but also throughout pregnancy, infancy, childhood, and adolescence, when toxicants may permanently alter the function of a system. Children may also be more vulnerable than adults because of differences in absorption, metabolism, storage, and excretion, resulting in higher biologically effective doses to target tissues. Children can be more highly exposed than adults because of proportionately higher food intake and breathing rates, different diets, and activities such as playing on floors that result in greater contact with environmental contaminants.

These health threats to children are often difficult to recognize and assess because of limited understanding of when and why children's exposures and responses are different from those of adults. Research is needed to address these issues and find opportunities and approaches for risk reduction. This document provides the strategic direction for EPA's research program in children's health, conducted by the Office of Research and Development (ORD).

The primary objective of the ORD Children's Health program is to conduct the research and provide the methods to reduce uncertainties in EPA risk assessments for children, leading to effective measures for risk reduction.

Objectives of the *Strategy for Research on Environmental Risks to Children*

- Establish direction for a long-term, stable core research program in children's environmental health that leads to sustained risk reduction through more accurate, scientifically based risk assessments for children.
- Identify research to answer the key questions about children's environmental health risks and increase our understanding of when children respond differently from adults to toxic agents and why.
- Identify research that will help to reduce children's risks.
- Provide a research agenda that identifies research priorities for the ORD intramural and extramural research programs.
- Inform EPA scientists, risk assessors, and risk managers of the research related to children at EPA and other Federal agencies.
- Provide guiding principles for implementation.

Research Questions

Children's risk is a topic as broad and varied as human health risk assessment. Groups of experts have identified dozens if not hundreds of research issues and needs, addressing various age groups, subpopulations, disease endpoints, biomarkers of disease, mechanisms of action, exposure pathways, environmental contaminants, and physiological and biological characteristics affecting doses.

Children's Risk Topics

Health Endpoints

- # Cancer
- # Neurotoxicity
- # Immune system effects
- # Asthma and other respiratory effects
- # Reproductive effects
- # Other birth defects (e.g., death, malformation, growth alteration)

Environmental Health Threats

- # Outdoor and indoor air pollution
- # Pesticides
- # Environmental tobacco smoke
- # Microbes and other drinking water contaminants
- # Endocrine disruptors
- # Specific compounds such as lead, mercury, PCBs, vinyl chloride
- # Mixtures of pollutants

A strategy for research in children's environmental health must be broad enough to address diverse environmental contaminants, endpoints, and special groups such as children living on farms and urban children. Priorities may shift rapidly as more becomes known about the impact of environmental agents on children's health.

Research Questions

- # What are the effects from children's exposures to environmental agents that are different from effects in adults?
- # What are the periods of development when exposure to environmental substances can cause adverse health effects?
- # What are the best in vitro models and in vivo animal models for screening for and identifying hazards to children?
- # To what environmental substances are children more highly exposed? What factors contribute to higher exposures?
- # What are the relationships between exposures to children and adverse health effects observed in childhood or later?
- # How can laboratory and human data be used to predict responses to childhood exposures?
- # What is the variation in exposure and susceptibility within members of the same age group?
- # What are the adverse effects from children's exposures to mixtures?
- # What are the uncertainties in estimating environmental risks to children?
- # What are the most effective methods for communicating and reducing environmental risks to children?

Research Approach

The strategy was developed by a science team composed of members from ORD; the Office of Prevention, Pesticides, and Toxic Substances (OPPTS); the Office of Water; and the Office of Children's Health Protection (OCHP). The strategy is organized into 5 main topics encompassing 13 research areas. The science team ranked each research area as high, medium, or low. The areas ranked high were those judged to have the greatest potential to improve EPA risk assessments or to address directly the reduction of risks specific to children. Feasibility based on the current state of scientific knowledge, ORD's capacity and capability to perform the research, opportunities to build upon the research conducted in other agencies, development and maintenance of needed expertise within ORD, and the balance between short- and long-term research were also considered in the rankings.

Research Priorities

 # Development of data to reduce uncertainties in risk assessment

- **S** Mode-of-action research (High)
- **S** Epidemiology and clinical studies (High)
- **S** Exposure field studies (High)
- **S** Activity pattern and exposure factor studies (High)

 # Development of risk assessment methods and models

- **S** Methods and models for assessing dose-response relationships in children (High)
- **S** Methods and models for using exposure data in risk assessments for children (High)

 # Experimental methods development

- **S** Methods for hazard identification and studying mode of action (High)
- **S** Methods for measuring exposure and effects in children and to aid in extrapolations between animals and children (Medium)

 # Risk management and risk communication

- **S** Multimedia control technologies (Low)
- **S** Reduction of exposure buildup of contaminants indoors (High)
- **S** Communication of risk (High)

 # Cross-cutting research

- **S** Variation in human susceptibility (Medium)
- **S** Cumulative risk (Medium)

Implementation

Implementation of the strategy will be accomplished through detailed research plans developed by ORD's laboratories and centers. To assist in the development of these plans, the strategy provides long-term outcomes and short-term results for each of the highly ranked research areas and guiding principles for implementation.

Mode-of-Action and Dose-Response Assessment (§§4.3.1.1, 4.3.2.1, 4.3.3.1)

Long-Term Outcomes

Mechanism-of-action experimentation facilitates the extrapolation of animal and experimental model data to humans, enhancing ability to predict and study adverse effects in humans. Mode of action becomes an integral component of risk assessment. Advances in genomics/proteomics are incorporated into EPA's risk assessment methodologies.

Broadly applicable physiologically based pharmacokinetic (PBPK) models and biologically based dose-response (BBDR) models are routinely used to produce more accurate risk assessments for children, making full use of pharmacokinetic and mode-of-action data.

Short-Term Outputs

Develop better quantitative characterizations of dose to target tissue in developing organisms to replace default assumptions in children's risk assessments.

Link developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels. Develop first-generation biologically based predictive models.

Develop and validate sensitive and predictive methods using laboratory animals to determine mode of action by linking developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels.

Validate in vitro assays (using either animal or human biological material) for inclusion in the overall risk assessment process.

Validate and apply currently available test methods and emerging methods in genomics/proteomics and molecular biological approaches, useful for understanding and elucidating mode of action, in developmental toxicity testing.

Evaluate the appropriateness of the assumptions in current EPA risk assessment approaches and how they may be supported or modified by biological data.

Develop and refine PBPK models applied to the developing animal, with the intent of eventual extrapolation to embryos, fetuses, infants, and children.

Develop and refine BBDR models applied to the developing animal with the intent of extrapolation to embryos, fetuses, infants and children.

Identify biological pathways, environmental factors, and their interactions that are important to understanding normal and abnormal development, with a focus on incorporation of such information into predictive models of developmental toxicology and not solely on the generation of basic information on child development.

Define how experimental animal models mirror child development and develop appropriate correction factors for species differences.

Incorporate information from dose-response, pharmacokinetic, and mode-of-action studies in animals into models that more accurately predict children's risks.

Develop first-generation methods, guidance, and data for broad application of modes of action and pharmacokinetics in EPA risk assessments for children

Exposure and Epidemiologic Research (§§4.3.1.2, 4.3.1.3, 4.3.1.4, 4.3.2.2)

Long-Term Outcomes

Environmental agents and other factors contributing to adverse effects in children are identified, status and trends in children's health and exposure to environmental agents are characterized, and risk reduction methods are successfully implemented.

Status and trends in children's exposures to environmental agents are characterized using baseline data developed in this program. Highly exposed subpopulations of children are identified, important sources and pathways of children's exposures are delineated, and risk management interventions are successfully implemented.

Residential exposure factors for children are characterized by age and sex for the national population, regional populations, highly exposed groups, and susceptible groups. Factors include activity patterns (time spent in a given activity and frequency of occurrence), soil and dust ingestion rates, factors reflecting transfer of environmental agents from objects and surfaces children commonly touch, and factors related to ingestion of chemical residues on surfaces.

A broadly applicable probabilistic total-exposure model capable of linking to a PBPK model is available to estimate children's exposure to pesticides, producing more accurate assessments of children's exposure and reducing use of default values and safety factors in the assessment when sufficient input data are available.

Short-Term Outputs

Analyze relationships between childhood exposures to air pollutants and respiratory effects under the ORD Science To Achieve Results (STAR) extramural grants program.

Analyze relationships between childhood exposures to pesticides and neurological effects under the STAR program.

Develop, refine, and pilot methods for conducting a hypothesis-based longitudinal study of developmental disorders in a large birth cohort under the U.S. Task Force on Children's Environmental Health and Safety.

Conduct analysis of existing data from the National Human Exposure Assessment Survey (NHEXAS), the National Health and Nutrition Examination Survey (NHANES), and the STAR grants to provide answers to the extent possible on whether children are more highly exposed, which age groups are more highly exposed, and important sources and pathways.

Develop new sampling protocols, questionnaires, and study designs based on previous studies of children's exposure.

Design and initiate field studies to answer questions about children's exposure, with Federal partners where feasible.

Identify high-priority exposure variables for study through preliminary exposure analysis.

Design and complete activity pattern survey addressing high-priority issues for children.

Complete two studies on other high-priority exposure variables for children.

Assess children's total pesticide exposure and refine existing exposure models based on data from NHEXAS, NHANES, and the STAR program.

Analyze models in EPA's Office of Pesticide Programs (OPP) Standard Operating Procedures for estimating exposure of children to pesticides, identify important pathways of exposure, and provide assessment support.

Risk Management and Risk Communication (§§4.3.4.2, 4.3.4.3)

Long-Term Outcomes

Broadly applicable methods for removing chemicals from residential environments and for preventing exposure in the residential environment (e.g., through encapsulation) are used by the Superfund program, EPA Regional Offices, State and local public health and environmental agencies, and others to achieve cost-effective cleanup to safe levels for children.

Through implementation of better methods of communicating scientific information about risk and working with communities to reduce risk, EPA strengthens its community-based risk assessment and risk management programs.

Short-Term Outputs

Develop a method to remove pesticides and other chemicals from building structures and carpets or to prevent exposure (e.g., through encapsulation), using methyl parathion as a prototype.

Implement risk intervention programs in several communities and publish journal articles on effectiveness of risk intervention approaches (output of STAR program's Centers for Children's Environmental Health and Disease Prevention).

Compare methods for communicating risks of pesticides on foods (output of current STAR program grant).

Guiding Principles for Implementation

- When designing a research study, investigators should consider the impact of the results on EPA risk assessments for children. Requests for Applications (RFAs) in ORD intramural and STAR programs should ask investigators to specify the potential impact of results on the EPA risk assessment process.
- A multidisciplinary research program that is coordinated across the ORD laboratories and centers is encouraged. RFAs for cross-laboratory/center intramural projects and fostering of contact between extramural grantees and ORD scientists are encouraged.
- Outreach, coordination, and partnership with other Federal agencies is essential, particularly in the areas of human studies and biological mechanisms of action.
- Toxicologists, epidemiologists, clinicians, and exposure scientists are encouraged to work collaboratively during all phases of research planning, development, and implementation.
- ORD needs to develop and maintain intramural expertise to be able to incorporate new data and methods into EPA risk assessments. Use of biological data in risk assessment is a high priority. A stable intramural research program with adequate support is essential to achieving this capability.
- Research across more than one endpoint is encouraged where possible, such as research on mechanisms that can lead to multiple endpoints and endpoints affecting the same target organ.
- Risk reduction research and risk management goals should be considered throughout the course of this program.

OFFICE OF RESEARCH AND DEVELOPMENT STRATEGY FOR RESEARCH ON ENVIRONMENTAL RISKS TO CHILDREN

1. INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is committed to promoting a safe and healthy environment for children through regulations, standards, policies, and risk assessments that consider special childhood vulnerabilities to environmental agents (EPA 1996a). Many environmental health threats to children may not be recognized because we do not have a complete understanding of when and why children's exposures and responses differ from those of adults. This may affect EPA's ability to identify environmental hazards, assess risks, and act to protect children.

EPA's Office of Research and Development (ORD) is responsible for conducting research to provide the scientific foundation for risk assessment and risk management at EPA. In 1998, ORD initiated the Children's Health program to support research on environmental risks to children. ORD and the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) charged a team of ORD and OPPTS scientists with developing the Strategy for Research on Environmental Risks to Children (EPA 1997a)[1] to provide strategic direction for the Children's Health program.

1.1. Scope and Definitions

This strategy addresses adverse effects on the developing organism that may result from exposure to environmental agents, starting with preconception exposures to parents and continuing through gestation and postnatally up to the time of maturation of all organ systems.[2] Because organ systems reach maturity at different times, developmental phases of interest will vary by organ system. Variation in exposure resulting from age-related differences in activity patterns, diet, and physiological characteristics will also help define developmental phases of interest. The scope includes effects that are not observed until adulthood. For convenience, the terms "childhood," "child," and "children" are used to refer to all the individuals within the scope of the strategy.

The Children's Health program began as part of an Administrator's Initiative aimed at ensuring that risks to children are considered in all EPA actions. An expanded program of research in children's issues is part of the Initiative. Historically, ORD has conducted research in male and female reproductive toxicity, embryo and fetal toxicity, and postnatal functional deficits. ORD research supporting the Air, Water, Waste, and Pesticides and Toxics programs deals with media-specific issues, such as the impact of air pollution on childhood asthma and the effects of lead on small children. This strategy builds upon the ongoing research program.

1.2. Rationale for the Children's Health Program

There is evidence of age-related differences in exposure and susceptibility to some environmental agents that warrants further investigation (ILSI 1992, ILSI 1996, NRC 1993, WHO 1986). Depending on the agent, age-related differences may increase, decrease, or have little impact on the risk to children.

As a rationale for the Children's Health program, this section provides a brief description of some of the documented vulnerabilities of children. A more detailed description of potential postnatal vulnerabilities is contained in Appendix A.

There are specific periods or windows of vulnerability during development, particularly during early gestation but also throughout pregnancy and early childhood through adolescence, when toxicants might permanently alter the function of a system (Rodier 1980, Bellinger et al. 1987). At birth, most organs and systems of the body have not achieved structural or functional maturity. Physical growth and functional maturation continue through adolescence, with the rates varying among the different tissues, organs, and systems of the body. Organs and systems that continue to undergo maturation during infancy and childhood include the lungs, kidneys, and liver, and the immune, nervous, endocrine, reproductive, and gastrointestinal systems (Hoar and Monie

[1] Representatives of the EPA Office of Water and the EPA Office of Children's Health Protection (OCHP) were added to the team at the request of those offices.

[2] In the Guidelines for Developmental Toxicology Risk Assessment (EPA 1991), EPA defined developmental toxicology, in part, as follows: "The study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or post natally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism...."

1981, Langston 1983, Anderson et al. 1981). A physiological or functional perturbation resulting from exposure to an environmental agent during a critical period of development may increase risk. Children may be more susceptible qualitatively, suffering adverse effects not experienced by adults, or quantitatively in that effects occur at a lower exposure level or are more severe at the same exposure level (Faith and Moore 1977).

Children may be more vulnerable to specific environmental pollutants because of differences in absorption, metabolism, and excretion. Elevated rates of gastrointestinal absorption of nitrates in infants and lead in young children are well known. Percutaneous absorption is elevated during the first few days of life until keratinization of the skin occurs. Age-related differences in both the rates and the pathways of metabolism affect excretion rate and the half-life of a chemical in the body. Young children have higher resting metabolic and oxygen consumption rates than do adults. These higher rates are related to a child's rapid growth and larger cooling surface area per unit of body weight. Developmental regulation of metabolic pathways can result in the activation and deactivation of a pathway as individuals pass through life stages, affecting internal dosages (Bearer 1995).

Children's exposures to environmental pollutants are often different from those of adults because of different diets and different activities, such as playing on floors and in soil and mouthing of their hands, toys, and other objects, that can bring them into greater contact with environmental pollutants (Bearer 1995). Because children consume proportionately more food and fluids, have a greater skin surface area relative to their body weight, and breathe more air per unit body weight than adults, they may receive greater exposure to environmental substances. For example, an infant weighs about one-tenth as much as a typical adult, but consumes about one-third as much water daily (Goldman 1995). The diets of infants and young children are very different from adult diets. Certain food types, such as juices, for example, can make up a larger proportion of the child's diet, resulting in a higher exposure to pesticides (NRC 1993).

The causes of most developmental effects and childhood diseases are unknown, but there is evidence that environmental agents play a role in some adverse outcomes. Exposure to environmental agents affecting development both in utero and postnatally can result in a wide array of adverse developmental endpoints, such as spontaneous abortions, stillbirths, malformations, early postnatal mortality, reduced birth weight, mental retardation, sensory loss, and other functional or physical changes (NRC 1993). Lead, methylmercury, polychlorinated biphenyls (PCBs), ethyl alcohol, and ionizing radiation have been implicated in human studies as causes of developmental effects (EPA 1991), while other chemicals have been implicated in animal studies. Lead and methyl mercury exposures in children are related to a variety of neurological problems that do not occur in adults exposed at comparable levels, including reading and learning disabilities, IQ deficiencies, impaired hearing, reduced attention spans, antisocial behavior, and hyperactivity. Prenatal and perinatal exposure to PCBs has been associated with delayed development and learning disabilities in children (Jacobson et al. 1990).

Childhood exposure to air pollutants, including ozone, sulfur dioxide, particulate matter (PM), and nitrogen dioxide, has been associated with decreased lung function, increased incidence of bronchitis, increased respiratory illness, increased hospital admissions for respiratory causes, and exacerbation of asthma (Bates 1995).

The self-reported prevalence rate for asthma increased 75% from 1980 to 1994, with the greatest increase occurring among children aged 0-4 years (160% from 22 per 1,000 to 57.8 per 1,000) and aged 5-14 years (74% from 42.8 per 1,000 to 74.4 per 1,000). The estimated annual number of physician office visits for asthma more than doubled from 4.6 million to 10.4 million between 1975 and 1995 for all age, sex, and racial groups. Asthma-related hospitalization increased between 1979-80 and 1993-94, while the rate of hospitalizations remained constant. Hospitalization rates were consistently higher among African Americans. Children aged 0-4 years had the highest hospitalization rate of any age group. Rates of death with asthma as the underlying cause decreased between 1960-62 and 1975-77 and then gradually increased. Most deaths occur in people over 65 (Mannino et al. 1995).

Currently, the most important factor associated with asthma is a genetic susceptibility to become allergic. Indoor allergens including cockroaches, dust mites, and animal dander have been identified as the most common triggers of asthma symptoms. Environmental tobacco smoke, upper respiratory tract viral infections, ozone, sulfur dioxide, and PM have also been suggested as asthma triggers (Etzel 1995).

In children, exposure to environmental tobacco smoke is causally associated with an increased risk of lower respiratory tract infections such as bronchitis and pneumonia, an increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract irritation, small reductions in lung function, and additional episodes and increased severity of symptoms of asthma. Maternal smoking is considered a high risk factor for Sudden Infant Death Syndrome (EPA 1992).

These examples show a relationship between exposure to environmental agents and adverse health effects in children. However, most causes of adverse developmental effects and the reasons for the increase in asthma rates in children are unknown. It has been hypothesized that the thousands of man-made chemicals introduced into the environment in recent years, most of which have not been tested for developmental effects, may be precipitating or contributing factors in some cases. Another unknown is the extent to which the biologically effective dose differs between

children and adults. The response to a chemical could be identical for children and adults at a given dose at the target site, but a child could receive a higher dose than an adult in the same environment. These uncertainties make it difficult to answer the question of whether EPA's health-based standards are protective of children, and they provide the impetus for a research program on children's health.

1.3. Research Questions

This strategy outlines a research program that will address questions about children's vulnerabilities to adverse effects from exposure to environmental agents, the quantitative risk from exposure to environmental agents, and how the risk can be reduced. The following research questions are addressed in the strategy:

1. What are the adverse effects from children's exposures to environmental agents that are qualitatively or quantitatively different from effects in similarly exposed adults? What are the near-term and delayed effects of childhood exposures? What are the characteristics of the environmental agents associated with these effects?

2. What are the specific periods of development when exposure to environmental substances can cause adverse health effects?

3. What are the best in vitro models and in vivo animal models for screening for and identifying hazards to children?

4. To what environmental substances are children more highly exposed? How do exposures differ with age? What factors contribute to higher exposures?

5. What are the relationships between exposures to children and adverse health effects observed in childhood or later? What factors in the child's environment can increase risks?

6. How can laboratory and human data be used to predict responses to childhood exposures?

7. What is the variation in exposure and susceptibility within members of the same age group, and what are the factors that contribute to this variation?

8. What are the adverse effects from children's exposures to mixtures that are quantitatively or qualitatively different from effects in similarly exposed adults?

9. What are the uncertainties in estimating environmental risks to children and how can they be characterized in risk assessment? What are the most effective methods for communicating results, data, and risks to risk assessors, risk managers and the public?

10. What are the specific agents and pathways of exposure where risk management research will be effective in addressing known risks to children? What are the most effective methods for reducing environmental risks to children?

1.4. Goals and Objectives

This strategy was developed within the framework established in the EPA and ORD strategic plans (EPA 1997b, c). EPA developed its strategic plan in compliance with the Government Performance and Results Act (GPRA) passed by Congress in 1993. The EPA strategic plan lists ten broad GPRA goals that serve as a framework for EPA's planning and resource allocation. This strategy addresses Goal 8: Provide sound science to improve the understanding of environmental risk and develop and implement approaches for current and future environmental problems. The EPA program has been arrayed under the GPRA goals as a series of objectives, subobjectives, and annual milestones for purposes of reporting under GPRA. The ORD Children's Health program, which is the topic of this strategy, is part of the ORD Sound Science program in Human Health Risk Assessment under Goal 8. The objectives of this strategy are shown in Figure 1.

1.5. ORD Research Strategies and Plans

The ORD strategic plan identifies six high-priority research topics: safe drinking water (with a near-term focus on microbial pathogens, disinfection by-products, and arsenic), high-priority air pollutants (with a near-term focus on particulate matter), emerging environmental issues (with a near-term focus on endocrine disruptors), research to improve ecological risk assessment, research to improve human health risk assessment, and pollution prevention and new technologies for environmental protection. Research strategies are being developed for the six high-priority areas and for specific subtopics (see Appendix B), including children's health. ORD is developing a strategy for research on asthma, which will include research on childhood asthma (EPA 2000a).

1.6. Organization

Section 2 provides a brief overview of the risk assessment/risk management framework within which ORD organizes its human health risk assessment research and a discussion of new directions in risk assessment. Section 3 discusses the legislative, regulatory, and policy decisions that encouraged development of the strategy and the relevant EPA Program and Regional Office activities. Section 4 summarizes research recommendations from many sources, and outlines the research program. Section 5 presents guidance for implementation.

Figure 1. Objectives of the ORD Strategy for Research on Environmental Risks to Children

- Establish direction for a long-term, stable core research program in children's environmental health that leads to sustained risk reduction through more accurate, scientifically based risk assessments for children.
- Identify research to answer the key questions about children's environmental health risks and increase our understanding of when children respond differently from adults to toxic agents and why.
- Identify research that will help to reduce children's risks.
- Provide a research agenda that identifies research priorities for the ORD intramural and extramural research programs.
- Inform EPA scientists, risk assessors, and risk managers of the research related to children at EPA and other Federal agencies.
- Provide guiding principles for implementation.

2. APPROACHES TO RISK ASSESSMENT

This strategy was developed within the framework of the risk assessment-risk management paradigm proposed by the National Academy of Sciences (NRC 1983) and covers a wide range of topics and disciplines. Readers will have varying degrees of familiarity with the use of quantitative risk assessment to support environmental risk management decisions. A brief description of the EPA risk assessment process is presented here to help readers understand the potential impact of the research outlined in this strategy on EPA programs.

Risk assessment is the process used to evaluate the hazards of and exposures to environmental agents to produce estimates of the probability that populations or individuals will be harmed and to what degree. It is one component of the process by which EPA and many other organizations recognize a potential risk and decide how to respond. Risk assessment has been defined by the National Academy of Sciences (NAS) to consist of four steps: hazard identification, exposure assessment, dose-response assessment, and risk characterization (NRC 1983).

The hazard assessment describes the likelihood that an environmental agent will produce adverse effects and the mechanisms by which agents exert their toxic effects. The exposure assessment specifies populations that might be exposed, identifies routes of exposure (usually inhalation, ingestion, and dermal contact), and estimates the magnitude, duration, and timing of the doses received. The exposure assessment may also determine the sources of exposure and the contribution of each source to the total exposure. The dose-response assessment describes the relationship between dose level and degree of toxic response. The risk characterization integrates information from the first three steps to develop estimates of the likelihood that any of the identified effects will occur in exposed people (NRC 1994).

2.1. The Standard Regulatory Approach

The standard regulatory risk assessment of an environmental agent is organized according to the four steps of the NAS paradigm and is based on the available data most relevant to the population being evaluated. If population-specific data are not available and cannot be collected, extrapolation methods and default assumptions are used to complete the assessment.[3]

The exposure assessment links environmental and personal exposure measurements with activity patterns using exposure models to estimate dose. Exposure models may be as simple as an estimate of inhalation dose as the product of concentration, breathing rate, and time of exposure. Or they may be complex, with many exposure pathways and dozens of variables. Understanding the sources of exposure and how the environmental agent is transported from its sources to the exposed individual may be critical to estimating concentrations in the air, water, soil, dust, and food to which individuals are exposed. It is also important to know the sources of exposure in order to identify, evaluate, and implement risk management options.

Estimates of exposure or dose from the exposure assessment are combined with information on toxic response to produce estimates of risk. The process for determining the likelihood of an adverse effect at a particular exposure or dose is the dose-response assessment. Human data suitable for developing dose-response relationships are usually obtained from groups that have been highly exposed in the workplace, by accident, through diet, and the like. Studies of groups outside the United States that have been historically exposed to high levels of environmental pollution are sometimes used. Even when such highly exposed groups exist, however, the difficulty in determining and quantifying individuals' exposure histories as well as the presence of other possible causes of the adverse effect can prevent even the observation of a cause-effect relationship. Therefore, the quantitative dose-response assessment is usually based on data from controlled laboratory studies where effects on animals are evaluated and the results extrapolated to humans.

Under the current EPA default approach to hazard and dose-response assessment, cancer is thought of as the consequence of chemically induced DNA mutations. Because a single chemical-DNA interaction may lead to a mutation and since cancer is thought to arise from single cells, any dose, no matter how low, is assumed to have the potential to cause the adverse effect. This is referred to as a nonthreshold effect. Nonthreshold effects are modeled as linear relationships between response and dose across the entire dose-response curve. Dose-response relationships observed at the relatively high doses administered in the laboratory are assumed to hold true at the lower doses usually experienced by humans in the environment (ERG 1997, 1998).

Effects other than cancer (threshold effects) have been assumed to result from multiple chemical reactions within multiple cells. EPA's policy is to assume that, for noncancer effects, there is a safe exposure, and that no adverse effects are likely to occur below that threshold. The threshold is estimated based on the highest exposure at which no effect was observed in an experimental study--the NOAEL (no-

[3]EPA assessment methods are described in a series of assessment guidelines for exposure and cancer and noncancer endpoints (e.g., EPA 1996b, EPA 1996c, EPA 1991).

observed-adverse-effect level) or the NOEL (no-observed-effect level) (NRC 1994). To establish a safe limit for human exposure, the NOAEL is divided by uncertainty factors to account for differences in susceptibility among humans, differences between test species and humans, and other uncertainties resulting from lack of key data such as a long-term dosing study or a NOAEL. A typical assessment uses a factor of 10 to account for variability in human response and a factor of 10 to account for interspecies differences. At EPA, this quotient is termed Reference Dose (RfD) when derived for ingestion exposure and Reference Concentration (RfC) for inhalation exposure (NRC 1994).

The standard regulatory approach is extremely useful in that it has allowed EPA to assess and make regulatory decisions on thousands of chemicals, often with limited data, while providing some assurance that the decisions are protective of public health. However, questions often arise about whether the current approaches accurately account for the many uncertainties introduced when assessments are based on data from the laboratory. Available dose-response data must be extrapolated from the high exposures used in laboratory experiments to the lower exposures usually found in the environment. The internal dose to the target tissue in humans is usually unknown. The frequency and duration of exposure in the laboratory study is often different from what can be expected in the environment. It is often difficult to find an appropriate animal model for the substance and endpoint of concern or to predict differences in the magnitude of the response between animals and humans. There is a major difficulty in extrapolating from immature laboratory animals to children because growth rates and the level of development and maturation of organs and systems at and after birth can be considerably different across animal species, as well as between animals and humans. Current default approaches do not easily allow for incorporation of all relevant data in the dose-response assessment. Factors that can cause significant age-related differences in exposure and toxicity, such as metabolic pathways and rates, distribution in the body, dose to target organ, excretion, DNA repair, and growth and cell proliferation are not accounted for except through uncertainty factors.

2.2. Future Directions in EPA Risk Assessment

The exposure-dose-response relationship can be envisioned as a continuum of events in which exposure to a substance occurs, the substance enters and moves through the body and may be chemically transformed, and interacts to cause changes in molecules, cells, and tissues, leading to disease. The series of events by which a substance exerts its toxic effects is referred to as a mechanism of action. The term “mechanism of action” will be used here to refer to the complete sequence of biological events that must occur to produce the adverse effect. Typically, only partial information on the mechanism of action is available. In such a case the term “mode of action” will be used to refer to mechanisms for which some but not all of the steps are known. In many cases, exposures and early effects in the biological sequence can be measured through biological markers. An assessor is often able to describe qualitatively many of the processes that lead from exposure to effect, but lacks the data and methods to use the information in the quantitative risk assessment.

Better understanding of the sequence of events leading to adverse effects and availability and use of biological data will increase EPA’s ability to assess risks. Early biological effects are more prevalent in the population than is actual disease, and biomarkers of early effects may sometimes be more specific to environmental agents. A better understanding of the pharmacokinetics and toxic modes of action of environmental agents will improve hazard identification and reduce uncertainties in extrapolation from laboratory measurements of the dose-response relationship to events in the environment (e.g., see EPA 1996b). Expanded development and use of biological data is essential to quantifying variability in human susceptibility, understanding responses to mixtures of chemicals, and harmonizing risk assessment methods for cancer and noncancer endpoints.

One method of incorporating information on the mode of action in the dose-response assessment is the use of biological models. Physiologically based pharmacokinetic (PBPK) models address the exposure-dose relationship in an organism taken as a whole, estimating the dose to a target tissue or organ by taking into account rates of absorption into the body, metabolism, distribution among target organs and tissues, storage, and elimination. Biologically based dose-response (BBDR) models describe specific biological processes at the cellular and molecular levels that link the target-organ dose to the adverse effect (Faustman and Omenn 1996). PBPK and BBDR models are useful in extrapolating between animals and humans and between children and adults because they allow consideration of species- and age-specific data on physiological factors affecting dose levels and data on biological responses that are different or more intense in children.

With advances in the ability to measure and model the biological events in the exposure-dose-response continuum, the science of risk assessment is moving toward a harmonization of the methodology of cancer and noncancer assessments and away from a consideration of endpoints in isolation. Carcinogenesis is now recognized to embody changes in key genes that regulate the cell replication cycle and that can be influenced by mutagenic and nonmutagenic modes of action. When direct mutagenic events do not pertain and other modes of action apply, the likelihood exists that cancer is secondary to other events (e.g., stimulation of cell division) and that a potential for cancer exists only at doses sufficient to produce the events. Thus, in some cases, thresholds could apply. Conversely, it is now recognized that

threshold considerations may not apply to all noncancer effects. For example, effects of lead exposure are manifested at existing environmental exposure levels, and no apparent NOAEL exists (ERG 1997, 1998).

Thus, the current scientific database indicates that automatic separation of dose-response relationships for cancer and noncancer effects may not be justified. A focus on modes of action of carcinogenesis directs attention away from tumors toward earlier biological and toxicological responses critical in the carcinogenesis process. Such responses are relevant to both cancer and noncancer effects and serve as a bridge to link their risk assessments. Use of biological data and harmonization of assessment methods may also provide new means by which to study relationships between environmental agents and rare endpoints such as the various childhood cancers. If it could be demonstrated, for example, that childhood cancer and birth defects of a particular target organ result from similar modes of action, these endpoints might be combined in an epidemiology study. The higher percentage of cases in the population resulting from combining cases involving different endpoints would increase the ability to observe relationships between the adverse effects and exposure to environmental agents hypothesized to produce the effects by the common mode of action.

New directions in risk assessment at EPA also include more emphasis on total exposure via all pathways, consideration of cumulative risks when individuals are exposed to many chemicals at the same time, and use of probabilistic modeling methods such as Monte Carlo analysis to provide better estimates of the range of exposure, dose, and risk in individuals in the population.

3. IMPLEMENTATION OF LEGISLATION AND POLICY ON CHILDREN'S ENVIRONMENTAL HEALTH

In 1996, Congress enacted two statutes requiring that EPA consider children and other potentially susceptible groups when setting health-based standards: the Food Quality Protection Act of 1996 (FQPA) and the Safe Drinking Water Act (SDWA) Amendments of 1996.

Because of the risk assessment requirements in FQPA, EPA's Office of Pesticide Programs (OPP) is very active in addressing children's risk issues. FQPA calls for a reassessment of pesticide tolerances and registrations to ensure that they are protective of children. The statute provides that in making a finding of reasonable certainty of no harm for threshold effects, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to the exposure and toxicity of infants and children." The Administrator may use a different margin of safety "only if, on the basis of reliable data, such margin will be safe for infants and children" (FQPA, section 405, amending the Federal Insecticide, Fungicide, and Rodenticide Act, section 408(b)(2)(C)).

OPP has developed a draft policy on application of the tenfold margin of safety (the 10X Factor) (EPA 1999a), which identifies a core set of toxicity tests that will be accepted as a complete toxicity database for infants and children. OPP will consider the completeness of the toxicity data as part of RfD development. If one or more of the key studies in the core is missing or inadequate, an Uncertainty Factor for database uncertainty will be used in deriving the RfD. Decisions on the completeness of the exposure database will be made as part of the exposure assessment, based on whether sufficient data exist either to accurately determine exposure or to assure that exposures to infants and children are not underestimated. If for some reason, the RfD process does not consider all possible uncertainties related to toxicity, residual uncertainties will be considered in the risk characterization.

The final decision on the 10X Factor will be made by considering together the use of Uncertainty Factors to account for database uncertainty and potential toxicity to infants and children in developing the RfD, the recommendations in the exposure assessment regarding the need to account for incompleteness in the exposure database, and any residual uncertainties and concerns identified in the risk characterization. On the weight of the evidence, OPP may decide to retain the 10X Factor, or remove, reduce, or raise it.[4]

ORD supported OPP's development of toxicity and exposure data requirements for the 10X Factor through leadership of and participation in EPA working groups addressing these issues (EPA 1999b, c). The FQPA data requirements were considered in developing this strategy.

In other activities related to implementation of FQPA, OPP has developed standard operating procedures for assessing exposure by multiple routes (Versar 1997) and methods for conducting aggregate exposure and risk assessments (EPA 1999d). These methodologies consider dietary and drinking water exposures using intake values for young age groups. They also consider such childhood exposure pathways as contact with dust and soil followed by ingestion, exposure to pesticides on toys, and ingestion of pesticide pellets.

The SDWA Amendments of 1996 require that EPA take into account the effect of contaminants on sensitive subpopulations, including infants and children, when deciding which drinking water contaminants present the greatest public health concerns and whether to regulate contaminants. Office of Water activities are focused on protecting infants and children from contaminants such as microbes and chemicals in drinking and recreational water and fish. The Drinking Water Health Advisory program develops guidance for short-term exposures to drinking water contaminants to protect children against noncancer health effects.

In addition to implementing these statutes, EPA has a policy of specifically considering children throughout its programs. U.S. Executive Order No. 13045 requires that each Federal agency shall make it a high priority to ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks (US Executive Order No. 13045 1997). In 1995, the EPA Administrator established a policy to explicitly take into account health risks to children and infants from environmental hazards when conducting assessments of environmental risks (EPA 1995a). The announcement of the policy was followed by a 1996 EPA Administrator's report, *Environmental Health Threats to Children* and EPA's *National Agenda to Protect Children's Health from Environmental Threats* (EPA 1996a). The National Agenda calls for an evaluation of all EPA standards to ensure sufficient protection for children, expansion of scientific research on childhood susceptibilities and exposures, and an emphasis on outreach to parents and communities through education and other measures to reduce and prevent childhood risks. All EPA

[4]There are many important issues related to the FQPA Safety Factor that cannot be addressed here. OPP may change some parts of its draft policy before it is finalized. The latest information can be found at the Internet site of the OPP Science Advisory Panel: http://www.epa.gov/scipoly/sap/

Program Offices and Regions have programs to implement these policies.

OPPTS is authorized by statute to require manufacturers to test new and existing pesticides and other toxic substances and submit data for evaluating safety. Much of the toxicity testing in the United States is performed by the private sector under the Toxic Substances Control Act (TSCA). OPPTS provides test protocols and recently issued an updated set of testing guidelines that will provide better information on health effects in children, particularly reproductive and developmental effects. Guidelines have been updated and expanded to include chemical effects on metabolism, developmental neurotoxicity, and reproductive and prenatal developmental toxicity (EPA 1998a). New guidance is provided for testing for toxic effects on the immune system.

Part 50 of the Clean Air Act and its supporting legislative history require that EPA establish National Ambient Air Quality Standards (NAAQS) to protect the health, with an adequate margin of safety, of susceptible subpopulations. The innate developmental and physiologic characteristics and the activity patterns leading to higher exposures that make children susceptible to these air pollutants have been considered in every NAAQS promulgated under the Clean Air Act.

The Office of Solid Waste and Emergency Response (OSWER) routinely considers children's exposure at waste sites through dermal contact and ingestion of contaminants in dust and soil. OSWER is expanding its efforts through such actions as conducting consistent, comprehensive assessments to evaluate the impact on children of lead-contaminated hazardous waste sites.

The EPA Regional Offices are leading and participating in outreach, risk assessment, risk intervention, and community educational projects, often in cooperation with State and local governments, private organizations such as the American Lung Association and the Parent-Teacher Association, and members of local communities. The Regions address important environmental problems, including children's risks from proximity to hazardous waste sites, asthma in children and its relationship to allergens and other contaminants in indoor environments, and lead and pesticides in residences.

4. RESEARCH DIRECTIONS

In developing this strategy, the science team followed the approach outlined in the ORD Strategic Plan (EPA 1997c). Research recommendations of conferences, workshops, and scientific reports on children's environmental health were reviewed. Comments were sought from the ORD national laboratories and centers. The ORD Science Council, composed of the ORD Deputy Assistant Administrator for Science, the ORD Associate Directors for Health and Ecology, and other ORD science managers, was consulted. EPA Program Offices and the Office of Children's Health Protection (OCHP) contributed recommendations through membership on the science team. The science team formulated the set of research questions in Section 1.3 and a set of research areas to address the questions. Criteria were developed and the research areas were assigned a priority of high, medium, or low. Section 4.1 discusses research needs and recommendations. Section 4.2 summarizes current research sponsored by EPA and other Federal agencies. Section 4.3 describes possible research areas for the ORD Children's Health program, the feasibility of conducting the research at EPA, and the priority of the research. Section 4.4 discusses the impact of the research on risk assessment and management and the relationships between the research areas.

4.1. Research Needs and Recommendations

Over the past two decades, many groups of experts have considered how exposure to environmental agents affects children. Hundreds of research issues have been defined, addressing numerous age groups, disease endpoints, biomarkers of disease, modes of action, exposure pathways, environmental agents, physiological and biological characteristics affecting dose, and methods of risk communication and risk reduction. Research on children's environmental health is performed by members of many disciplines, among whom are physicians; classical and molecular epidemiologists; developmental toxicologists, including specialists in neurotoxicity, immunotoxicity, and childhood cancer; environmental scientists; engineers; and statisticians.

The sources of research recommendations considered by the science team and the topic areas covered are shown in Table 1 and Appendix C.

4.2. Current Research

ORD conducts research on exposures to environmental agents and related adverse effects in children. Other Federal agencies also study the occurrence and causes of childhood developmental disorder and disease. The Federal public health agencies of the Department of Health and Human Services, especially the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Allergy and Infectious Disease (NIAID), the National Institute for Child Health and Human Development (NICHD), and the Centers for Disease Control and Prevention (CDC), support much of the Federal research, surveillance, and data collection on children's health in the United States. Although much of this research is relevant to EPA's mission, only a fraction of the Federal program investigates the specific role of environmental agents in causing adverse effects in children. This section describes some of the Federal programs directed at children's environmental risks and gives examples of projects underway at EPA. The Children's Environmental Health and Safety Inventory of Research (CHEHSIR), which is available via the Internet (EPA 2000b), reports relevant Federal research at the project level. Appendix D describes the roles of the Federal research programs that are most relevant to children's environmental health.

4.2.1. National Testing Programs

The Federal Government develops testing protocols and tests pesticides and other chemicals in animals to identify potential hazards to humans. Under programs administered by OPPTS (Section 3), EPA may require manufacturers to test substances in commerce to identify those that may be hazardous to human health. ORD supports the OPPTS testing program through research in improved methods of chemical testing. The National Toxicology Program (NTP) also conducts toxicity testing. NTP consists of relevant activities of NIEHS, the National Institute of Occupational Safety and Health (NIOSH), and the U.S. Food and Drug Administration (FDA). NTP develops and conducts in vitro and in vivo tests for long-term carcinogenesis, reproductive and developmental effects, genotoxicity, teratogenicity, immunotoxicity, neurotoxicity, and other disease endpoints. NTP is responsible for one-third of all toxicity testing performed world-wide (NIEHS 2000a). EPA is a voting member of the Interagency Testing Committee (ITC), through which chemicals are nominated and selected for NTP toxicity testing.

4.2.2. Modes of Action and Modeling of Physiological/Biological Processes

In addition to routine chemical testing to identify substances of concern, the Federal Government sponsors research to investigate the biological processes by which toxic effects, including effects in children, occur. ORD is developing methods to evaluate hazards for noncancer human health endpoints, including new and refined test methods for neurotoxicity, immunotoxicity, and reproductive toxicity, and predictive models to improve the biological basis for human

Table 1. Research Recommendations and Needs		
Source	**Description**	**Topic Areas**
ILSI (1992)	•EPA-sponsored workshop conducted by International Life Sciences Institute (ILSI): *Similarities and Differences Between Children & Adults* •Invited investigators	•Development and genetics •Physiological and biochemical differences between children and adults •Animal models for developmental toxicology •Age-related responses in cancer bioassays •Drug case studies •Environmental case studies (ionizing radiation, lead, vinyl chloride, polyhalogenated biphenyls) •Pesticide case studies
NRC (1993)	•NRC panel report: *Pesticides in the Diets of Infants and Children*	•Differences between infants, children, and adults •Selection of appropriate animal models •Toxicity •Methods of toxicity testing •Food and water consumption •Estimating exposures •Estimating risks
ILSI (1996)	•EPA-sponsored workshop: *Research Needs on Age-related Differences in Susceptibility to Chemical Toxicants: Report of an ILSI Risk Science Institute Working Group* •Invited experts	•Cancer •Neurotoxicity •Immune system effects
CEHN (1997)	•Children's Environmental Health Network conference: *1st National Research Conference on Children's Environmental Health: Research, Practice, Prevention, Policy* •Invited speakers	•Asthma and respiratory effects •Childhood cancer •Neurodevelopmental effects •Endocrine disruptor effects •Exposure •Risk prevention and reduction through community involvement and education
EPA (1998b)	•EPA interim final guidance: *Guidance for Considering Risks to Children During Establishment of Public Health-Related and Risk-Related Standards*	•Hazard considerations •Dose-response/susceptibility considerations •Exposure considerations
EPA (1998c)	•EPA-sponsored conference: *Preventable Causes of Cancer in Children* •Invited speakers	•Epidemiology & prevention of childhood cancer •Susceptibility factors for childhood cancer •Molecular markers of exposure and effect for childhood cancer •Quantitative measurement of exposure to potential childhood cancer agents
NRDC (1997)	•National Resources Defense Council report: *Our Children at Risk: the 5 Worst Environmental Threats to Their Health*	•Lead •Air pollution •Pesticides •Environmental tobacco smoke •Drinking water contamination

Table 1. Research Recommendations and Needs (continued)		
Source	**Description**	**Topic Area**
EPA (1998d)	•EPA workshop: *Assessment of Health Effects of Pesticide Exposure in Young Children* •Invited experts from many disciplines •Focus on identification of health effects associated with exposure to pesticides and how to measure those effects in children	•Neurotoxicity •Developmental toxicity •Carcinogenicity •Immunological effects •Respiratory effects
EPA (1998e)	•Annual EPA Regional risk assessor's meeting: session on risk assessment issues related to children's health assessments •EPA Regional risk assessors and interested EPA Program Office and ORD representatives	•Consistent approaches to toxicity assessment for children •Consistent approaches to exposure assessment for children •Default assumptions for children's risk assessments in absence of data •Childhood cancer and childhood exposure resulting in adult cancer •Effects of children's exposure to mixtures •Risk communication to the public on children's issues.
EPA 10X Task Force (EPA 1999a, b, c)	•Task Force reports providing recommendations on application of FQPA 10X Factor: -*Toxicology Data Requirements for Assessing Risk of Pesticide Exposure to Children's Health* - *Exposure Data Requirements for Assessing Risk from Pesticide Exposure of Children* - *The Office of Pesticide Programs Policy on Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance Setting Process*	•Toxicity •Exposure •Integration (decisionmaking on 10X Factor based on all toxicity and exposure considerations)
U.S. Task Force established under Executive Order 13045	•U.S. Task Force established four working groups to develop Government-wide initiatives for FY2000 on children's environmental health and safety issues	•Developmental disorders •Childhood cancers •Childhood asthma •Unintentional injury

health risk assessment. This research includes pesticide-specific studies to determine long-term health effects of exposures during development. At issue are reproductive competency and function, neurobehavioral changes, neurochemistry, neural growth and differentiation, allergic response, and immune function. Some of the ongoing studies attempt to understand and characterize the mechanisms by which toxicants interact at the cellular and molecular levels to produce adverse effects. As we obtain more data on these modes of action, we will be able to test the assumptions underlying our risk assessment methodologies and to develop new methods that will more accurately predict children's risks. Research in the pharmacokinetics of toxicants and modes of toxic action are providing results that will help develop PBPK and BBDR models for target organs (e.g., respiratory, reproductive, and nervous systems) leading to improved hazard identification and methods of extrapolation between animals and humans.

The ORD extramural grants program, Science To Achieve Results (STAR), is supporting grants to investigate the biological and physiological characteristics of different age groups, variability in response within particular age groups, and the biological basis for instances of increased susceptibility to environmental contaminants in children.

At ORD's National Health and Environmental Effects Research Laboratory (NHEERL), batteries of cellular and molecular markers, as well as functional tests, are being developed to aid in the identification and characterization of

toxicant-induced alterations in the ontogeny of the reproductive, immune and central nervous systems. Studies are underway to determine if there are long-term, persistent, or latent effects in animals exposed to environmental toxicants during development and, if so, to identify the mechanisms responsible for these effects. Scientists at NHEERL are also investigating the toxicodynamic and toxicokinetic mechanisms that underlie age-dependent responses to toxicants.

NIEHS's research program is closely allied with that of ORD in studying the impact of environmental contaminants on public health. Under their extramural programs, EPA and NIEHS jointly sponsor eight Centers for Children's Environmental Health and Disease Prevention Research (EPA 2000c). The centers conduct research to improve detection, treatment, and prevention of environmentally related diseases in children. The NIEHS Intramural Division conducts basic and applied research on how environmental exposures affect biological systems and human health, on the identification of susceptible subpopulations, and on the interaction between the environment, genes, and age. NIEHS is sponsoring the Environmental Genome Project, which will investigate the interaction of genes and environmental contaminants in causing human disease (NIEHS 2000b). The role of gene-environment interactions on human development and childhood disease could be studied under the Environmental Genome Project.

NCI is the primary sponsor of research on the biology of cancer. Investigations are focused on identifying and understanding the genes whose activity allows DNA changes that result in a normal cell becoming a cancer cell. NCI is developing and using experimental biological models that mimic the wide variety of human cancers (NCI 2000).

NICHD supports research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children and adults (NICHD 2000). The NICHD program includes research on the effects of exposure to environmental agents on human development. In 1999, EPA and NICHD sponsored a Request for Applications (RFA) for research on genetic susceptibility and variability of human malformations. EPA's efforts in this area focus on identifying environmental agents that cause birth defects and other developmental disorders, the molecular mechanisms of birth defects, and how to use mechanistic and other data in the risk assessment process (EPA 2000c).

4.2.3. Studies in Human Populations

Five of the EPA/NIEHS-sponsored Centers for Children's Environmental Health and Disease Prevention are studying the influence of the environment on asthma and other respiratory diseases in groups of children hypothesized to be highly exposed to airborne contaminants and devising ways to prevent or reduce exposures where necessary. ORD is participating in the Inner-City Asthma Study, a prevention trial led by NIAID aimed at developing intervention methods to reduce high asthma morbidity in inner-city children and adolescents. The Inner-City Asthma Study identified factors associated with asthma severity, including high levels of indoor allergens, high levels of smoking among family members and caretakers, and exposure to high levels of nitrogen dioxide, a respiratory irritant (Fauci 1997).

Some studies are conducted in cities where high levels of air pollution increase the ability to observe relationships between pollutants and respiratory effects. ORD is studying the relationship between air pollution and children's respiratory health in four Chinese cities. An ORD study is also underway to determine whether children are more susceptible than adults to nasal metaplasia and whether biochemical tests can detect morphological alterations caused by high ambient ozone and PM10 pollutants in Mexico City (EPA 2000b).

Three of the EPA/NIEHS Centers for Children's Environmental Health and Disease Prevention are examining the relationship between developmental disorders and exposure to neurotoxicants such as organophosphate pesticides in groups of children believed to be highly exposed. ORD is also sponsoring studies of children's exposures to pesticides in Minneapolis-St. Paul under the National Human Exposure Assessment Survey (NHEXAS); along the U.S.-Mexico border in Arizona and Texas; and under STAR grants in Arizona, Washington State, and Minnesota. Depending on the study, measurements include levels of pesticides in air, water, food, dust, and soil; personal biomarkers of exposure such as pesticide levels in blood, breath, and urine; and activity information (questionnaire, diary, observation, and videotaping). Some of these studies will focus on total exposure, sources of exposure, and differences in exposure between children and adults, and some also investigate the relationship between exposure and health endpoints.

ORD has recently begun to investigate exposure of pre-elementary school children to persistent organic compounds through ingestion, inhalation, and dermal contact. Targeted compounds include polycyclic aromatic hydrocarbons, pesticides, phthalate esters, phenols, and polychlorinated biphenyls. Environmental samples will be collected in homes, classrooms, and outdoor play areas. Children will be videotaped to determine activity patterns and urine samples will be collected. Children and adult caregivers in approximately 450 households will be studied.

ORD and CDC are supporting a number of studies to evaluate health and environmental conditions along the U.S.-Mexico border in the context of risk to children. The goals of one such study are to determine whether children are at increased risk of adverse health effects from exposure to pesticides, to identify risk factors, and to develop intervention and prevention strategies. Another study deals with the identification of lead exposure sources and risk reduction. Associations between ambient air quality and acute pediatric

respiratory health are being evaluated in a retrospective epidemiologic study. A case-control study of risk factors for neural tube defects is underway. The potential association of neural tube and cardiac defects and exposure to disinfectant byproducts in drinking water is also under examination. A separate study in Chile is investigating the relationship of chronic arsenic exposure in drinking water to congenital abnormalities and fetal, neonatal, and maternal morbidity and mortality.

Examples of other current ORD studies include determination of the ability to link recent pesticide exposure and elevated cholinesterase levels to defined symptomatologies of young children in agricultural communities; evaluation of arsenic metabolic profiles in children and adults in order to determine if differences in metabolism are age-related or are due to differences in ingestion habits; and application of test methodologies for evaluating associations between estimated insecticide exposure and immunologic, developmental, and enzymatic endpoints.

Many Federal agencies conduct surveillance of childhood disease and sponsor population-based studies of exposure and disease in children. These programs produce data and results vital to EPA's risk-based programs. CDC's National Center for Environmental Health (NCEH) tracks asthma emergency room visits, asthma hospitalizations, and asthma mortality on a national level and in four geographic regions in partnership with State and local governments. Hospitals and clinics routinely report obvious birth defects. NCEH surveys children aged 3 to 10 in metropolitan Atlanta to document developmental disabilities that require time to appear, including mental retardation, vision and hearing impairment, and cerebral palsy, and conducts surveillance and epidemiology studies of human exposure to lead, radiation, air pollution, and other toxicants. A major focus of the NCEH Strategic Plan is the incorporation of advances in genetics into its research, epidemiology studies, and disease prevention programs (CDC 2000a). NCEH has a laboratory with expertise in analyzing biological samples for environmental contaminants, which is developing improved analytical methods for blood and urine samples from children (CDC 2000b).

CDC's National Center for Health Statistics (NCHS) is conducting the fourth National Health and Nutrition Examination Survey (NHANES IV), a national survey of health and nutrition. NHANES IV will have about 30,000 respondents and will include sufficient numbers of children in selected age ranges to allow statistical inferences about their health, nutrition, and food intake, and the concentrations of some environmental contaminants in their blood and urine. ORD is collaborating with NCHS to collect information on children's exposure to pesticides and other environmental contaminants. NHANES has been conducted since 1971, and data from NHANES III are now available (CDC 2000c).

NCI conducts population-based research on environmental and genetic causes of cancer and on the role of biological, chemical, and physical agents in the initiation, promotion, and inhibition of cancer. NCI's Agricultural Health Study (AHS) is a large epidemiology study of cancer in farm workers and their families. ORD is participating in the AHS through an exposure study of a subgroup of participants. NCI also supports human-subject research aimed at understanding the molecular causes of specific cancers in children and the reasons for treatment failure. The pediatric Clinical Trials Cooperative Groups (Children's Cancer Group, Pediatric Oncology Group, National Wilms' Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group) develop research protocols used in the treatment of the majority of children with cancer in the United States and represent a significant portion of the U.S. clinical research on childhood cancers. A significant portion of children with cancer in the United States are enrolled in Federal programs. NCI also supports grants including laboratory and epidemiological studies of pediatric cancer survivors. To date, these studies have not focused on possible environmental causes of childhood cancer (NCI 2000).

NIEHS is conducting a study in Norway investigating the hypothesis that the interaction between environmental agents and genetic polymorphisms makes the fetus more susceptible to cleft palate. For this study, both genetic samples and data on environmental exposure of mothers and infants are being collected (NIEHS 2000c).

The National Survey of Lead and Allergens in Housing is a joint effort of the Department of Housing and Urban Development (HUD) and NIEHS. HUD is studying the prevalence of lead-based paint, lead in house dust, and lead in soil (HUD 2000). NIEHS is studying the prevalence of allergy-inducing materials in house dust. This study involves visits to more than 8,000 homes from 75 areas selected to reflect the national housing stock, collection of environmental samples, and interviewing of occupants (NIEHS 2000d, e).

4.2.4. Exposure-Dose-Response Modeling and Risk Assessment

The number and types of direct exposure measurement studies are limited by their relatively high cost and the difficulties in studying children. Another type of exposure study design uses a mathematical model to combine spatial and temporal information on pollutant concentrations with population distributions of time-activity and location data and other exposure-related data to estimate exposure. Variables in the models are evaluated using existing data from many sources. ORD is using the results of data from completed and ongoing studies to develop age-specific exposure models. ORD also sponsors research to understand and quantify factors, such as intake and contact rates and durations and frequencies of exposures, that contribute to estimates of total exposure. Children's exposures to pesticides

via the dermal route, through nondietary ingestion of pesticides on surfaces and in soil and dust, and through contact with pesticide-treated pets are being studied. Transport of pesticides from outdoors to indoors and movement and persistence in the indoor environment are also being studied. Existing data are being analyzed to determine children's activities and dietary and nondietary exposures. Measurement protocols and models are being developed to account for exposures that occur when children eat food they have placed on floors recently treated with pesticides.

Exposure-to-dose models are being developed for estimating concentrations of contaminants in biological media (blood and urine) and doses of contaminants to target organs. These models take into account age-related differences in absorption, metabolism, distribution, and elimination and differences in the structure, composition, and function of organs and systems. ORD, OPPTS, and the Office of Emergency and Remedial Response (Superfund) developed the Integrated Exposure Uptake Biokinetic (IEUBK) model (EPA 1995b), which estimates children's blood lead levels from environmental concentrations of lead, taking into account physiologic characteristics of a small child. The IEUBK model is used to assess risk at Superfund sites and was used in an EPA risk assessment to determine lead cleanup levels in residences (EPA1998f). Work is ongoing to develop a modeling framework and an integrated group of models that can be easily modified for a variety of environmental agents and exposure scenarios for children. The models will describe transport in microenvironments and contact with and uptake into the body by multiple routes of entry. Another research effort is focused on collecting child-specific data on lung structure and respiration and incorporating it into dose-response methods for estimating exposures and risks from inhalation of contaminants. This project will be expanded to include the ingestion and dermal routes.

Long-term research is being conducted to design a BBDR model for developmental toxicity. Thus far, research has focused on prenatal development and chemicals for which metabolic pathways, cellular mechanisms of action, and toxicity profiles are known. In the shorter term, ORD is working on BBDR models that will incorporate differences in carcinogenic effects resulting from childhood and adult exposures to permit estimation of cancer risk from partial lifetime exposure of any given duration beginning at any given age.

EPA develops and distributes risk assessment information through the Integrated Risk Information System (IRIS), including oral RfDs and inhalation RfCs for chronic noncarcinogenic health effects and slope factors or unit risks for carcinogenic effects (EPA 2000d). Information on children is included in IRIS where data are available. ORD guidance documents such as the *Exposure Factors Handbook* (EPA 1997d) provide analyses of existing data on children and recommendations for evaluation of exposure variables for use in risk assessments. A companion project examines the differences in exposure to environmental contaminants in children by racial, ethnic, and socioeconomic groups. ORD supports the Developmental and Reproductive Toxicology (DART) Database in collaboration with the National Institutes of Health (NIH) and FDA. DART is an online bibliographic database containing about 80,000 references. Ongoing maintenance by the National Library of Medicine includes adding 3,500 to 4,000 references per year and improving the search capability.

4.2.5. Risk Management and Risk Communication

A basic tenet of risk management is that public health problems resulting from exposures to environmental contaminants can be more efficiently corrected by preventing the exposures than by administering medical treatment after the effects occur. The U.S. Government's most highly visible action relating to children's health is the control of lead exposure through removal of lead from gasoline and paint and the accompanying rapid reduction in blood concentrations of lead in the nation's children.

One way to reduce risk is by using engineering controls and treatment and cleanup methods to reduce the amount of a substance released to the environment. Currently, ORD is developing new technologies to control emissions that disproportionately affect children. This research includes development of drinking water treatment technologies that reduce *Cryptosporidium* oocysts in water, indoor air treatment procedures that remove fine particulates, and development of efficient and cost-effective particulate controls for large industrial combustors and incinerators.

Controls at the source often require disposal of pollutants and may simply transfer the problem from one environmental medium to another. Pollution prevention avoids this problem by reducing the amount of contaminant available for release to the environment through increased efficiency in the use of raw materials, energy, water, or other resources (EPA 1998g). ORD is developing processes and products that will generate or release lower levels of substances that have a disproportionate impact on children. Pollution prevention research projects aimed at reducing exposure to particulate matter include development of better consumer products to mitigate indoor air problems originating from indoor sources, development of better construction techniques to reduce the infiltration of outdoor pollutants to the indoor environment, studies on emissions from several types of oil and coal under differing combustion conditions and with different pollutant controls, testing of emissions from new and older designs for diesel engines, and improved choice of materials and design of automobile and truck tires to reduce creation of fine particulate during use.

EPA is exploring ways to address children's environmental health risks through partnerships with

communities. NIEHS requires that all of its centers develop and maintain community outreach and participation programs. All of the EPA/NIEHS Centers for Children's Environmental Health and Disease Prevention have projects in which the grantees work closely with parents and other members of the community to mitigate unacceptably high exposures to environmental contaminants. In another ORD study, the impact of improved community drinking water supplies is being evaluated by assessing the occurrence of microbial enteric disease in children 2 to 10 years old before and after changes in drinking water supplies or treatments are implemented. ORD is investigating pesticide poisoning reports in children six years and younger in the Lower Rio Grande Valley to determine whether they are at increased risk of pesticide poisoning, identify risk factors, and develop intervention and prevention strategies.

EPA's Regional Offices are working with communities to address environmental health threats to children. For example, Region 5 is conducting intervention studies on childhood asthma in Milwaukee and working to improve indoor air quality in Chicago schools. Regions 2 and 7 are planning to develop an instructional video for urban poor populations recommending techniques for controlling asthma by reduction of children's exposure to cockroach and dust mite allergen, pesticides, molds, pet dander, and secondhand smoke. The Chippawa Cree Tribe and Region 8 have entered into a cooperative agreement to identify and reduce environmental health threats to the Tribe's children in north-central Montana, initially focusing on lead hazards, unsafe drinking water, and second hand smoke. The Office of Air and Radiation (OAR) has developed and implemented the EPA SunWise School program to mitigate children's health risks related to overexposure to ultraviolet radiation. Descriptions of more EPA community-based projects can be found in the CHEHSIR database (EPA 2000b).

The Agency for Toxic Substances and Disease Registry (ATSDR), created to deal with hazardous waste issues, has a major role in communicating and working with individuals and communities. ATSDR advises community members and others of the health impacts of Superfund sites, identifies communities where people might be exposed to hazardous substances, conducts health studies in communities, determines hazards, and recommends actions to safeguard health (ATSDR 2000).

4.3. Research Areas and Priorities

A strategy for research in children's risk must be broad enough to address diverse environmental contaminants, endpoints, and special groups such as farm children and urban children. The relative importance of research areas may shift rapidly as more becomes known about the impact of environmental contaminants on children's health and new methods become available to study the gene-environment interactions that lead to adverse effects. The science team decided that a research strategy directed at specific environmental problems and endpoints would not provide sufficient flexibility and might impede the development of new approaches to risk assessment. Issues surrounding children's environmental health are too numerous to address individually in this strategy, and current knowledge is limited, making it difficult to foresee emerging issues and future directions. Other EPA groups are developing research recommendations for addressing children's environmental health, including the U.S. Task Force, the EPA 10X Task Force, the Office of Children's Health Protection, and ORD programs under GPRA goals 1 through 5 (Clean Air, Clean Safe Water, Safe Food, Safe Communities, and Safe Waste Management). The strategy is organized into 5 main topic areas encompassing 13 research areas that cut across all environmental problems and address the research questions presented in Section 1:

- # Development of data for risk assessment
  - S Mode-of-action research
  - S Epidemiology studies
  - S Exposure field studies
  - S Activity pattern and exposure factor studies
- # Development of risk assessment methods and models
  - S Methods and models for using mode-of-action data in risk assessments
  - S Methods and models for using exposure data in risk assessment
- # Experimental methods development
  - S Methods for hazard identification
  - S Methods for measuring exposures and effects in children and to aid in extrapolations between animals and humans
- # Risk management and risk communication
  - S Multimedia control technologies
  - S Reduction of exposure buildup of contaminants indoors
  - S Education and communication of risk and risk reduction techniques
- # Cross-cutting issues
  - S Variation in human susceptibility and exposure
  - S Mixtures/cumulative risk

Appendix E contains a cross tabulation showing relationships between the research areas and the research questions.

After developing the research areas, the science team considered how the research might be conducted. ORD has intramural and extramural research programs. The intramural program is organized into three national laboratories and a national center: NHEERL, the National Exposure Research Laboratory (NERL), the National Risk Management Research Laboratory (NRMRL), and the National Center for

Environmental Assessment (NCEA). The extramural Science to Achieve Results (STAR) program is administered by the National Center for Environmental Research (NCER). The science team considered the following possibilities for conducting research:

- ORD scientists as principal investigators, often in collaboration with scientists in government, academia, and private firms through interagency agreements, cooperative agreements, and contracts (the intramural program);
- academic scientists as principal investigators under grants funded through the STAR program; and
- scientists supported by other Federal agencies without active ORD collaboration or support.

Priorities were determined for both the intramural and the STAR programs. In setting priorities, the science team first considered using the criteria set out in the ORD Strategic Plan (EPA 1997c). The ORD criteria were found to be specific to particular health effects, methods or models for assessing risk, or risk management techniques. They are problem-specific and difficult to apply to research areas that are more broadly defined. Therefore, the science team developed and used the following criteria to rank the topic areas:

- importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats;
- feasibility of conducting the research in the ORD intramural or STAR programs;
- availability of resources, including the capacities and capabilities of ORD's laboratories and centers and the extramural resources;
- opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessment;
- opportunities for collaboration with other Federal agencies and with other ORD research programs; and
- maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research that may identify hazards and exposures to children or change EPA's way of doing risk assessments and ultimately produce more accurate and less costly assessment procedures.

This section describes each research area and discusses the feasibility of conducting the research in ORD. Each research area is rated as high, medium, or low; and a rationale is provided for the rating. For the high-priority areas, long-term outcomes and short-term outputs for the next 5 years are also provided. Appendix F shows the application of the criteria to each research area.

4.3.1. Laboratory Studies and Surveys

This section describes the laboratory and field research that will provide the database to identify and assess environmental health threats to children. It includes human, animal, and in vitro studies, and studies of sources, pathways, and other factors influencing exposure.

4.3.1.1. Biology of Toxicant-Induced Tissue and Organ Damage in the Developing Organism

***Description*.** Sound biological data are needed to facilitate the interpretation and extrapolation of animal and human data for risk assessment. Even though certain agents have been identified as causing developmental abnormalities, current understanding of the pharmacokinetics and modes of action underlying these alterations is minimal. In this research area, data will be developed to link environmental exposures and doses with biologically effective doses at the cellular and molecular levels.

Data on absorption, metabolic pathways and rates, distribution and storage in the body, and elimination will be developed for sensitive age groups. Hypothesis-based studies will be conducted to study modes of action with the goal of linking developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels. Investigation of modes of action may include, for example, examination of disturbances resulting from alterations in metabolism, DNA repair, cell viability, and receptor-mediated alterations in gene expression. The biologic bases for age-related differences in target organ development, detoxification, repair, and compensation will be investigated using in vivo and in vitro experimental models. At a minimum, studies will be conducted during the period of development that is the most sensitive to perturbation by the toxicant in question. Data are also needed to determine if the pharmacokinetics and modes of action of a toxicant are similar across different age groups and across different species. The ideal study would include more than one age group so that an overall model at various developmental stages could be produced.

A critical review of studies of prescription drugs to elucidate what mechanisms of action might be expected to produce the greatest age-related susceptibilities might be a useful exercise to help design studies of environmental contaminants. A first exercise might be to explore whether appropriate models have been developed for organ systems of concern and how well existing models match up across organ systems.

Feasibility. ORD has the expertise to study the pharmacokinetics and modes of action that result in adverse effects in children. As discussed in Section 4.2.2, ORD supports ongoing research in this area in both the intramural and the STAR program. The current effort directed at children's issues needs to be expanded, however, particularly in the intramural program. NIEHS also supports research aimed at identifying the underlying modes of action by which toxicants affect biological systems, and it is important to continue collaborations and make full use of results from the NIEHS program.

Priority and Rationale. High. These studies and the methods and models described under Sections 4.3.2.1 and 4.3.3.1 are critical to increasing the use of biological data in children's risk assessments, particularly in selecting appropriate animal models and endpoints and for improving extrapolations from animals to children. Current approaches in risk assessment rely on assumptions that in many cases have only limited explanations based on biology. These include assumptions that are made in extrapolating (or interpolating) from laboratory animals to humans, from high to low exposure levels, over various exposure durations, and over changing critical periods of susceptibility, especially in the case of the developing child. Biologically based dose-response models should lead to refined risk assessment approaches that no longer rely solely on whole-animal toxicity testing, but incorporate the growing knowledge of molecular mechanisms and their involvement in a toxic response. It should be possible to develop testing paradigms using in vivo and in vitro approaches that are more biologically based and that address such issues as complex mixtures, varying exposure patterns, and critical periods of susceptibility. This research can be conducted in both the STAR and intramural programs and will require a long-term commitment of resources. It is essential to maintain and expand ORD capability through a strong intramural program to support the focused research necessary to improve EPA assessments.

Long-Term Outcomes. Mechanism-of-action experimentation facilitates the extrapolation of animal and experimental model data to humans, enhancing ability to predict and study adverse effects in humans. Mode of action becomes an integral component of risk assessment. Advances in genomics/proteomics are incorporated into EPA's risk assessment methodologies.

Short-Term Outputs. ORD will

- # Develop better quantitative characterizations of dose to target tissue in developing organisms to replace default assumptions in children's risk assessments.
- # Link developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels to develop first-generation biologically based predictive models.
- # Develop and validate sensitive and predictive methods using laboratory animals to determine mode of action by linking developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels.
- # Validate in vitro assays (using either animal or human biological material) for inclusion in the overall risk assessment process.

4.3.1.2. Relationship Between Exposure to Environmental Agents and Adverse Health Effects in Human Populations

Description. Well-designed epidemiological and clinical studies are needed to evaluate associations between prenatal and postnatal toxicant exposure and altered development, maturation of organs and systems, and developmental disorders such as childhood cancer, asthma, neurotoxic effects, reproductive effects, and birth defects. These studies will improve our ability to identify, characterize, and quantify toxicant-induced alterations in the structure and function of organs and systems during growth and development. A variety of criteria could be used to identify candidate populations. These criteria would include, but would not be limited to, inadvertent or accidental exposure to a known toxicant, exposure of a number of different age groups, the likelihood of obtaining useful dosimetric information (i.e., the ability to obtain data useful for quantifying age-specific external and internal dose), and availability of sensitive and predictive test methods for the target organ or system of concern.

One such study is a case-control study of a group of children with health effects that are known or suspected to be related to exposure to environmental pollutants. Based on the existing human and animal database for neurotoxicity of lead, certain pesticides, and PCBs, individuals with neurological diseases would be an appropriate group for such studies. Retrospective data on cases and controls could be collected through questionnaires, and both biological and environmental samples might be appropriate. It would be advantageous if subjects could also be monitored through early adulthood to test for persistent and latent effects.

Alternatively, prospective studies of childhood exposures to environmental contaminants and their associated effects in juvenile populations could be undertaken. A longitudinal study, similar to the 50-year-old Framingham Heart Study, sponsored by the National Heart, Lung, and Blood Institute, has been recommended by some experts to attempt to clarify the connection between childhood exposures to environmental agents and adverse health effects in childhood or adulthood (NHLBI 2000). In such a study, individuals would be enrolled at an early age, perhaps at birth, and followed into adulthood. Data on health and nutrition would be collected, as well as exposure data.

Feasibility. Human studies of the cause-effect and dose-response relationships between environmental contaminants and adverse health endpoints are most feasible for ambient contaminants, such as air and drinking water pollutants, and for easily observed effects associated with a single route and pathway of exposure, such as respiratory distress and enteric disease. The ORD intramural and STAR programs have experience in conducting human studies. Many of the current ORD-supported human studies of children involve respiratory endpoints. The impact of pesticide exposure on children, which can occur by multiple routes and have more than one source, is an expanding research area (see the discussion of EPA 1998b, in Appendix C). As discussed in Section 4.2.3, the STAR program is funding eight centers, each of which includes an epidemiology/intervention study.

One of the problems in conducting epidemiology studies of environmental agents is obtaining an accurate estimate of exposure levels over time. ORD, with a research laboratory (NERL) devoted to exposure science, is well positioned to address this issue. For example, as discussed in Section 4.2.3, NERL and NHEERL are collaborating in an exposure and epidemiology study of health effects in children along the U.S.-Mexico border.

ORD is collaborating with other Federal agencies in pilot studies to investigate the feasibility of a longitudinal birth cohort study under the auspices of the Developmental Disorders Working Group of the U.S. Task Force. The proposed study would enroll as many as 100,000 mothers during pregnancy and follow the children over time. EPA, NICHD, and CDC are the lead agencies in this effort.

A longitudinal study is expensive and would require a long-term commitment of resources and partnerships with other agencies. Relationships between exposure to environmental agents and adverse health effects are usually difficult to observe. If only a small percentage of the population experiences an effect, a large sample size is a prerequisite for testing hypotheses related to environmental exposures. Exposure levels are often difficult to quantify and other possible causes of the adverse effect are usually present.

More focused epidemiological and clinical studies will have varying costs and chances for successful outcome. Studies conducted in human populations should be carefully designed to ensure the maximum potential for identifying hazards and developing dose-response relationships. Collection of exposure data adequate to develop dose-response relationships is essential. One less costly and potentially effective study would be to test hypotheses using existing databases such as NHANES.

Priority and Rationale. High. Human studies are crucial to understanding whether children are more susceptible to environmental contaminants than are adults. The results of current Federal research into the causes of childhood asthma and the effects of exposure to organophosphates and PCBs, for example, may provide ORD with insights to guide the design of future studies of children.

Hypothesis-based human epidemiologic and clinical studies are necessary to confirm that adverse effects occur in humans, to improve extrapolations from animal data to humans, and to develop data to incorporate into risk assessments. Human studies should be conducted as needed for high-priority environmental agents and to assist in model development and validation. It is expected that human studies will be supported for particular high-priority agents and populations under program-specific research, as well as under the STAR program. Factors that improve the probability of observation of cause-effect and dose-response relationships, such as existence of sensitive biomarkers of effect, would also raise the priority of a human study. The strategy for the intramural Children's Health program is to focus on mode-of-action research and modeling and to incorporate clinical and epidemiology studies as necessary to reach this primary goal. Such studies should be hypothesis based and the biological basis for conducting the study should be clearly defined.

As discussed in Section 4.2.3, several Federal agencies in addition to EPA, including CDC, NCI, NIAID, and NIEHS, support epidemiologic and surveillance programs. A major objective of some of these studies (e.g., the Inner-City Asthma Study) is to identify relationships between exposures to environmental contaminants and adverse effects in children. Other studies, such as the CDC surveillance and epidemiology studies of developmental disorders in children in Atlanta, have not yet focused on environmental agents as risk factors. Through the Developmental Disorders Working Group of the President's Task Force on Children's Environmental Health and Safety, EPA, CDC, and several of the Institutes of NIH are exploring the feasibility of an interagency longitudinal birth cohort study to address children's environmental health and safety issues. The study would have a core protocol that would be followed for each member of the cohort and special studies that would allow for collection of additional data addressing specific issues of participating agencies. It is recommended that ORD continue with this process and explore implementation through the STAR program or through a proposal for an Initiative in FY2003.

Long-Term Outcome. Environmental agents and other factors contributing to adverse effects in children are identified, status and trends in children's health and exposure to environmental agents are characterized, and risk reduction methods are successfully implemented.

Short-Term Outputs. By 2005, ORD will

Analyze relationships between childhood exposures to air pollutants and respiratory effects under the

STAR program.

Analyze relationships between childhood exposures to pesticides and neurological effects under STAR program.

Develop, refine, and pilot methods for conducting a hypothesis-based longitudinal study of developmental disorders in a large birth cohort under the U.S. Task Force on Children's Environmental Health and Safety.

4.3.1.3. Multimedia, Multipathway Exposures in Human Populations

Description. Exposure studies are closely related to the epidemiological studies described in the preceding section. Epidemiology studies examine the link between exposure and disease. Exposure studies quantify exposure levels, investigate the reasons for exposure, identify sources of exposure, and provide information needed to devise strategies to reduce the risk. Ideally, epidemiological and exposure studies are combined. However, as the number of issues being studied increases, the number of measurements taken, questions asked, and time required can become intolerable to respondents, who will refuse to participate or drop out of the study. Consequently, human studies are carefully designed to limit respondent burden to an acceptable level and sometimes address only the exposure questions.

In a typical exposure study, samples of the child's environment (e.g., air, soil, dust), biological samples (e.g., blood, urine, feces, breath, hair), and personal exposure samples (e.g., personal air samples taken by a collection device worn by the child, samples of food and drinking water) are collected, as well as questionnaire data on activities, sources of exposure, and sometimes health status. Analysis is performed on the samples for suites of chemicals in one or more chemical classes.

Some current studies target the national population, but more typically, exposure studies focus on subgroups hypothesized to be highly exposed or on a city or region. National studies tend to have larger numbers of people in the sample, but to collect fewer samples per individual. The NHANES-IV study of children's exposure to pesticides, for example, will provide a urinalysis and responses to a few questions about pesticide exposure for about 1,800 subjects. More targeted studies collect and analyze samples from many media on fewer subjects. In NHEXAS, EPA sponsored studies of the general population and special subgroups in regional and local areas, including a six-State study in the Midwestern Great Lakes Region with a special study of children in Minnesota, a State-wide study in Arizona with a special study of people living along the U.S.-Mexico border, and a five-county study in and around Baltimore to test temporal variability in exposure. These studies asked more than 300 questions and collected thousands of samples on approximately 60 to 300 respondents per study.

Some critical questions can best be answered through probability-based exposure studies: What are children exposed to? Are particular age group, such as toddlers, more highly exposed? If so, what are the most important contaminants and exposure pathways for these age groups? What are the most highly exposed groups of children (e.g., farm children, inner-city children)? Does exposure vary with climate and region? How does exposure vary over time?

Feasibility. ORD has extensive experience in both the intramural and STAR programs in conducting and supporting exposure studies.

Priority and Rationale. High. It has been repeatedly hypothesized that children are more highly exposed to chemicals in the environment than are adults and that some age groups, such as toddlers may be more highly exposed than other children. However, data to test these hypotheses are limited. Probability-based exposure studies, where respondents are randomly selected to represent the study population, can be used to:

document exposures and determine whether certain age groups are more highly exposed to certain environmental agents;

provide baseline data on children's exposures by age to determine national exposure levels, evaluate status and trends, and identify and characterize highly exposed subgroups;

assess exposure and risk for specific populations of children;

assess total exposure to multiple chemicals via multiple pathways and determine the relative importance of the sources contributing to the exposure;

develop models to estimate multimedia, multipathway exposures; and

evaluate exposure variables in models, such as children's activity patterns.

Some exposure questions may be answered for specific chemicals through an analysis of existing data or data that will soon be available from NHEXAS, NHANES, and the STAR grants. As the questions are answered for specific chemicals, the information can be generalized to other chemicals to which children might be exposed by the same pathways, reducing uncertainty for entire classes of chemicals.

Exposure studies should be directed toward chemicals of high concern because of their known or

suspected hazards. In designing studies, investigators should consider the research questions of interest, the various types of information (health, exposure, source) that could be collected, and the uses of that information in risk assessment and risk management before deciding whether health data should be collected or whether health data should be foregone in favor of more data on sources, exposures, and exposure factors.

Because of the high cost of exposure studies, ORD should explore partnerships with other Federal agencies and the possibility of conducting some of this work under other ORD research programs such as the Safe Food program and Human Health Risk Assessment program.

Long-Term Outcomes. Status and trends in children's exposures to environmental agents are characterized using baseline data developed in this program. Highly exposed subpopulations of children are identified, important sources and pathways of children's exposures are delineated, and risk management interventions are successfully implemented.

Short-Term Outputs. By 2005, ORD will

- Conduct analysis of existing data from NHEXAS, NHANES, and STAR grants to provide answers to the extent possible on whether children are more highly exposed, which age groups are more highly exposed, and important sources and pathways.
- Develop new sampling protocols, questionnaires, and study designs based on previous studies of children's exposure.
- Design and initiate field studies to answer questions about children's exposure, with Federal partners where feasible.

4.3.1.4. Analysis of Factors Contributing to Exposure

Description. Exposure models allow risk assessors to generalize from existing data and estimate exposures to subpopulations and environmental agents for which data are not available. This capability is crucial to EPA's regulatory programs, where thousands of assessments are performed yearly, often for subgroups, locations, and environmental agents for which there are few data. Questionnaire-based surveys and laboratory studies are used to develop data for evaluation of exposure variables used in risk assessments.

For key exposure variables and factors, exposure measurement studies help to characterize distributions of values by age groups in the U.S. population and in important subgroups. Key variables include duration and frequency of exposure, dietary intakes, physiologic parameters, and many others. Some pathways of interest for children are exposure through pollutants on floors, in household dust, and in the small child's indoor breathing zone through inhalation, ingestion, and dermal contact; exposure to pollutants in soil (inadvertent ingestion, pica, inhalation while playing sports); exposure away from the home; and exposure to pollutants in water and sediment during swimming and wading through dermal contact and ingestion. It is especially important to determine how, when, and for how long children come in contact with media that have higher concentrations of toxic chemicals. For example, does baby food have more contaminants than a frozen dinner? How does the breathing zone for indoor air in a day care center compare to that in a typical residence? How often do children touch contaminated surfaces and lick or suck on their fingers, toys, and other objects? What is the distribution of ingestion rates of soil and dust among children in various age ranges? What are typical transfer rates of soil, dust, and pollutants from hand to mouth and what factors determine transfer rates?

Feasibility. It is feasible to conduct some of these studies under the STAR program. For example an investigator working under an EPA grant, is treating dogs with pesticides and measuring the dislodgeable residue over a period of time to address transfer of pesticides in flea treatments from pets to children. It is feasible to design and conduct studies to collect data on children's activities that parents and caretakers can easily observe. Some types of activities, however, such as ingestion of dust and soil by young children or trespassing by older children on waste sites are very difficult to document. Studies to collect data on dermal exposure and nondietary ingestion are difficult to design because of lack of validated measurement methods and models for these pathways.

Priority and Rationale. High. EPA needs data that can be used to improve risk assessments for children in the short term. Data on one or two key factors could have a substantial impact on reducing uncertainty in hundreds of assessments as well as in helping to design future studies. The variables need to be selected to maximize the reduction of uncertainty. For example, by studying the exposure pathways that are common to many chemicals and are highly applicable to children's activities, uncertainties could be reduced for a number of assessments through a single study. This approach could have a higher information return on investment than a detailed study of all pathways for one chemical. Some studies will need to be conducted within the ORD intramural program to obtain data for EPA risk assessments. Others could be conducted under the STAR program and under media-specific ORD programs. For example, FQPA resources could be used to study important exposure variables in the OPP Standard Operating Procedures (Versar 1997).

Long-Term Outcomes. Residential exposure factors for children will be characterized by age and sex for the national population, regional populations, highly exposed groups, and susceptible groups. Factors include activity patterns (time spent in a given activity and frequency of occurrence), soil and dust ingestion rates, factors reflecting

transfer of environmental agents from objects and surfaces children commonly touch, and factors related to ingestion of chemical residues on surfaces.

Short-Term Outputs. By 2005, ORD will

- # Identify high-priority exposure variables for study through preliminary exposure analysis.
- # Design and complete an activity pattern survey addressing high priority activity pattern issues for children.
- # Complete two studies on other high-priority exposure variables for children.

4.3.2. Risk Assessment Methods and Models

In order to make full use of research in risk assessments, EPA needs methods and models that will help generalize the results. This section discusses development of methods and models for using biological and exposure data in risk assessments for children.

4.3.2.1. Methods and Models for Using Biological Data in Risk Assessment

Description. Although there is a considerable amount of research directed at the biology of normal and abnormal development, these data have not been fully used in EPA assessments, in part because agreed-upon biological assessment methods do not exist. This research area is aimed at developing methods and models for routine use of biological data in risk assessment. A major focus is to develop models linking developmental effects at the tissue, organ, and system levels with the underlying interactions at the cellular and molecular levels. A second focus is to link PBPK and BBDR models to provide an integrated biological model of the exposure-dose-response continuum for children. Additional focus is on improving extrapolations of laboratory data to the human condition. The research area will consist of both short-term research to improve existing methods and models and long-term research to develop better, biologically based models that are able to make use of pharmacokinetic and mode-of-action data to relate exposures and effects. There is a need to develop exposure-dose-response models for vulnerable ages from conception through adolescence that reflect the effects of toxicant exposure during early development. This research area is closely related to the development of biological data for risk assessment (Sections 4.3.1.1 and 4.3.3.1). Existing biological data and the results of the laboratory program will provide the basis for the development of biological methods and models. As the assessment methods evolve, hypotheses will be generated and data gaps highlighted to help design future laboratory studies.

Feasibility. Although some prototype models could be developed through the STAR program, the greater part of this research will need to be done intramurally so that ORD has the ability to direct the research toward EPA's risk assessment needs. The resources required to address the above issues will be extensive. A suggested approach is to begin expanding ORD's capabilities in several critical areas (developmental toxicology, neurotoxicology, immunotoxicology, respiratory toxicology) with the specific aim of building from the considerable expertise that EPA has developed in these areas. Realistic financial and scientific resources should be made available, based on how current efforts in the critical areas can be expanded to the periods of child development of interest. These efforts should be coordinated with ORD's STAR program. The science team noted that a critical mass of scientists dedicated to this research area and maintained consistently over a long-term period is necessary to make progress in this area. An accompanying program of laboratory experiments as described above in Sections 4.3.1.1 and 4.3.3.1 must also be maintained.

Priority and Rationale. High. The rationale is presented in Section 4.3.1.1.

Long-Term Outcome. Broadly applicable PBPK and BBDR models will be routinely used to produce more accurate risk assessments for children, making full use of pharmacokinetic and mode-of-action data.

Short-Term Outputs. By 2005, ORD will

- # Evaluate the appropriateness of the assumptions in current EPA risk assessment approaches and how they may be supported or modified by biological data.
- # Develop and refine PBPK models applied to the developing animal, with the intent of eventual extrapolation to embryos, fetuses, infants, and children.
- # Develop and refine BBDR models applied to the developing animal with the intent of extrapolation to embryos, fetuses, infants and children.
- # Identify biological pathways, environmental factors, and their interactions that are important to understanding normal and abnormal development with a focus on incorporation of such information into predictive models of developmental toxicology and not solely on the generation of basic information on child development.
- # Define how experimental animal models mirror child development and develop appropriate correction factors for species differences.
- # Incorporate information from dose-response,

pharmacokinetic, and mode-of-action studies in animals into models that more accurately predict children's risks.

Develop first-generation methods, guidance, and data for broad application of modes of action and pharmacokinetics in EPA risk assessments for children.

4.3.2.2. Exposure Modeling and Use of Exposure Data in Risk Assessment

Description. Exposure models are needed when it is not possible to measure exposure directly, either because there is currently no way to make the measurement (e.g., concentration in target organs) or the measurement is too costly or too burdensome on the study subjects. Most exposure assessments for children at EPA rely on models rather than direct measurements of exposure.

Exposure models are used in research to help understand the relationships between exposure variables and to generate hypotheses to be tested in the field or the laboratory. They are used in risk assessments to identify and quantify risks that may require risk management actions. And they are used to identify sources of exposure for the purpose of developing and evaluating risk management options and regulations that reduce risk through approaches such as testing for adverse effects, limiting releases to the environment, and banning chemicals from commerce.

Models will be developed to assess pathways of exposure important to children. Models capable of estimating total absorbed dose via multiple pathways and predicting variability of individual exposures in a population whose members are simultaneously exposed to multiple chemicals via multiple pathways are needed to estimate children's exposure. Models need to be capable of performing probabilistic analysis and taking into account correlations among input variables. Exposure models that estimate dose by accounting for bioavailability need to be developed in concert with PBPK models (see Section 4.3.2.1) so that the continuum from exposure through disease can be assessed.

Feasibility. ORD has expertise and a program in exposure modeling that is turning its efforts toward children's issues. There are opportunities to combine resources from the Children's Health program with ongoing activities. Exposure modeling is also appropriate for the STAR program. An intramural effort is required to ensure that ORD addresses the specific issues of concern to EPA and to maintain the expertise to perform exposure modeling.

Development and testing of multipathway, multichemical models require large amounts of data. Accuracy depends heavily on the quality and representativeness of the data used to evaluate the input variables. This research area is dependent to a large extent on the current field studies being completed and the data made available to modelers and assessors in a timely fashion. Model development using literature and other existing data is feasible now.

Priority and Rationale. High. EPA is moving toward assessment of total exposure for pesticides and other toxic chemicals that are found in many environmental media – food, drinking water, breast milk, ambient air, indoor air, soil, and house dust, for example. The use of a multimedia exposure assessment process will improve the quality of children's assessments by reducing the uncertainty of the relationships among environmental measurements, biomarker measurements, human activities, and toxicological parameters. Distribution of exposures in populations is also of increasing concern to risk assessors and managers. Computer modeling approaches and consideration of multiple pathways is thus of high priority for children's research because these approaches are required to identify and quantify risks to children.

Long-Term Outcomes. A broadly applicable probabilistic, total exposure model, capable of linking to a PBPK model, will be available to estimate children's exposure to pesticides, producing more accurate assessments of children's exposure and reducing use of default values and safety factors in the assessment when sufficient input data are available.

Short-Term Outputs. By 2005, ORD will

Assess children's total pesticide exposure and refine existing exposure models using data from NHEXAS, NHANES, and the STAR program.

Analyze models in OPP Standard Operating Procedures (Versar 1997) for estimating exposure of children to pesticides, identify important pathways of exposure, and provide assessment support.

4.3.3. Methods for Studying Effects and Exposure in Humans and Animal Models

This section includes research to develop in vivo and in vitro methods of hazard identification for children and methods for measuring effects and exposure in children.

4.3.3.1 In Vivo/In Vitro Methods for Hazard Identification

Description. Research is needed on the development and validation of more sensitive and predictive test methods for identifying perturbation of normal development by environmental toxicants. The fields of developmental biology and toxicology are rapidly progressing to a more sophisticated understanding of the basic mechanisms of normal development and the way in which these can be

altered. EPA is focusing more on the use of mode-of-action considerations in risk assessment and has included the harmonization of cancer and noncancer approaches in its research strategies. Most recently, the National Research Council released a report entitled *Scientific Frontiers in Developmental Toxicology and Risk Assessment* (NRC 2000), which points up the importance of developing and incorporating methods that can help in defining and modeling mechanisms of developmental toxicity. These methods will not only reveal important information on the underlying mechanisms of toxicity, but will also provide a more complete analysis of the quantitative dose-response relationship of the exposure and effect.

This section should be viewed together with Sections 4.3.1.1, Biology of Toxicant-Induced Tissue and Organ Damage in the Developing Organism, and 4.3.2.1, Methods and Models for Using Biological Data in Risk Assessment. There will be overlap among these three areas in developing future risk assessment methodology. In addition, there should be careful coordination between these three areas and the research developed under Section 4.3.1.2, Relationship Between Exposure to Environmental Agents and Adverse Health Effects in Human Populations, to ensure that the emerging technology provides the most benefit to the human population and that human studies are developing databases compatible with laboratory databases.

Feasibility. This research is very feasible. ORD's intramural program has the expertise, and has been involved over the years, in the development and validation of sensitive and predictive test methods for agent-induced organ/system alterations. The STAR program also has supported this effort.

Priority and Rationale. High. Methods development has been and is an important part of EPA's overall research program. As noted above, viewed together with Sections 4.3.1.1, 4.3.1.2, and 4.3.2.1, this research will be important for EPA to continue its leadership in risk assessment and to maintain a current understanding of the databases that will be created with the emerging technology.

Long-Term Outcomes. Mechanism-of-action experimentation facilitates the extrapolation of animal and experimental model data to humans, enhancing ability to predict and study adverse effects in humans. Mode of action becomes an integral component of risk assessment. Advances in genomics/proteomics are incorporated into EPA's risk assessment methodologies.

Short-Term Output. By 2005, ORD will

Validate and apply currently available test methods and emerging methods in genomics/proteomics and molecular biological approaches, useful for understanding and elucidating mode of action, in developmental toxicity testing.

4.3.3.2. Methods for Measuring Exposures and Effects in Infants and Children and to Aid in Extrapolations Between Animals and Humans

Description. This research will provide measurement methods suitable for application in very young children to predict health effects currently not detected until later in development (i.e., school age). Earlier detection, when combined with exposure data, will facilitate the establishment of cause-and-effect relationships and provide information needed to develop intervention strategies. Development of supplemental work in laboratory animals for purposes of extrapolation and elucidation of underlying modes of action is also included. The research includes tests where the subject actively participates and tests where samples, x-rays, or other measurements are taken.

In some cases, such as evaluation of cognitive effects, methods currently available for application in school-age children will be adapted for use in younger subjects. In other cases, such as measures of sensory function (e.g., vision and hearing), available methods require further validation prior to use in risk assessment. Other research will involve the application of available techniques, such as eye-blink response and visual contrast, to compare responses of human infants and neonatal laboratory animals. Establishment of strong predictive relationships between animal tests and outcomes in humans may lead to the incorporation of additional evaluative endpoints in the standard test batteries used to evaluate pesticides and other chemicals under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and TSCA.

There is a need to develop biomarkers of effects that occur either only in young individuals (i.e., developmentally mediated) or with the first exposure (e.g., vaccination response). This research will focus on the development of biomarker assays for effects expected only in children and adaptation of general biomarker assays for use in young subjects. Laboratory animals will be used for the development of the assays. Validation will require samples from both animal and human subjects. Evaluation of biomarkers allows rapid and relatively inexpensive determination of potential effects following known exposure as well as general screening of selected populations for exposure and effect. For example, biomarkers of immune system development and competency may be useful in the prediction of increased susceptibility to asthma or allergy in very young children.

There is also a need to revise currently available biomarker assays for use in epidemiology studies focused on young children. In many assays, the medium (e.g., serum or urine) or needed quantity of the sample (e.g., 100 mL) makes a standard biomarker assay unsuitable for use in infants and young children. Methods adapted to provide data with minimal intrusiveness and discomfort are needed for young children, such as breath measurements and analytical methods for small

quantities of blood obtainable from a finger prick.

In addition, new methods are required for a range of exposure-related research issues. Because of the high cost of field studies, it is important to develop the most accurate and cost-effective methods of sampling and chemical analysis and of conducting questionnaire surveys. Consideration of the successes and limitations of past and current field studies and questionnaire surveys will lead to better methods. Issues such as the ability to detect and quantify substances above levels of concern in environmental and biological samples, the ability to analyze for speciation and metabolites, and the ability of sampling protocols to capture intermittent high exposures, longer-term average exposures, and personal total exposures need to be addressed. Cost-effective screening methods using questionnaires and simple sampling methods are also needed. Dermal exposure methods are needed for surface transfer, adhesion, adsorption, and ingestion from hand-to-mouth and object-to-mouth transfers of contaminants. Methods for improving survey response rates and for collection of activity data are needed. Development of a cost-effective, feasible protocol for biological and residential environmental sampling for children is needed.

Feasibility. Expertise to conduct biomarker research is available in the NHEERL Experimental Toxicology, Neurotoxicology, Reproductive Toxicology, Environmental Carcinogenesis, and Human Studies Divisions. ORD currently has a small program investigating the development of immune system biomarkers. An effort to develop cholinesterase assays requiring smaller quantities of blood, and therefore suitable for use in children, is in the pilot phase in NHEERL under the Sensitive Subpopulation program. Other agencies, such as CDC and NIEHS, have an interest in the application of this work but, other than specific cancer biomarker work underway at NCI, no focused research program is funded. CDC is developing methods to screen for multiple pesticides in smaller serum samples suitable for use in children. NERL develops methods for survey design and implementation and methods to measure contaminant concentrations in environmental media. The STAR program solicited proposals for research on biomarkers for the assessment of exposure and toxicity of children and will award grants in 2000.

Priority and Rationale. Medium. Better methods of sampling, analysis of samples, and test protocols for infants and children will support the collection and generation of better data for risk assessment. A separate program in methods development, although valuable, is somewhat less directly related to answering questions about risk than are the studies in which the methods will be used. In the Children's Health program, methods development needs to take place within a larger study with broader objectives. For example, methods development in exposure measurements, recruitment and retention of study participants, and assessment of neurobehavioral toxicity is being conducted as part of the pilot studies for the Longitudinal Cohort Study.

4.3.4. Risk Management Research and Risk Communication

This section discusses research to reduce environmental risks to children through development of control and cleanup technologies, prevention of risk, and approaches to community education and intervention.

4.3.4.1. Multimedia Control Technologies That Account for the Susceptibilities of Children

Description. This research area will build upon existing methodologies, which range from drinking water treatment to air emission controls to bioremediation and phytoremediation. The new focus on children's health issues highlights the dichotomy that often exists in risk management. Frequently, EPA must respond to a crisis caused by an environmental agent without having a risk assessment to provide the quantitative goals for risk reduction. For example, recent outbreaks of cryptosporidiosis, an infection caused by exposure to the *Cryptosporidium* microbe, usually through ingestion of contaminated drinking water or food, have required immediate efforts to remove the microbe from drinking water. Children, the elderly, and those with compromised immune systems are particularly susceptible to cryptosporidiosis, even to the extent of being at risk of death. Acceptable concentrations of *Cryptosporidium* in drinking water for children and other susceptible subpopulations have not yet been determined through risk assessment. Until such levels are established and the technology is available to achieve them, efforts will continue to refine and modify existing methods of drinking water treatment so that devastating outbreaks do not occur and children are protected. For example, ORD is working toward the goal of having water treatment methods that will reduce concentrations of protozoan oocysts and bacterial spores in raw water by six orders of magnitude.

Children are hypothesized to be particularly susceptible to pesticides, and nonpoint source runoff containing pesticides often contaminates areas attractive to children, such as streams and ponds. Research will be conducted on utilization of microorganisms and plants to treat nonpoint source contamination resulting from spray drift of pesticides and residual pesticides. Strategic placement of selected plants can offer means to interdict water flows contaminated with pollutant chemicals occurring as part of runoff or contaminated subsurface waters. Use of selected plants or microorganisms may result in reduction of chemical pollutants and provide active land restoration options.

In addition to these treatment technologies, particular attention will be directed to air treatment methods including treatments for the indoor environments in which children's inhalation exposure may be different from that of adults.

Feasibility. ORD has expertise in the development of engineering solutions to respond to children's health

problems. Research in control technology for water, air, and hazardous waste is conducted at the NRMRL.

Priority and Rationale. Low for the Children's Health program. Although it will contribute to reducing risks to children, research in control technology is not a specific children's issue and is more appropriately conducted under the ORD research programs for Air, Water, Hazardous Waste, and Pesticides and Toxics.

4.3.4.2. Methods for Reducing Exposure Buildup of Contaminants in Indoor Environments

Description. Children spend most of their time in indoor environments. Contaminants in air and on surfaces are expected to result in significant childhood exposures. Consumer products that are used indoors, such as pesticides, cleaning products, building materials, and floor coverings, may release toxic agents into a child's environment, causing exposure. This exposure can be reduced by cleaning up the contaminants after they have been released. It may also be reduced by designing consumer products that use or release smaller amounts of toxic materials.

Recent occurrences of household applications of methyl parathion, in which residents, particularly children, were placed at risk, serve as useful examples of the need for development of methods and processes to remove pesticides and other toxic compounds from structures. Children, especially infants and toddlers, may be highly exposed to chemicals that accumulate in carpets and construction joints and cracks near the floor. Accumulations of methyl parathion resulted in the demolition and disposal of many structures, including homes and day care centers, because no methods exist for the removal of chemicals from structures. High exposures can also be discovered during epidemiology and exposure studies, and ORD must be able to provide individuals and public health departments with assistance in reducing exposures where possible. This research area will focus on methods to reduce exposure to indoor contaminants through cleaning, encapsulation, chemical deactivation, and other approaches that will be more cost effective than demolition and disposal.

Feasibility. It is feasible to conduct this research in the ORD intramural program. Although no work is currently being done in this area, research in the areas of reactive gates and iron-sediment washing may be directly applicable.

Priority and Rationale. High. The impact of developing and applying specific procedures for dealing with accidental methyl parathion applications within homes will be highly significant. Recent episodes involving children have occurred in urban settings, primarily as the result of illegal application in homes by unlicensed pesticide applicators. In this specialized setting, the only appropriate solution was to evacuate the homes and destroy them. In a large-scale outdoor setting, chemical oxidation and neutralization methodologies have been successfully applied at the Gila River site in Arizona for treatment of methyl parathion, and it is feasible that these methodologies could be modified for use in a domestic setting.

In addition to these specific child-related problems with methyl parathion, recent studies in agricultural States have indicated that farm children are exposed within their homes to levels of pesticides that are seven to ten times higher than outdoors, specifically chlorpyrifos and endosulfan. Even though the most pressing need is for specialized techniques for treating methyl parathion in the confined setting of homes, it is quite plausible that these technologies could be further modified for use with other pesticides.

Development of cost-effective methods for reducing exposure and risk occurring via child-specific pathways such as dermal and hand-to-mouth contact has several advantages that make it a high priority for ORD. It will help the EPA Regions to provide solutions to the public for known and possible health risks to children in indoor environments. On a chemical-specific basis where risk reduction methods can remove exposure, such research may even avoid the need for further risk assessment research. In addition, ORD needs to be able to advise and assist individual study subjects in EPA-sponsored epidemiology and exposure studies who are found to be highly exposed within their residences, day care centers, and schools.

Long-Term Outcome. Broadly applicable methods for removing chemicals from residential environments and for preventing exposure in the residential environment (e.g., through encapsulation) are used by the Superfund program, EPA Regional Offices, State and local public health and environmental agencies, and others to achieve cost-effective cleanup to safe levels for children.

Short-Term Output. By 2005, ORD will

- **#** Develop a method to remove pesticides and other chemicals from building structures and carpets or to prevent exposure (e.g., through encapsulation), using methyl parathion as a prototype.

4.3.4.3. Communication of Risks and Development of Risk Reduction Techniques Through Community Participation

Description. ORD will support research on methods of education and intervention that encourage and offer assistance to members of communities working together to reduce risks to their children. Examples include projects where researchers work with the community to reduce children's exposure to pesticides at home and at school, intervention programs to help parents reduce the likelihood of asthma attacks in their children, community-based studies to determine

which types of intervention are most successful, dissemination of information to medical personnel, and studies of how to communicate risks and risk reduction methods most effectively to diverse groups of people. For example, dialogue could be initiated between scientists and the community regarding infectious disease threats to children such as E. coli strain O157.

An effective exposure or epidemiology study will involve the community being studied. Through civic and religious groups, teachers and day care workers, primary care physicians, and other community members, researchers can enlist the community in study design and implementation, advertise the study and recruit participants, and communicate results. It is important for researchers to understand and to be sensitive to cultural practices, to address anxiety related to the study or to real or perceived environmental hazards, and to assist local public health departments in dealing with problems that are found, such as the need for alternate food or water sources or for remediation and treatment interventions.

Feasibility. The eight Centers for Children's Environmental Health and Disease Prevention have projects in risk communication, intervention, and reduction. There is little, if any, expertise in this area within the ORD intramural program, except to the extent that individual scientists have dealt with some of these issues in epidemiology and exposure studies. In any future studies of children, ORD will provide for community involvement, communication of study results to the respondents, advice about lowering exposures, and cooperation with local public health departments to reduce risks where necessary.

Priority and Rationale. High. Developing cost-effective methods for reducing children's exposures and risks through education and community involvement has several advantages that make it a high priority for ORD. It will help EPA Regions to provide solutions to the public for both known and possible health risks to children. This research will also improve ORD's ability to advise and assist individual study subjects who are found to be highly exposed in EPA-sponsored epidemiology and exposure studies. It is recommended that research in this area continue to be conducted under the STAR program. Any intramural efforts should be planned as part of an exposure or epidemiology study, rather than a separate research program.

Long-Term Outcome. Through implementation of better methods of communicating scientific information about risk and working with communities to reduce risk, EPA strengthens its community-based risk assessment and risk management programs.

Short-Term Outputs. By 2005, ORD will

- Implement risk intervention programs in several communities and publish journal articles on effectiveness of risk intervention approaches (output of STAR program Centers for Children's Environmental Health and Disease Prevention).
- Compare methods for communicating risks of pesticides on foods (output of current STAR program grant).

4.3.5. Cross-Cutting Issues

4.3.5.1. Variation in Susceptibility and Exposure in Children

Description. Variation in susceptibility and exposure within an age group may be as important as variation between groups. Factors such as genetic traits, pre-existing disease, nutrition, behavioral traits, medications, coexisting exposures, sex, and ethnicity may result in great variation in risk within an age group. Epidemiological and 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. Exposure studies that first identify scenarios and pathways of greatest concern and then perform the research to fill the data gaps will also be useful.

This research area is closely related to the laboratory and field studies described in Section 4.3.1. Two exposed age groups might exhibit the same means, but their statistical variation may be different. Researchers need to look at the individuals in the high ends of distributions within age groups for clues to toxic mechanisms, adverse health effects, and high exposures.

This research area covers issues related to variation in susceptibility and exposure that are unlikely to be systematically examined under the research areas in Section 4.3.1, although they may be part of a study of a particular environmental agent or endpoint.

Feasibility. Variation in susceptibility and exposure to environmental agents is a major focus of ORD's Human Health Risk Assessment program. Many of the issues that might be addressed here are also being addressed in other research areas. Current and planned ORD exposure and epidemiology studies, for example, address exposure and sometimes effects in groups of children hypothesized to be highly exposed, including children living in agricultural areas and inner cities. Research into modes of action will of necessity examine why some individuals respond to exposure while other individuals exposed at the same level do not. For example, a compromised immune system in the form of allergies to environmental pollutants is being studied as a potential major cause of asthma. Interactions between environmental agents and genes will be important in studying modes of action and in using such data to assess risk.

Priority and Rationale. Medium. Given the limited

knowledge about which are the vulnerable ages and how and why individuals in these age ranges tend to be vulnerable, and the fact that many issues related to variability will be addressed in other research areas, the science team concluded that this area was not of as high a priority as other areas in its potential contribution to reducing uncertainty in risk assessment. Some of the research described in this area, such as variation related to genetic traits and high exposures, will be carried out under other research areas. As more becomes known about how children's vulnerabilities and exposures differ from those of adults, the priority of issues such as the impact of nutrition, behavior, and co-existing disease on susceptibility will increase.

4.3.5.2. Cumulative Risks to Children

Description. Children are exposed to many environmental compounds simultaneously. Mixtures of chemicals indoors, in the air, and on surfaces come from a variety of sources, including outdoor air and outdoor dust, indoor heating sources, building materials, and consumer products. Volatile organic air pollutants occur in mixtures with ozone. Mixtures of heavy metals and organic pollutants at waste sites can contaminate ground water, surface water, drinking water, and residential areas both indoors and out.

Historically, toxicity testing, mechanistic research, human studies, risk assessments, and many of EPA's regulations have been directed at single chemicals. There is little information on the effects on children of simultaneous exposure to many environmental agents, let alone any information on the toxicokinetics and toxicodynamics of chemical interactions in this population group. As a first step, research is needed to compare the individual toxicokinetics and toxicodynamics of known developmental toxicants to those of simple mixtures of two or three of the same chemicals in animal models. The selection of chemicals should be made on the basis of the availability of similar information on mature animals.

Methods of estimating both aggregate exposure to mixtures and dose-response relationships are not generally available and need to be developed.

Feasibility. EPA is starting to address the issue of cumulative risk, but methods are not well developed. EPA's Risk Assessment Forum is developing guidelines for cumulative risk assessment. ORD has sponsored studies of exposure to multiple chemicals and chemical classes under NHEXAS. Research on the effects of exposure to mixtures and how such data can be used in risk assessment will be a major focus of ORD's Human Health Risk Assessment program. The STAR program and NIEHS are co-sponsoring a research program on chemical mixtures in environmental health. OPP is developing a risk assessment of organophosphate pesticides with like modes of action. These efforts are not focused on children's issues, but rather on learning as much as possible about health effects of mixtures. Methods for cumulative risk assessment are not well developed.

Priority and Rationale. Medium. Given the current lack of knowledge about which are the vulnerable ages and how and why individuals in these age ranges tend to be vulnerable, as well as the general lack of knowledge about the biological effects of exposure to mixtures, this area is a lower priority for the Children's Health Program..

4.4. Linking and Summary of Research Areas

The preceding sections have focused on each separate research area. Table 2 is an overview of Section 4.3 containing a short description of each research area, the contribution of the research to EPA's risk assessments and risk management decisions, and its relation to other research areas.

Table 2. Summary of Research Areas

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Biology of Toxicant-Induced Tissue and Organ Damage in the Developing Organism (§4.3.1.1) High Priority		
Investigate absorption, metabolic pathways and rates, distribution and storage in the body, and elimination in sensitive age groups. Investigate biologic basis for age-related differences in target organ development, detoxification, repair, and compensation. Link effects at tissue, organ, and system level with underlying effects at cellular and molecular levels. Identify common modes of action for multiple developmental endpoints and chemicals.	Identification of more appropriate animal models for critical ages and endpoints. Improved extrapolation from animals to children. Improved risk assessment models relying less on data from whole animal toxicity testing and able to incorporate biologic data specific to children. Identification of classes of chemicals with the same modes of action.	The necessary data to develop biologically based dose-response models (§4.3.2.1) will be developed under this research area. Mode-of-action studies will help identify pollutants that are good candidates for human studies and may develop biomarkers that could be used in human studies (§4.3.1.2). Development, validation, and application of new test methods (§4.3.3.1) will be needed to conduct mode-of action research. This research also provides some of the basic science that will be necessary to understand the complicated issues of variability within susceptible age groups (§4.3.5.1) and cumulative risk resulting from exposure to multiple pollutants (§4.3.5.2).
Relationship Between Exposure to Environmental Agents and Adverse Health Effects in Human Populations (§4.3.1.2) High Priority		
Conduct studies of the relationship between exposure and effects in human populations. Explore feasibility of interagency longitudinal birth cohort enrolling children at birth and continuing through childhood or adolescence. Conduct hypothesis-based analysis of existing data sets to investigate relationship between exposure and effects in children.	Identification of hazards and important sources and pathways of exposure. Opportunities to test hypotheses related to human exposure and effects and the ability of animal testing and risk assessment methods to predict exposure and effects in children. Testing of intervention and risk reduction techniques. Collection of data for dose-response assessments.	Studies in humans will be indicated by results of research into the biological bases of adverse effects (§4.3.1.1) in order to verify predictions of response in children and to aid in developing models to extrapolate between animals and children (§4.3.2.1). Epidemiology studies and exposure field studies (§4.3.1.3) are closely related, and ORD should explore opportunities to combine these studies in such a way that the objectives of both types of studies are met. Methods of studying effects and exposure in humans (§4.3.3) will be used in human studies and often developed in the context of these studies. Investigators will need to work with communities and participants in conducting studies in human populations and will need communication methods (§4.3.4.3) and practical intervention methods to offer to individuals and local public health departments to deal with problems that may be uncovered (§4.3.4.2). Human studies designed to consider multiple chemicals have the potential to provide information on variability within age groups (§4.3.5.1) and responses to complex mixtures (§4.3.5.2).

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Multimedia, Multipathway Exposures in Human Populations (§4.3.1.3) High Priority		
Measure exposure in various age groups in the national population and selected subgroups hypothesized to be more highly exposed. Collect environmental concentration data, personal exposure data, biological samples, and questionnaire data.	Determination of when children are exposed and which age groups are more highly exposed and should be subjects of further study and assessment. Development of baseline data and data on distributions of exposure in the general population and highly exposed subgroups. Development of data for risk assessment of chemicals in study and data on activity patterns and other exposure variables for direct use in EPA risk assessments. Identification of important sources and pathways of exposure for risk management decisions. Collection of data for use in model development and predictions of exposure.	Information on the most highly exposed age groups and their patterns of exposure is useful in selecting relevant chemicals for pharmacokinetic and mode-of-action studies (§4.3.1.1), designing biological models compatible with actual exposure patterns (§4.3.2.1.), and designing human studies of the relationship between exposure and effect (§4.3.1.2). Ideally, epidemiologic and complex exposure studies would be combined in cases where it is possible to do so without sacrificing the ability to obtain the studies' objectives. Multimedia, multipathway measurement studies can often be designed to collect information on exposure variables (§4.3.1.4) and for use in designing and testing exposure models (§4.3.2.2) suitable for use in many risk assessments. The strategy recommends that methods of measuring exposure applicable to infants and toddlers (§4.3.3.2) be developed in the course of conducting these studies. Investigators will need to work with communities and respondents to conduct exposure studies and will need both communication methods (§4.3.4.3) and practical methods to offer help to individuals and local public health departments to deal with problems that may be uncovered (§4.3.4.2). Studies designed to consider multiple chemicals have the potential to provide information on variability in exposure within age groups (§4.3.5.1) and exposures to complex mixtures (§4.3.5.2).
Analysis of Factors Contributing to Exposure (§4.3.1.4) High Priority		
Develop data on distributions of values of key exposure variables within critical age groups, including activity pattern data, intake rates, and other factors that may cause higher exposures for children.	Development of data on exposure variables that introduce the greatest uncertainty into EPA risk assessments as identified by EPA Program Offices and Regions and ORD analysis.	Multipathway studies (§4.3.1.3) often collect data that can be used directly in risk assessment to evaluate exposure factors. However, this is usually a secondary objective of such studies. Data on exposure factors and how factors influence each other is key to developing exposure models (§4.3.2.2). Measurement methods are often developed (§4.3.3.2) in the context of studying particular exposure pathways and variables. Studies of critical exposure variables, such as food intake and ingestion of soil and dust, can provide insight into variability in exposures within age groups (§4.3.5.1).

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Methods and Models for Using Biological Data in Risk Assessment (§4.3.2.1) High Priority		
Develop integrated biological models of the exposure-dose-response continuum that routinely use pharmacokinetic and mode-of-action data in risk assessments for children. Develop models incorporating biological data to aid in extrapolation between animals and children.	Risk assessment models that take into account age-related differences in size, absorption, metabolism, distribution, and storage, and response to exposure at the cellular and molecular level. Improved ability to identify age-appropriate animal models and extrapolate from animals to children.	Data for model development are generated through mode-of-action research (§§4.3.1.1, 4.3.3.1). Human studies also provide relevant data for model validation and extrapolation between animals and humans (§4.3.1.2). Exposure studies (§4.3.1.3) often provide relevant data on uptake, body burden, and elimination. Exposure models (§4.3.2.2) and biological models are connected through PBPK modeling. It should be an objective of chemical-specific modeling to develop exposure, PBPK, and BBDR models that can be linked to connect effects with exposures through the PBPK model. With a sufficient input database, probabilistic models will be useful in predicting distributions of exposure, dose, and risk within an age range, allowing for estimates of variability (§4.3.5.1).
Exposure Modeling and Use of Exposure Data in Risk Assessment (§4.3.2.2) High Priority		
Develop models for important pathways of childhood exposure, models of total dose via multiple pathways, and probabilistic assessments combining exposure data on multiple pathways.	Identification and quantification of exposure and dose in the risk assessment. Identification and quantification of sources and pathways in order to develop appropriate risk management options. Estimation of child-specific exposures and aggregate exposures for children in EPA assessments where measurements must be supplemented with modeling approaches to fill data gaps.	Data for model development are provided through studies of exposure variables (§4.3.1.4). Human studies (§§4.3.1.2 and 4.3.1.3) may provide data to evaluate model variables and to develop and test exposure models. Exposure models and biological models (§4.3.2.1) are connected through PBPK modeling. It should be an objective of chemical-specific modeling to develop exposure, PBPK, and BBDR models that can be linked to connect effects with exposures through the PBPK model. With a sufficient input database, probabilistic models will be useful in predicting distributions of exposure within an age range, allowing for estimates of variability (§4.3.5.1). Probabilistic models will also be helpful in predicting distributions of dose from multiple chemicals via multiple pathways (§4.3.5.2)
In Vivo/In Vitro Methods for Hazard Identification (§4.3.3.1) High Priority		
Develop methods for identifying and modeling mechanisms of toxic action in children.	Development of animal models and protocols that will provide information on mode of action to be used in risk assessment.	Predictive tests will be developed as part of a program investigating the biological basis of risk (§4.3.1.1) and provide data for extrapolation between animals and children (§4.3.2.1).

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Methods for Measuring Exposures and Effects in Infants and Children and to Aid in Extrapolations between Animals and Children (§4.3.3.2) Medium Priority		
Develop measurement methods suitable for use in infants and toddlers, such as biological sampling methods and cognitive testing methods. Develop biomarkers of effect and exposure in young subjects.	Improved methods for collecting data on children that, when applied in a study, contribute to better data for risk assessment.	Some of these methods are likely to be developed in the context of laboratory studies and other human studies (§§4.3.1.1., 4.3.1.2, 4.3.1.3, and 4.3.1.4)
Multimedia Control Technologies (§4.3.4.1) Low Priority		
Develop control technologies for releases of substances to which children are believed to be exposed, including drinking water treatment for *Cryptosporidium*, control of air emissions, bioremediation of chemicals at waste sites, and control of pesticide releases in point sources and nonpoint source runoff.	Reduced risks to children and adults through control of a substance at its source.	Risk assessments based on the results of research described in other research areas help identify substances for which control methods are needed. Risk assessments also help set numerical targets for cleanup, effluent control, and other risk management options, and are used to assess the efficacy and benefits of the options.
Methods for Reducing Exposure Buildup of Contaminants in Indoor Environments (§4.3.4.2) High Priority		
Cleanup and remediate children's environments that have unacceptable environmental concentrations. Engineer consumer and building products to reduce release of environmental agents to the indoor environment.	Reduced risks to children in their homes and schools through remediation and pollution prevention.	Risk assessments based on the results of research described in other research areas will help identify substances for which control methods are needed. Risk assessments also help identify and evaluate remediation and pollution prevention options and their efficacy. Intervention methods can be used in conjunction with human studies (§§4.3.1.2 and 4.3.1.3) to assist residents and local public health departments when high exposure levels are found.
Communication of Risks and Development of Risk Reduction Techniques Through Community Participation (§4.3.4.3) High Priority		
Investigate intervention and education methods that enlist members of the community to work together to reduce risks to their children.	Reduced risks to children through intervention by parents, schools, medical personnel, and others in the community.	Risk assessments based on the results of research described in other research areas help identify substances for which intervention methods are needed. Risk assessments also help evaluate efficacy of community-based intervention. Intervention methods can be used in conjunction with human studies (§§4.3.1.2 and 4.3.1.3) to assist residents and local public health departments when high exposure levels are found.

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Variability in Susceptibility and Exposure in Children (§4.3.5.1) Medium Priority		
Investigate impact of factors on variability in response or exposure within the critical age range. Factors include preexisting disease, lifestyle and nutrition, genetic characteristics, sex, and ethnicity.	Identification and quantification of risk in susceptible and highly exposed subpopulations.	Many factors that influence variability within a critical age range will be assessed as part of studies to identify the age range and determine why that age range is critical. Studies of mode of action (§4.3.1.1) will often consider genetic and other susceptibility factors. Human studies as well as risk assessments often focus on special groups that are expected to be more susceptible or more highly exposed (§§4.3.1.2, 4.3.1.3, and 4.3.1.4).
Cumulative Risks to Children (§4.3.5.2) Medium Priority		
Investigate simultaneous exposures to multiple environmental agents and other stressors in a child's environment.	Data for assessment of risk of simultaneous exposures, including chemicals by the same route, chemicals with common modes of action by multiple routes, and all environmental agents and other stressors found in the child's environment.	The results of mode-of-action studies (§4.3.1.1) will be important in understanding effects of mixtures. Epidemiology and exposure studies (§4.3.1.2 and §4.3.1.3) often provide data on the multiple chemicals (although only a small fraction of all chemicals) to which infants and children are exposed. Dose-response methods for assessing toxicity of simultaneous exposures are critical to development of models and assessment methods for summing multichemical exposures and risks.

5. GUIDANCE FOR IMPLEMENTATION

The strategy will be implemented by ORD's three national laboratories and two national centers. Approximately 75% of the extramural resources of the Children's Health program are expected to be dedicated to investigator-initiated grants under the STAR program. The intramural program will be conducted by ORD scientists supported by the remaining 25% of the extramural funding. Research on children's issues performed to address specific concerns of EPA Program Offices, such as epidemiology studies conducted for the air program and exposure studies conducted for the pesticides program, will continue.

Criteria for selection of research projects and topics for extramural RFAs have been adapted from criteria proposed in the ORD Ecological Research Strategy (EPA, 1998h). ORD will undertake projects that meet the following criteria:

- The project is directly related to assessing or reducing risks to children.
- Intramural projects address research areas identified as of high priority in this strategy.
- Extramural STAR projects address research areas identified as of high or medium priority in this strategy.
- The project is consistent with a short- or long-term need of an EPA program. Long-term needs include the development of data, models, and methods for using biological information in risk assessment.
- The project allows ORD to establish or maintain a core competency and ability to meet future needs.

The expertise needed for this research program is distributed throughout ORD. Interdisciplinary research across a diverse and geographically dispersed organization such as ORD is a challenge. Collaborations across ORD laboratories and centers are essential to successful implementation. Figure 2 shows an example of the type of collaborations that the strategy encourages--a combined exposure and epidemiology study of children in a population along the U.S.-Mexico border conducted by NERL and NHEERL.

ORD scientists are also encouraged to become familiar with relevant research in the STAR program. There are opportunities for ORD scientists to participate in developing RFAs for extramural grants, reviewing proposals that are highly rated in external peer review, attending meetings of investigators, and even collaborating with investigators in appropriate situations. Figure 3 shows an example of a collaboration between ORD, the Minnesota Department of Public Health, a nonprofit consortium operating under NHEXAS, and a grantee under the STAR program.

Figure 2. Pesticides in Young Children along the U.S.-Mexico Border: A NERL/NHEERL Collaboration

This project assesses the relationship between health outcomes in young children along the U.S.-Mexico border and repeated pesticide exposures via multiple sources and pathways. NERL and NHEERL formed a partnership with a co-chair from each laboratory and joint planning, implementation, participation of staff, and peer review and publication.

Preliminary studies included review of existing data, development of geographic information system maps of the area, and a workshop to identify relevant health endpoints and appropriate epidemiology studies. Methods of screening of infants and children are now being identified and implemented. More extensive exposure screening will then take place, and if warranted by the results, an epidemiology study will be conducted to assess the relationship between exposures and specific health endpoints.

Coordination and collaboration with other Federal agencies are keys to successful implementation. One mechanism for collaborating with other Federal agencies is EPA's continued leadership of and participation in the U.S.

Figure 3: Pesticides and Children in Minnesota: A NHEXAS Study and a STAR Grant

Under the NHEXAS Program, ORD sponsored a study under cooperative agreement with Research Triangle Institute and the Environmental and Occupational Health Sciences Institute in which environmental, personal, and biological samples were collected and analyzed for pesticides and a questionnaire was administered for a sample of children in Minneapolis-St. Paul. The State of Minnesota also participated. An investigator at the University of Minnesota proposed a study under the STAR program for a population of the same age in rural Minnesota. At the grantee's instigation, the two studies used similar protocols so that the results can be compared.

Task Force on Children's Environmental Health Risks and Safety Risks. The Task Force, chaired by the EPA Administrator and the Secretary of Health and Human Services, was established by Executive Order in 1997 (U.S. Executive Order No. 13045 1997). The members of the Task

Force are Federal agencies with programs that address children's environmental health and safety, including EPA; ten Institutes of NIH; CDC; ATSDR; FDA; the Departments of Education, Labor, Justice, Energy, Housing and Urban Development, Agriculture, and Transportation; the Consumer Product Safety Commission; and the Office of Science and Technology Policy.

Through the efforts of the Task Force Working Group on Developmental Disorders, EPA, NICHD, NIEHS, and the National Institute of Dental and Craniofacial Research (NIDCR) are sponsoring a joint RFA to study susceptibility and mechanisms of human congenital malformations, including research on the contribution of genetic and environmental factors, identified at the molecular level, to the etiology, distribution, and prevention of disease within families and across populations. As discussed in Section 4.3.1.2, the working group is also actively exploring the feasibility of establishing a longitudinal birth cohort, as a joint effort of the concerned Federal agencies. Through the Task Force, EPA and the Department of Health and Human Services also developed a national strategy to address childhood asthma.

Other examples of EPA's collaborations include the Centers for Children's Environment Health and Disease Prevention cosponsored with NIEHS, sponsorship of special exposure studies in CDC's NHANES on urine levels of pesticides in children and adults and levels of persistent organic compounds in adolescents, and collaboration with CDC and FDA in the NHEXAS study of children in Minneapolis-St. Paul.

Information on Federal research and EPA activities can now be found on the Internet. The ORD home page provides electronic copies of publications, including research strategies. The OPP home page posts issue papers and deliberations of the OPP Science Advisory Panel on children's risk issues. Several agencies, including NIEHS, CDC, NCI, and the ORD STAR program, publish current budget requests and descriptions of their research programs and initiatives and provide lists of their intramural and extramural research. CHEHSIR, which reports on Federal research on children's environmental health and safety risks at a project level, is online (EPA 2000b). ORD managers and scientists are encouraged to consult these online sources to learn about Federal research and activities on children and to provide similar information on their Internet home pages.

Figure 4 summarizes principles for implementation of the strategy.

Figure 4. Guiding Principles for Implementation

- When designing a research study, investigators should consider the impact of the results on EPA risk assessments for children. Requests for Applications (RFAs) in ORD intramural and STAR programs should ask investigators to specify the potential impact of results on the EPA risk assessment process.
- A multidisciplinary research program that is coordinated across the ORD laboratories and centers is encouraged. RFAs for cross-laboratory/center intramural projects and fostering of contact between extramural grantees and ORD scientists are encouraged.
- Outreach, coordination, and partnership with other Federal agencies is essential, particularly in the areas of human studies and biological mechanisms of action.
- Toxicologists, epidemiologists, clinicians, and exposure scientists are encouraged to work collaboratively during all phases of research planning, development, and implementation.
- ORD needs to develop and maintain intramural expertise to be able to incorporate new data and methods into EPA risk assessments. Use of biological data in risk assessment is a high priority. A stable intramural research program with adequate support is essential to achieving this capability.
- Research across more than one endpoint point is encouraged where possible, such as research on mechanisms that can lead to multiple endpoints and endpoints affecting the same target organ.
- Risk reduction research and risk management goals should be considered throughout the course of this program.

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APPENDIX A. GROWTH AND DEVELOPMENT FROM BIRTH THROUGH ADOLESCENCE

At birth, most organs and systems of the body have not achieved structural or functional maturity. Physical growth and functional maturation continue through adolescence, with the rates of growth and functional maturation varying among the different tissues, organs, and systems of the body. There are specific periods or windows of vulnerability during development when toxicants can permanently alter the function of a system (Bellinger et al. 1987, Roder 1995). Although these critical periods often occur during gestation, some systems that continue to mature postnatally may be adversely affected by exposure to toxicants after birth. Organs and systems that continue to undergo maturation during infancy and childhood include the lungs, kidneys, and liver, and the immune, nervous, endocrine, reproductive, and gastrointestinal systems (Dobbing and Sands 1973, Hoar and Monie 1981, Andersson et al. 1981, Langston 1983). It is important to emphasize that a physiological or functional perturbation during a critical period of development increases the overall risk associated with childhood environmental exposure. For example, exposure to a neurotoxicant that adversely impacts cognitive function is integrated over a lifetime when applied to a child (Gilbert and Grant-Webster 1995).

Differences in susceptibility between children and adults may be due to either qualitative or quantitative differences in the toxicity of an environmental agent. Qualitative differences in toxicity between children and adults are a result of structural or functional alterations that occur as a consequence of exposure during a particularly vulnerable period of organ or system development. On the other hand, quantitative differences are due in part to age-related differences in pharmacokinetic and pharmacodynamic processes. The alterations induced may be immediately apparent or may manifest as delayed toxicity later in life as a result of short-term or low-level exposure during development. An example of delayed toxicity, due to enhanced susceptibility during development, is the increased incidence of vaginal and cervical cancers in the daughters of mothers who took diethylstilbestrol (DES) to prevent miscarriage during pregnancy (Herbst et al. 1972). Another example is the exposure of newborns to chloramphenicol which resulted in cyanosis, progressive circulatory collapse, and ultimately death, and which was attributed to decreased clearance of this chemical (Weiss et al. 1960). Decreased metabolic and excretory capacity of newborns has also been associated with the increased toxicity of other chemicals during the postnatal period. These include the "gasping syndrome" associated with benzol alcohol-preserved drugs (Gershanik et al. 1982) and neurological damage and death as a result of dermal application of hexachlorophene-contaminated talcum powder (Hay 1982). Cases of infant poisoning and death by hexachlorobenzene have also been reported following ingestion of highly contaminated human milk (Peters 1976). The consumption of mercury-contaminated fish by nursing mothers resulted in severe neurological disorders in their breast-fed infants (Amin-Zaki et al. 1980). The antibiotic tetracycline produces tooth discoloration and enamel hypoplasia as well as interfering with bone growth in infants prior to first dentition and in children prior to permanent dentition (Kacew 1992).

The lungs are the major portal of entry of volatile and airborne chemicals. The lungs are structurally immature in neonates and continue to mature during early childhood. Not until several years after birth is the full complement of mature cells in the lungs achieved (Langston 1983). There is little information available on the pulmonary absorption and bioavailability of inhaled chemicals in infants and children.

Ingestion is a major route by which infants and children are exposed to environmental chemicals. Absorption of chemicals from the gastrointestinal tract is influenced by factors such as the total mucosal surface area, pH, perfusion rate, blood supply, and the gastric emptying and intestinal transit time. All of these factors change during postnatal development (WHO 1986). Consequently, the absorption of some chemicals is greater in infants than in adults. For example, lead is absorbed better by infants than by adults (Ziegler et al. 1978). The rates of activation and deactivation of chemicals are also related to the stages of maturation and development of enzyme activity (Besunder et al. 1988).

Chemicals also enter the body via absorption through the skin. The surface area to body weight ratio of children is much greater than that of adults. As such, the total body dermal dose to a chemical for a young child can be as much as two to three times greater, on a per-unit body-weight basis, than for an adult (Wester and Maibach 1982). The EPA interim report on dermal exposure assessment (EPA 1992) indicates that this may be the primary difference between adults and children with respect to dermal absorption. The data available on childhood or comparable laboratory animal exposures via the dermal route are limited (NRC 1993).

The structure and function of the kidneys are immature at birth (Dean and McCance 1947). This is an important consideration, given that the elimination of most chemicals from the body occurs primarily via renal excretion. Both glomerular and tubular function increase with age in the infant, with glomerular function somewhat more advanced than renal tubular function in the neonate (NRC 1993). Reabsorption of chemicals from the tubular lumen into tubular cells also varies with age. Weak organic acids are more readily reabsorbed by the infant than the adult. Some metals

(i.e., cadmium, mercury, and manganese) depend on the kidneys for their elimination. The elimination of these metals by neonatal rats is less than that in adults (Kostial et al. 1978). Smaller proportions of absorbed lead are also excreted via the renal route in infants compared to adults (WHO 1986). Because chemical excretion by the kidneys is dependent primarily on glomerular filtration, tubular secretion, and reabsorption, a decrement due to the immaturity of any of these functions in the infant may result in delayed clearance of a chemical from the body. Consequently, an increased risk of toxicity may ensue from the prolonged presence in the body of a chemical or its active metabolite(s) (Braunlich 1981). Unfortunately, there is only limited information about age-related differences in elimination of environmental chemicals in experimental animals, let alone in humans (NRC 1993).

As with other organs, development of the liver involves a series of integrated structural and functional changes that continue postnatally. This includes tissue cell composition, hepatocyte differentiation, and the appearance of hepatic enzyme activity. After birth the parenchymatous cells outnumber all other types of cells in the liver (WHO 1986). Another important cell type in the neonatal liver is the hemopoietic cell, as the liver is the site of hematopoiesis prior to birth (Owen 1972). Biotransformation of organic chemicals via phase I and phase II metabolic reactions is generally slower in the neonate than in the adult. Consequently, degradation and elimination of chemicals that are dependent on these biotransformation reactions are generally reduced in infants compared with adults. Different isoenzymes and enzymes also mature at different ages. Maturation of mechanisms responsible for the biotransformation of organic chemicals varies for each reaction and chemical (Klinger 1982). Examples of toxicities associated with the newborn's decreased ability to conjugate and eliminate chemicals include chloramphenicol (Sutherland 1959), diazepam (Nau et al. 1984), and hexachlorophene (Tyrala et al. 1977).

Children are more vulnerable because they have less ability to metabolize and excrete some environmental pollutants. Young children have higher resting metabolic and oxygen consumption rates than do adults, which are related to a child's rapid growth and larger cooling surface area per unit weight (Hill 1964). During the first 4 to 6 months of age an infant gains weight more rapidly than during the rest of its life (Tanner et al. 1966). Adolescent children are also growing and adding new tissue at a more rapid rate than are adults. Because of rapid growth during infancy and puberty, accumulation of chemicals in the body may be greater than during adulthood, when growth is less rapid. Respiratory and circulatory flow rates as well as energy and fluid requirements are greater in infants and young children than in adults, giving rise to a greater potential for respiratory and intestinal exposure to chemicals per unit body weight (WHO 1986).

The nervous system is not fully developed at birth and continues to mature postnatally. During the first years of life, rapid brain growth occurs, with approximately 75% of the full complement of brain cells of all types present by approximately 2 years. The adult equivalent number of neurons is achieved by 2 years; however, complete myelination does not occur until adolescence. The brain weight of a 6-month-old infant is approximately 50% that of an adult's and approaches adult size by early childhood. In contrast, behavioral and physiological development of the brain continues into later childhood (Roder 1980, 1995; NRC 1993).

Because behavioral development is dependent on physical and functional maturation of the nervous system, chemical-induced toxic effects, which occur during critical periods of maturation, may permanently alter behavioral development. The various stages of nervous system development, which include differentiation, proliferation, migration, synaptogenesis and axonal growth, and myelination, all represent potential targets for chemical-induced neurotoxicity (Roder 1995). For example, myelination of nerve tracts in the spinal cord and peripheral nerves, which is a process that is not complete until puberty, may be affected by certain chemicals. Examples of the vulnerability of the developing nervous system include prenatal and early childhood exposure to lead, radiation therapy in children under 4 years old, and elevated serum bilirubin levels in neonates. Certain chemical toxicants that also have been implicated in causing effects on the developing nervous system include ethanol, mercury, polychlorinated biphenyls, and certain organophosphates (Schull et al. 1990, Chakraborti et al. 1993, Igata 1993, Needleman 1995, Jacobson and Jacobson 1996).

The developing endocrine system may be directly affected by chemicals or indirectly affected by chemical interactions, with some step of the regulating axis controlled by the hypothalamus, pituitary, or other part of the brain (McLachlan et al. 1981). The reproductive system, as well as other systems, can also be affected by chemical interactions with the neuroendocrine organs. For example, exposure of experimental animals to chemicals with estrogenic or androgenic activity during the early postnatal period can alter the sexual dimorphic pattern (Barraclough 1966). Exposure to chemicals with androgenic or estrogenic activity may also alter growth and time to onset of puberty (Saenz de Rodriguez and Toro-Sola 1982). Altered neuroendocrine function may also affect adrenal corticosterone release (Libertun and Lau 1972).

The immune system is not fully developed at birth. Consequently, full-term infants are immune deficient as compared with older children and adults in essentially all measurable immune parameters, resulting in their increased susceptibility to infections (Andersson et al. 1981). Both innate and specific immune responses of infants and children are suboptimal compared to those of adults. For example, natural killer cell activity is at about 60% of adult levels in newborns (Toivanen et al. 1981) and complement activity does not reach adult levels until about 6 months of age (Colten 1977). As for specific immune responses, certain T helper cell functions only reach adult levels by 6 months of age (Miyawaki et al. 1981). Whereas the ability of B cells to produce antibodies of the IgG and IgA classes increases with age, adult levels are reached only by 5 and 12 years of age, respectively (de Mauralt 1978). In addition, external factors play a role in the maturation of the immune system. For example, immune responsiveness and

maturation of newborns is influenced by active (i.e., vaccination) and passive (i.e., food, environment) exposure to antigens during perinatal development. Defects in the development of the immune system due to heritable alterations in lymphoid elements have provided clinical and experimental examples of the consequences of impaired immune development (Heise 1982).

While information on developmental toxicity following in utero exposure far exceeds that of developmental toxicity following exposure of the newborn and young animal, there are data that indicate the vulnerability of the developing animal to toxic-induced perturbations. It was recently recommended that testing be performed in appropriate animal models during the postnatal developmental period and that adverse effects that might become evident be monitored over a lifetime. It was also indicated that the nervous, immune, and reproductive systems were of particular importance for testing given the existing database (NRC 1993). For example, certain organophosphate and carbamate cholinesterase-inhibiting pesticides affect learning and behavioral development as well as development of the visual system. Other chemicals that affect the developing nervous system include methyl mercury, ethanol, methylazoxymethanol, hydroxyurea, phenytoin, trimethadione, retinoids, cadmium, tellurium, triethyltin, glutamate, and 6-hydroxydopamine (ILSI 1996). Rats exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin had reduced immune function that persisted through puberty and into adulthood (Faith and Moore 1977, Gehrs and Smialowicz 1999). A wide variety of drugs and toxic chemicals cause birth defects, abnormal reproductive development, and infertility in experimental animals following exposure during critical periods of development. Because sexual differentiation is dependent upon hormones and growth factors, a variety of drugs and chemicals with androgenic and estrogenic activity as well as adrenergic, serotonergic, and opiate activity can alter sexual differentiation. Examples of drugs and chemicals that cause developmental reproductive effects in experimental animals include DES, TCDD, o,p-DDT, methoxychlor, certain fungal mycotoxins, tamoxifen, chloredecone, certain PCBs, nitrofen, neuroactive drugs, and hexachlorophene (WHO 1986, NRC 1993, ILSI 1996).

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APPENDIX B. ORD RESEARCH PLANS AND STRATEGIES[1]

Name	Description
Final Plans and Strategies	
Final Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water (EPA 1997a)	This research plan was developed to describe research to support EPA's drinking water regulations concerning disinfectants, disinfection by-products, and microbial pathogens, focusing on key scientific and technical information needed. The research plan was developed by a team of scientists from EPA's national laboratories and centers within the Office of Research and Development and from the Office of Water. The plan is intended to provide guidance to both the intramural research program and the extramural grants program in terms of research priorities and sequencing of research.
Ecological Research Strategy (EPA 1998a)	The program goal is to provide the scientific understanding required to measure, model, maintain, and/or restore, at multiple scales, the integrity and sustainability of ecosystems now and in the future. The research strategy is organized around four fundamental research areas: (1) ecosystem monitoring, (2) ecological processes and modeling, (3) ecological risk assessment, and (4) ecological risk management and restoration.
Research Plan for Arsenic in Drinking Water (EPA 1998b)	This research plan addresses opportunities to enhance the scientific basis for understanding the health risks associated with arsenic in drinking water as well as research to support improved control technologies for water treatment. Better understanding of arsenic health risks will provide an improved science base for arsenic risk assessment and regulatory decisions in the United States. Further evaluation of control technologies will support cost-effective implementation of future regulatory requirements.
Strategic Research Plan for Endocrine Disruptors (EPA 1998c)	The plan addresses research needs in the areas of biological effects (both for human health and wildlife) and exposure assessment. Importantly, it also contains a "linkage" section that strives to integrate effects and exposure research to provide a more complete analysis of the risks than has generally been done in the past for endocrine disruptors.
Pollution Prevention Research Strategy (EPA 1998d)	The four long-term goals offered in the research strategy address: (1) tools and methodologies for making improved decisions related to pollution prevention, (2) technologies and approaches that are preventive or far less polluting than those currently in use, (3) verification of the performance of pollution prevention alternatives, and (4) economic, social, and behavioral issues related to pollution prevention.
Waste Research Strategy (EPA 1999a)	The goal of the EPA Office of Research and Development 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: (1) groundwater at contaminated sites, (2) soils and the vadose zone at contaminated sites, (3) active waste management facilities, and (4) emissions from waste combustion facilities. Associated technical support activities to assist EPA Program Offices, Regions and other stakeholders are also described.
Action Plan for Beaches and Recreational Waters (1999b)	The Beach Action Plan identifies EPA's multiyear strategy for monitoring recreational water quality and communicating public health risks associated with potentially pathogen-contaminated recreational rivers, lakes, and ocean beaches.

[1]This list contains final and draft ORD research plans and strategies as of July 31, 2000. Final reports and external review drafts can be found on http://www.epa.gov/ORD/WebPubs/final/

APPENDIX B. ORD RESEARCH PLANS AND STRATEGIES (continued)

Name	Description
ORD Strategy for Research on Environmental Risks to Children (EPA 2000).	The strategy describes the research directions that EPA's Office of Research and Development (ORD) will follow in its Children's Health program. The primary objective of the Children's's Health program is to conduct research to reduce uncertainties in EPA risk assessments for children, leading to effective measures to prevent/reduce risk.
Draft Plans and Strategies	
Mercury Research Strategy (EPA 1999c).	The strategy presents the goals and scientific questions and associated research areas and shapes the agenda for EPA's mercury research program.
Airborne Particulate Matter Research Strategy (EPA 1999d)	The strategy describes ORD's PM research in the areas of health, exposure, risk assessment, and risk management. The scope of the strategy corresponds to the dual responsibility of EPA to review the adequacy of the National Ambient Air Quality Standards (NAAQS) every 5 years and to achieve attainment of the NAAQS to protect public health and welfare. The EPA health effects and exposure research supports NAAQS review by providing scientific methods, models, and data needed for assessment of health risks from PM exposures. The EPA research to support implementation of PM standards is focused similarly on improving the methods, models, and data for attainment decisions.
Under Development	
Human Health Risk Assessment Research Strategy Global Change Research Strategy Air Toxics Research Strategy Environmental Monitoring and Assessment Program (EMAP) Research Strategy Drinking Water Contaminants Candidate List (CCL) Research Plan Asthma Research Strategy	

Source: This list contains final and draft ORD research plans and strategies as of July 31, 2000. Final reports and external review drafts can be found on http://www.epa.gov/ORD/WebPubs/final/.

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EPA. 1998b. *Research Plan for Arsenic in Drinking Water.* Washington, DC: Office of Research and Development. EPA/600/R-98/042.

EPA. 1998c. *Strategic Research Plan for Endocrine Disruptors.* Washington, DC: Office of Research and Development. EPA/600/R-98-087.

EPA. 1998d. *Pollution Prevention Research Strategy.* Washington, DC: Office of Research and Development.

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APPENDIX C. RESEARCH RECOMMENDATIONS

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

Differences Between Children and Adults

- # What are the structural and functional differences between neonates, children of various ages, and adults that can potentially influence toxicity of pollutants?
- # What are the specific periods of development when toxicity can permanently alter the function of a system at maturity? What systems continue to mature after birth?
- # What are the developmental stages of individual biochemical systems, tissues, or organs that enhance, diminish, or alter the infant's or child's sensitivity to the toxic effects of specific pesticides?

Selection of Appropriate Animal Models

- # Compare age-related physiological changes in humans and immature animals of various ages.
- # Develop appropriate organ-specific functional measures of adverse effect that take into account variable rates of organ development within and between species.

Toxicity

- # Are mechanisms of action comparable across species and between neonates, infants, children, and adults?
- # What are the differences in magnitude of response between juvenile test animals and infants/children?
- # How are neurodevelopmental effects and effects on the immune system in infants and young children measured and assessed?
- # What are the differences in metabolism and deposition in the infant, adolescent, and young adult?
- # How can physiologic pharmacokinetic modeling be used to forecast how information about metabolism in infant animals could be extrapolated to infant humans?
- # What is the comparison of toxicity in several representative classes of chemicals between adult and immature animals?

Estimating Exposures

- # What are the diets and drinking water consumption of infants and children and how do they differ from adult diets?
- # What are the foods most commonly consumed by young children?
- # What data are available to develop probability distributions of exposure factors for children?
- # What are the contributions of exposures from sources other than food and drinking water?

Estimating Risks

- # Consider physiological and biological characteristics of infants and children that influence metabolism and disposition and develop PBPK models for infants and children.
- # Develop biologically based models of carcinogenesis for infants and children.
- # Use benchmark dose for risk assessments for infants and children.
- # Use risk distributions rather than point estimates..

ILSI. (International Life Sciences Institute). 1996. *Research Needs on Age-related Differences in Susceptibility to Chemical Toxicants*. Report of an ILSI Risk Science Institute Working Group. Washington, DC: ILSI Risk Science Institute.

This workshop summarized current knowledge and provided lists of research needs in three areas: cancer, immune system effects, and neurotoxicity.

Cancer

- # Make better use of existing information on physiological differences between children and adults and information derived from common animal models.
- # Develop appropriate dose metrics for infants and children for given routes and exposure modes. Use PBPK models in understanding age-related effects on absorption and distribution in experimental animals and humans.
- # Develop a comprehensive profile of age-dependent changes in key metabolic enzyme systems of importance in activation and deactivation of carcinogens. Perinatal period and time around puberty and adolescence should be high priority.
- # Perform systematic collection data on changes in cell proliferation rates in various tissues as a function of age in humans and relevant experimental animals.
- # Study age-dependent changes in DNA repair capacity in various tissues from birth through adolescence and for rodent

models in normal populations and populations with heritable DNA defects.

Find biomarkers of carcinogenicity in children as compared with adults.

Conduct more studies of age-dependent effects of nongenotoxic compounds focusing on mechanisms.

Focus in future epidemiology studies on methodologies designed to increase the likelihood of detecting susceptibility differences between children and adults. Develop a better understanding of critical time periods for exposure, either for certain tumor types or for certain classes of carcinogens.

Examine well-characterized exposures associated with carcinogenesis for age-related differences in the effect. Consider feasibility of retrospective studies with data for chemotherapy regimes and appearance of second cancers.

Immune System Effects

Do chemicals that are known to be immune suppressive or elicit hypersensitivity in adult rodents have similar effects in immature animals? (Highest priority).

Assess the responses of children to known protein and/or chemical allergens.

Development of clinical laboratory procedures with sufficient sensitivity to detect changes in measures of immune status.

Wherever possible, identify and characterize genes important in immune ontogeny and immune response.

Neurotoxicity

Seek consistency with other reproductive /developmental study protocols.

Streamline current tests including neurotoxicity guidelines.

Seek understanding of basic developmental neurobiology and its application in risk assessment.

Develop ability to connect neurobiological function with neurobiological substrates is incomplete: Major categories of effects include deficits in cognitive, sensory, autonomic, affective, and motor functions.

Understand the relationship of the neuroendocrine system to the developing nervous system.

CEHN. (Children's Environmental Health Network). 1997. *1st National Research Conference on Children's Environmental Health: Research, Practice, Prevention, Policy.* Conference Report. Washington, DC: Children's Environmental Health Network.

This 3-day conference was organized into six sessions: asthma and respiratory effects, childhood cancer, neurodevelopmental effects, endocrine disruptor effects, exposure, and risk prevention and reduction through community involvement and education. The recommendations listed below are recommendations of the plenary group. Individual speakers also made research recommendations, which are summarized in the conference report. Most of the individual recommendations have been captured in the general recommendations.

General Recommendations

Study developmental processes and identify critical periods of vulnerability.

Study environmental exposures in early life and their relationship to the risk of adult disease and transgenerational effects.

Debate ethical and social issues associated with use of genetic and biomarker information.

Include communities in research agreements that incorporate respect, equity, and empowerment.

Asthma and Respiratory Disease

Conduct epidemiologic/biologic studies that address the role of environmental exposure to understand why asthma is increasing and why incidence is higher in urban minority children.

Develop methods to measure air and tissue levels of molds and mycotoxins and investigate their role in pulmonary hemorrhage among infants (recommendation of Ruth Etzel in paper on acute pulmonary hemorrhage).

Endocrine Disruptors

Continued focus on the relationship between endocrine disruptors and cancer, reproductive and developmental alterations, and neurological and immunological effects.

Improved understanding of basic endocrine function throughout all stages of human development.

Increase studies of exposure to environmental hormones and their effects at all stages of human development.

Childhood Cancer

Large biomarker-based case-control studies to evaluate suspect exposures.

Prospective longitudinal studies of children exposed to known or suspected carcinogens, including exposures in utero.

Study cancer susceptibility in children and the interaction between genetic alterations and environmental exposures in cancer etiology.

Neurodevelopmental Effects

Mechanisms of action of toxicants.

Health effects of mixtures of neurotoxins, especially pesticides.
Multigenerational studies of neurotoxicity.
Techniques to study gene-environment interactions of neurotoxicity.
Continue studies of neurotoxicity of mercury and PCBs using sensitive outcome measures.

EPA. (U.S. Environmental Protection Agency). 1998a. *U.S. EPA Conference on Preventable Causes of Cancer in Children.* Conference report. Washington, DC: Office of Children's Health Protection.

Four work groups, each chaired by two experts in the work group topic, developed research recommendations. The research recommendations appearing below are from the reports of the four work groups as published in EPA (1998c).

Epidemiology and Prevention

Establish a National Cancer Registry for Childhood Cancers, including information on exposures, especially pesticide exposure and dietary intake.
Expand large studies of childhood disease outcomes currently underway.
Develop improved techniques for analyzing clusters by redefining cancer occurring before age 5 as a birth defect.
Examine role of infection/viruses in childhood cancer.
Involve communities, families, and other stakeholders in designing and conducting studies.
Deliver results of research to physicians, nurses, teachers, communities.

Susceptibility Factors

Investigate differences in carcinogenic metabolism between children and adults, and differences among individuals that may predispose some to cancer.
Identify differences in DNA repair that are age-related or genetic. Differential organ development and cancer susceptibility. Why are only certain organs the sites of most childhood cancers? Why are there windows of opportunity for tumors to form in children?
Determine relationship between diet/obesity in children and cancer development.
Determine whether animal models appropriately reflect exposures and disease.
Increased support to clinical studies supporting prospective registries collecting social, dietary, and exposure factors, and stratification of disease subtypes by exposure and molecular marker studies.

Molecular Markers

Examine more closely the role of environmental exposures that occur preconception, transplacentally, and in the early years.
Develop sensitive biomarkers and validate in the laboratory.
Understand mechanisms reflected by biomarkers, their relationship to external exposure, and marker differences between children and adults.
Develop noninvasive, painless methods for collecting specimens from children.
Include application of biomarkers in hypothesis-testing studies in conjunction with exposure assessment, personal biomonitoring, and validated questionnaires.
Use biomarkers to identify exposed and sensitive populations.
Validate biomarkers for risk assessment.

Quantitative Measures of Exposure

More closely link exposure data and surrogates/endpoints.
Determine critical metrics researchers should be using (dose, range of dose).
Study children's activities by age, biology, or function.
Existing data needs to be used as baseline. IRIS-type National Tumor Registry needs to be created as a clearinghouse for cancer information.
Conduct exposure studies specifically for children.

NRDC. (Natural Resources Defense Council). 1997. *Our Children at Risk: the 5 Worst Environmental Threats to Their Health.* San Francisco, CA: Natural Resources Defense Council.

This document is directed toward legislators and regulators and toward parents, school systems, medical professionals, and communities. Most recommendations are for actions that can be taken now to reduce risks. However, it provides a few general research recommendations, which are as follows:

Food consumption surveys should include adequate sample sizes of children in the following groups: under 12 months, 13-24 months, 25-36 months, 37-48 months, 49-60 months, 5-10 years, and 11-18 years.
Measure levels of chemicals in food, air, water, homes, and schools. Identify exposure routes and develop effective

interventions.

- Monitor toxic substances in humans (blood and urine). Develop less costly methods of biomonitoring.
- Identify which toxins have a greater impact on children than on adults.
- Identify critical windows of vulnerability and study developmental processes during periods of vulnerability.
- Improve existing toxicity testing protocols.

EPA. 1998b. EPA *Workshop on the Assessment of Health Effects of Pesticide Exposure in Young Children.* Draft report. Research Triangle Park, NC: National Health and Environmental Exposure Laboratory.

Participants were assigned to workgroups corresponding to the disciplines considered relevant for pesticide research in children: neurobehavioral disorders, developmental disorders, pulmonary and immune system disorders, and childhood cancer. Participants were asked to recommend appropriate endpoints and study designs for human studies.

Neurobehavioral Work Group

Endpoints and Tests:

- Cognitive skills - Bayley Scales of Infant Development Mental Development Index.
- Motor skills - Bayley Scales of Infant Development Psychomotor Development Index.
- For older children, a wide range of intelligence, memory, learning, and motor skill tests are available.
- Sensory function tests – visual acuity, visual contrast sensitivity, tactile sensitivity.

Proposed Studies:

- Retrospective Acute, High-Exposure Study: Conduct a retrospective cohort study of a fairly small group of children with clearly defined, high-level exposure to determine unequivocally whether or not pesticide exposure at acutely toxic levels produces neurotoxic effects in young children. The study would address children who had been poisoned by pesticides.
- Cross-Sectional Chronic, Low-Exposure Study: If the first study indicates that acute high exposure causes neurotoxic effects, further study is warranted. Three chronically-exposed groups – high, medium, and low exposure – would be selected based on questionnaire responses with a total of 100 children, age 1.5 to 2.5 years. Purpose is to test whether children exposed at lest than acute levels have measurable adverse neurologic effects on psychometric neurologic testing.
- Longitudinal cohort study: If chronic low-level exposure is shown to affect neurobehavioral function, administer Bayley test and collect urine samples every 3 months starting at 1.5 to 2.5 years.

Developmental Work Group

This workgroup decided that in the absence of a clear understanding of the likely pathway and mechanisms by which pesticide exposure might influence child development, it would recommend health endpoints for study. Nine endpoints were identified.

Endpoints:

- Birth defects, stillborns, spontaneous abortions (priority ranking 1).
- Mental, motor, adaptation (priority ranking 1).
- Acute poisoning developmental sequelae (priority ranking 1.5).
- Growth (priority ranking 1.5).
- Language (priority ranking 1.5).
- Birth weight, gestational age (priority ranking 2).
- Social development (priority rank 4).
- Infant mortality, neonatal and postnatal (priority ranking 5).
- Puberty, age at menarche, secondary sex characteristics (priority ranking 5).
- Hearing (no ranking).

Proposed Studies:

- Prospective prenatal cohort study.
- Prospective case-control study of symptomatic children.
- Correlation between maternal and infant biologic samples.
- Geographic Information System (GIS) studies of infant health status.
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Immunology and Pulmonary Work Group

Endpoints:

- Upper respiratory infections.
- Acute bronchitis.

Asthma (reactive airway disease).
Interstitial lung disease.
Allergic diseases (allergic rhinitis, eczema, allergic bronchopulmonary aspergillosis).
Immunodeficiency.
Contact dermatitis.
Autoimmune disease.
Inflammatory bowel disease (added because of hypothesis of relation to disorder of immunological system; no known association with pesticide exposure).
Infectious disease (associated with immune disorders).
Adverse reproductive endpoints (Hypothesis that immunopathology in adult female may contribute to adverse reproductive outcomes).

Proposed Studies:
Pilot study of immunologic status and development of infants exposed to pesticides.
Longitudinal study of a birth cohort.
Survey of border families.
Case-control study of children exposed to pesticides.
Case-control study of children with hyper reactive airways.

Cancer

This work group focused on childhood cancer and considered several possible types of studies: (1) using existing databases, (2) performing an ecological study that would geographically compare pesticide usage and cancer incidence, (3) performing a case-control study that would identify cases and then determine if the cancers were associated with pesticide cancer, (4) conducting a prospective cohort study that might link exposure to a biomarker and then to cancer, (5) conducting a study that could link cancer-relevant biomarkers with pesticide exposure.

The work group's conclusion was as follows:

"....In all cases, the questions associated with the exposure assessment compromised the conclusions that might be done from the study....The workgroup...concluded and strongly recommended that the issues associated with proper exposure information be solved prior to conducting an analysis of the health outcome....

"....the group strongly recommended that resources be focused first on improving the approaches to exposure assessment. Also, other efforts are already underway investigating childhood cancers, developing databases, and evaluating approaches to using biological markers....Once the exposure assessment can be more adequately conducted, and the information about the cancer studies is available, it should be possible to revisit and make recommendations concerning studies to investigate the association of childhood cancers and exposures to pesticides."

APPENDIX D. FEDERAL RESEARCH ON CHILDREN'S ENVIRONMENTAL HEALTH

Agency	Examples of Collaborations with EPA on Children's Health Research	Other Major Programs of Interest
Department of Health and Human Services (DHHS) National Institutes of Health - conducts research in its own laboratories; supports the research of scientists in universities, medical schools, hospitals, and research institutions throughout the U.S. and abroad; helps in the training of research investigators; and fosters communication of medical information.	All Institutes of Health that are members of the U.S. Task Force on Children's Environmental Health and Safety are participating in an investigation of the feasibility of a federally sponsored longitudinal birth cohort study.	See the components of DHHS.
DHHS/NIH, National Cancer Institute - sponsors and conducts research on prevention, detection, and treatment of cancer, including research on biological, genetic, and environmental causes of cancer and clinical trials of treatments.	Agricultural Health Study - The goal is to establish a large prospective cohort of agricultural workers, their spouses, and dependents, that can be followed for 10 or more years, to evaluate the role of agricultural and related exposures in the development of cancer, neurologic diseases, reproductive and developmental outcomes, and other chronic diseases.	Clinical trials of treatment methods for childhood cancer (Children's Cancer Group, Pediatric Oncology Group, National Wilms' Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group)
DHHS/NIH, National Institute of Allergy and Infectious Diseases - provides the major support for scientists conducting research aimed at developing better ways to diagnose, treat, and prevent the many infectious, immunologic, and allergic diseases that afflict people worldwide.	Inner-City Asthma Study - This study examines respiratory symptoms and pulmonary function levels in children with moderate to severe asthma in seven communities. EPA is sponsoring monitoring of indoor and outdoor particulate matter and co-pollutants. Genetic Susceptibility and Variability of Human Malformations (STAR program with NICHD, NIDCR, and NIEHS) - This study examines relationships between genetic polymorphisms, gene-environment interactions, and birth defects.	
DHHS/NIH, National Institute of Child Health and Human Development - conducts and supports laboratory, clinical, and epidemiological research on the reproductive, neurobiologic, developmental, and behavioral processes that determine and maintain the health of children, adults, families, and populations.	Genetic Susceptibility and Variability of Human Malformations (ORD STAR program with NICHD, NIDCR, and NIEHS).	
DHHS/NIH, National Institute of Dental and Craniofacial Research - improves oral, dental and craniofacial health though science and science transfer.	Genetic Susceptibility and Variability of Human Malformations (ORD STAR program with NICHD, NIDCR, and NIEHS)	

APPENDIX D. FEDERAL RESEARCH ON CHILDREN'S ENVIRONMENTAL HEALTH (continued)

Agency	Examples of Collaborations with EPA on Children's Health Research	Other Major Programs of Interest
DHHS/NIH National Institute of Environmental Health Sciences - investigates the role and interaction of environmental factors, individual susceptibility, and age in human illness and dysfunction through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies.	Genetic Susceptibility and Variability of Human Malformations (ORD STAR program with NICHD, NIDCR, and NIEHS). Cosponsor of 8 Centers for Children's Environmental Health and Disease Prevention Research. (ORD STAR program). Agricultural Health Study (with NCI and NIEHS).	Environmental Genome Project - identification and establishment of a database of polymorphisms of environmental disease susceptibility genes.
DHHS, Centers for Disease Control and Prevention - conducts medical surveillance, reports public health statistics, seeks causes for public health emergencies, and conducts research.	Study exposure to pesticides and potential adverse effects in children living along the U.S.-Mexico border. NHANES IV study of children's exposure to pesticides and adolescents' exposure to persistent, bioaccumulative toxins.	Surveillance of childhood asthma and birth defects. NHANES IV - collection of data on health and nutrition in the U.S. population, including several thousand children and adolescents. NHANES study of lead exposures in children (with HUD).
DHHS, Agency for Toxic Substances and Disease Registry - advises EPA and others on public health impacts of hazardous waste sites, determines levels of public health hazard, conducts health studies in communities near sites, and supports research.	ATSDR conducts evaluations of the health of children and adults near Superfund sites and other hazardous waste sites. ATSDR makes recommendations to EPA on public health issues.	
Department of Housing and Urban Development - protects children in the home through regulations dealing with hazards such as lead-based paint and supports research on exposures and remedial actions.		NHANES study of lead exposures in children (with CDC).

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APPENDIX E. CROSS TABULATION OF RESEARCH QUESTIONS AND RESEARCH AREAS

	1. What are the adverse effects in children that are different from effects in adults?	2. What are the periods of development when adverse health effects in children can occur?	3. What are the best in vitro and animal models for identifying hazards to children?	4. To what environmental substances are children more highly exposed?	5. What are the relationships between exposures to children and adverse health effects?	6. How can laboratory and human data be used to predict responses in children?	7. What is the variability within members of the same age group?	8. What mixtures are children exposed to and what are the adverse effects?	9. What are the best methods for characterizing the uncertainties in risk assessments for children?	10. What are the most effective methods for communicating and reducing children's risk?
Mode-of-action research	∩	∩	∩			∩	∩	∩	∩	
Epidemiology and clinical studies	∩	∩		∩	∩	∩	∩	∩	∩	∩
Exposure field studies				∩			∩	∩	∩	∩
Activity pattern and exposure factor studies				∩			∩			
Methods and models for using mode-of-action data in risk assessment	∩	∩	∩		∩	∩	∩	∩		
Methods and models for using exposure data in risk assessment				∩			∩			
Methods for studying mechanisms of actions	∩	∩	∩							
Methods for measuring exposure and effects in children and to aid in extrapolation between animals and humans	∩	∩	∩	∩	∩					
Multimedia control technologies										∩
Reduction of exposure buildup of contaminants indoors				∩						∩
Education and communication of risk and risk reduction techniques										∩
Variation in human susceptibility and exposure	∩	∩	∩	∩	∩		∩		∩	∩
Mixtures and cumulative risk	∩	∩	∩	∩		∩		∩	∩	∩

APPENDIX F. APPLICATION OF RANKING CRITERIA TO RESEARCH AREAS

Research areas (priority)	Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats	Feasibility of conducting the research in the ORD intramural or STAR programs	The capacities and capabilities of ORD's laboratories and centers	Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments	Opportunities for collaboration with other Federal agencies and with other ORD research programs	Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research
4.3.1.1 Biology of Toxicant-Induced Tissue and Organ Damage in the Developing Organism (High)	High A greater understanding of the pharmacokinetics and mode(s) of action underlying agent-induced developmental abnormalities will facilitate the interpretation and extrapolation of animal and human data for risk assessment. This research will lead to more refined risk assessment approaches by linkage of environmental exposure with biologically effective dose at the cellular and molecular level.	High This research area is very feasible. Even though ORD's intramural program has the expertise to perform the pharmacokinetics and mode(s)-of-action research and apply it to children's risk assessment, these activities need to be expanded. Also, the success of this research area relies on linkage to the application of the data to model dose-response for risk assessment (4.3.2.1) and the validation and application of state-of-the-science methods (4.3.3.1).	Medium Although ORD has funded intramural developmental toxicology research over the years, the research in Section 4.3.1.1 goes well beyond what is currently being done. As such, it will require not only an increase in resources but also a long-term commitment to this research area. The STAR program has supported extramural research in this area and should continue to do so.	High ORD has excellent experimental research capabilities in this area; however, consideration should be given to bolstering the expertise of existing principal investigators in cutting-edge cellular and molecular biology and recruiting investigators with these skills. Also, ORD must maintain its scientific expertise for applying the data to risk assessment.	High There are several ongoing collaborations with other Federal organizations (e.g., NIEHS, NICHD, NIAID, CDC) and with other ORD programs, which undoubtedly will be expanded through support of this research area.	High Initially, information will be gained on pharmacokinetics with linkage to the underlying effects at the cellular and molecular levels for agent-induced developmental dysfunction. Over time, the data will be applied in risk assessment. This area will require a long-term commitment in resources (i.e., funding, equipment, personnel, etc.) in both the experimental and risk assessment arenas for it to be successful.

APPENDIX F. APPLICATION OF RANKING CRITERIA TO RESEARCH AREAS (continued)

Research areas (priority)	Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats	Feasibility of conducting the research in the ORD intramural or STAR programs	The capacities and capabilities of ORD's laboratories and centers	Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments	Opportunities for collaboration with other Federal agencies and with other ORD research programs	Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research
4.3.1.2 Relationship Between Exposure to Environmental Agents and Adverse Health Effects in Human Populations (High)	High Human studies are crucial to understanding whether children are more susceptible than adults, to identify and confirm adverse effects in human, to improve extrapolation between animals, and to develop data for use in risk assessments.	Medium to High Feasibility depends on the endpoints being studied and the availability of exposure data. Feasibility decreases for less common endpoints because studies must be very large to observe relationships and the large number of confounding factors.	Medium to High ORD has expertise in clinical and epidemiology studies, having sponsored and conducted many studies both in-house and through the STAR program. ORD also has expertise in exposure research. Size of studies may be limited by current amount of extramural resources available for this program.	High ORD is moving toward the integration of exposure and epidemiologic research in studies such as NAFTA and the Longitudinal Cohort Study. This direction will improve the utility of human study data for risk assessment through better exposure data.	High Through the U.S. Task Force, ORD is currently participating in a feasibility study for a longitudinal birth cohort as well as participating in collaborations through NHANES and the Inner-City Allergy Study. Many opportunities to join other studies are likely to arise.	High Studies can be designed with both short-term and long-term goals. The same study could both gather information on issues of immediate concern to Program Offices, test more speculative hypotheses, and generate hypotheses for future study.

APPENDIX F. APPLICATION OF RANKING CRITERIA TO RESEARCH AREAS (continued)

Research areas (priority)	Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats	Feasibility of conducting the research in the ORD intramural or STAR programs	The capacities and capabilities of ORD's laboratories and centers	Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments	Opportunities for collaboration with other Federal agencies and with other ORD research programs	Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research
4.3.1.3 Multimedia, Multipathway Exposures in Human Populations (High)	High Multimedia, multipathway exposure studies will reduce uncertainty by: (1) delineating sources and pathways of exposure; (2) replacing default assumptions with actual measured data; (3) determining which age groups are more highly exposed to certain environmental agents; and, (4) obtaining baseline data on children's exposures to characterize highly exposed subgroups and evaluate status and trends.	High ORD has the capability to conduct such studies as intramural and extramural programs, as evidenced by experience with TEAM, NHEXAS and NAFTA studies and STAR grants.	Medium to High In the short term, resources are sufficient to support limited work in this area, such as analysis of data from current studies, but not sufficient to support a new study in the intramural program and also conduct the other high-priority research described in this strategy. Resources are available in the STAR program to support field studies.	High This research provides opportunities to develop and maintain scientific expertise in designing, implementing, and analyzing multimedia, multipathway human exposure studies with the purpose of reducing uncertainty in risk assessments.	High Opportunities for partnerships are extremely important because resources are limited. However, other Federal agencies have similar interests (NIH, CDC, NIEHS, ATSDR, etc.), making partnerships feasible. In addition, ORD can leverage other ORD research programs, such as the FQPA program and the Human Health Risk Assessment program.	High This research provides opportunities to develop and maintain scientific expertise in designing, implementing, and analyzing multimedia, multipathway human exposure studies with the purpose of reducing uncertainty in risk assessments.

APPENDIX F. APPLICATION OF RANKING CRITERIA TO RESEARCH AREAS (continued)

Research areas (priority)	Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats	Feasibility of conducting the research in the ORD intramural or STAR programs	The capacities and capabilities of ORD's laboratories and centers	Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments	Opportunities for collaboration with other Federal agencies and with other ORD research programs	Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research
4.3.1.4 Analysis of Factors Contributing to Exposure (High)	High Analysis of factors contributing to exposure will reduce uncertainty in risk assessments by replacing default exposure factors with actual measured exposure variables and factors including micro-environmental and macroenvironmental activity patterns for children (time spent in various environments and frequency of occurrence), dermal transfer rates, inadvertent ingestion (hand-to-mouth activity, pica), inhalation rates by age and activity level, and ingestion consumption levels by age group.	Medium It is feasible to conduct some of these studies under both the STAR and intramural programs. However, innovative methods and techniques may be required to collect certain data, e.g., dermal exposure and nondietary ingestion. Some of these studies will need to be conducted by ORD intramural programs to obtain data needed for EPA risk assessments.	High Resources are available to conduct some of these studies under the STAR program, which can be supplemented with studies in other media-specific ORD programs. ORD is capable of developing an in-house program to develop exposure factors and variables, as evidenced by the production of the Exposure Factors Handbook.	High This research provides opportunities to develop and maintain scientific expertise in developing analysis of factors contributing to exposure with the purpose of reducing uncertainty in risk assessments.	High Opportunities for partnerships are extremely important because resources are limited. However, other Federal agencies have similar interests (CDC, NIEHS, ATSDR, etc.) making partnerships feasible. In addition, ORD can leverage other ORD research programs, such as FQPA to study important exposure variables in the OPP Standard Operating Procedures.	High This research area maintains a balance between short-term research and long-term, more speculative research. Short-term projects will emphasize the analysis of extant data including environmental media concentrations, personal exposure measurements, questionnaires, and biomarkers while long-term projects include development of future studies, e.g., inadvertent ingestion of soil, dermal contact rates and transfers, etc.

APPENDIX F. APPLICATION OF RANKING CRITERIA TO RESEARCH AREAS (continued)

Research areas (priority)	Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats	Feasibility of conducting the research in the ORD intramural or STAR programs	The capacities and capabilities of ORD's laboratories and centers	Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments	Opportunities for collaboration with other Federal agencies and with other ORD research programs	Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research
4.3.2.1 Methods and Models for Using Biological Data in Risk Assessment (High)	High Biologically based, dose-response models will lead to refined risk assessment approaches that no longer rely solely on whole-animal toxicity testing, but incorporate the growing knowledge of molecular mechanisms and their involvement in a toxic response. Based on these models, children's risk assessment will be able to better address such issues as complex mixtures, varying exposure patterns, and critical periods of susceptibility.	High The feasibility is very high. EPA's intramural research capability is very strong in this area and is recognized by the larger research community. Extramurally, there are a great many laboratories already working in this area. A potential limitation of the STAR program is that the research cannot be done in a cooperative manner with EPA investigators and may lack the necessary focus for ultimate application in risk assessment.	High This children's research strategy is significant step in defining a program specifically focused on children. The research in 4.3.2.1 will require a long-term commitment of resources. ORD has already made commitments through the general funding of its laboratories and the STAR program. A commitment to this specific program should be made, and opportunities to leverage the resources of similar programs in other Federal agencies and extramural groups should be identified.	Medium This is an area of major concern. ORD has a strong research capability in this area, but it must also maintain the scientific expertise to enable the use of the data in risk assessment. This will require an experience with traditional testing and risk assessment, coupled with an understanding of modeling and newer approaches in toxicology.	High In 2000, Federal public health agencies concerned with impacts of environmental agents (e.g., NIEHS, CDC) are focusing on mechanism of action research on topics such as gene-environment interactions. There will be many opportunities for development and use of models to assess environmental risks to children through collaboration.	High ORD has already begun moving its research in this area into risk assessment (e.g., benchmark dose modeling). Although this research area will take a long-term commitment, there will be short-term results that will be applicable to such issues as complex mixtures, varying exposure patterns, and critical periods of susceptibility, as well as to EPA's interest in harmonizing all approaches in risk assessment.

APPENDIX F. APPLICATION OF RANKING CRITERIA TO RESEARCH AREAS (continued)

Research areas (priority)	Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats	Feasibility of conducting the research in the ORD intramural or STAR programs	The capacities and capabilities of ORD's laboratories and centers	Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments	Opportunities for collaboration with other Federal agencies and with other ORD research programs	Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research
4.3.2.2 Exposure Modeling and Use of Exposure Data in Risk Assessment (High)	High The development of multimedia models and use of exposure data will improve the quality of children's assessments by reducing the uncertainty of the relationship between environmental measurements, biomarker measurements, human activities and toxicological parameters. By developing/evaluating multimedia models with actual exposure data more realistic predictions of exposure and risk are possible.	High The feasibility of conducting these studies is high. ORD has the capability to conduct such studies as intramural and extramural programs, as evidenced by experience with STAR grants and the intramural modeling program.	High Resources are available to fund intramural and STAR programs. ORD has demonstrated in-house expertise with university partnerships and modeling centers.	High This research provides opportunities to develop and maintain scientific expertise in developing, evaluating, and refining exposure models, and the analysis of exposure data with the purpose of reducing uncertainty in risk assessments.	High Opportunities for partnerships are extremely important since resources are limited. Other organizations have similar interests (CMA, ATSDR, ACPA, etc.), making partnerships feasible. In addition, ORD can leverage other ORD research programs, such as FQPA, to study important exposure scenarios such as the OPP Standard Operating Procedures.	High This research area maintains a balance between short-term research and long-term, more speculative research. Short-term projects will emphasize the refinement of current models (SHEDS, OPP's exposure scenarios, etc.), whereas long-tern projects include development of future models for multimedia cumulative exposure.

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4.3.3.1 In Vivo/In Vitro Methods for Hazard Identification (High)	High Development, validation, and application of state-of-the-science methods are essential to carrying out mode-of-action research (§4.3.1.1) and developing models and risk assessment methods incorporating mode of action (§4.3.2.1).	High This research area is very feasible. Even though ORD's intramural program has the expertise to develop methods for studying mode of action, these activities need to be expanded as part of an integrated program to support research described in §4.3.1.1. Also, the success of this research area relies on linkage to the application of the data to model dose-response for risk assessment (§4.3.2.1).	Medium Although ORD has funded intramural developmental toxicology research over the years, the research in §4.3.3.1. goes well beyond what is currently being done. As such, it will require not only an increase in resources but also a long-term commitment to this research area. The STAR program has supported extramural research in this area and should continue to do so.	High ORD has excellent experimental research capabilities in this area; however, consideration should be given to bolstering the expertise of existing principal investigators in cutting-edge cellular and molecular biology and recruiting investigators with these skills. Also, ORD must maintain its scientific expertise for applying the data to risk assessment.	High Most of the methods development related to genomics/ proteomics is taking place at NIH. It is expected that ORD will collaborate with these agencies in applying these methods to research questions related to risk assessment. There are ongoing collaborations in methods development and validation with other organization (e.g., NIEHS, WHO, CRADAs with industry), which undoubtedly will continue.	High In the short term, application of existing test methods and developmental-specific test methods will provide important information for children's risk assessment. But much of this research will involve a long-term effort that will fundamentally change the risk assessment paradigm.

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4.3.3.2 Methods for Measuring Exposures and Effects in Infants and Children and to Aid in Extrapolations between Animals and Humans. (Medium)	Medium Better methods of sampling, analysis of samples, and test protocols for infants and children supports better data for risk assessment. Methods development is often conducted in concert with a field or laboratory study. A separate program in methods development, although valuable, is somewhat less directly related to answering questions about risk than the studies themselves.	High Programs in development of test protocols for both animals and humans and methods of exposure sampling and analysis are part of ORD's core expertise.	Medium ORD's laboratories and the academic community have the capability and capacity to support these studies. The resources to devote to a program standing alone from a particular study are currently lacking.	High Methods development will continue to be a key component of ORD's effects and exposure program, through ORD's core Human Health Risk Assessment program and as part of specific studies conducted under the Children's Health program.	High ORD often works with agencies and programs such as CDC and NTP in developing testing protocols.	Medium Research in methods development in ORD is expected to be problem driven and directed at issues relevant to a particular ongoing study.
4.3.4.1 Multimedia Control Technologies That Account for the Susceptibilities of Children (Low)	Low Control technologies such as removing microbes from water and pollutants in indoor air will reduce risks. However, control technologies do not specifically address children's risk and therefore for this program are rated low.	High Very feasible, and the NRMRL has a strong capability to develop these technologies.	Medium ORD laboratories have the capability and capacity to perform this research. Extramural resources under the Children's Health program are not currently available.	Low The results of control technology research are not directly applicable to assessment of children's risks.	Low Collaboration in this area is not likely.	Medium By design, risk management research is mostly long-range.

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4.3.4.2 Methods for Reducing Exposure Buildup of Contaminants in Indoor Environments (High)	High This research area addresses remediation and prevention of exposure to children in indoor environments. It directed at the types of issues important with respect to the pesticides 10X factor, for example.	High Very feasible, and the NRMRL has a strong capability to develop these technologies .	High The NRMRL has both a capability and capacity to conduct this research.	Medium An important element of the EPA risk assessment process is the evaluation of competing risk management options and the analysis of the efficacy of control and cleanup methods. Supporting this research will help ORD to maintain the scientific expertise to perform a risk-based evaluation of management options.	High Opportunities exist to collaborate with other ORD research program such as the exposure and the risk assessment program in evaluating the efficacy of this research in reducing risk. Collaboration with State and local governments is also likely.	High This research area will have an impact in the short term by providing cleanup methods for particular chemicals, such as pesticides. In the long term, it will lead to more general technologies.
4.3.4.3 Communication of Risks and Development of Risk Reduction Techniques through Community Participation (High)	High Effective communication of risks and risk intervention methods is an important way to reduce risks, as well as becoming an increasingly important part of human studies (§§4.3.1.2 , 4.3.1.3).	Medium ORD has little expertise in conducting research in risk communication. However, ORD does conduct many studies in communities. The STAR program has supported risk communication research.	Medium Capabilities for research reside mainly in the STAR program. The Intramural program applies communication approaches but has no current capability to conduct such research.	High ORD should develop an expertise for risk communication and intervention if needed, as this is an important component of community-based research studies.	High Opportunities exist for cross-laboratory/center collaboration as well as collaboration with State and local government agencies and Federal agencies such as ATSDR.	Low This is a very applied area of research that, while key to a Children's Health program, is not likely to involve any long-term, speculative research.

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4.4.5.1 Variability in Susceptibility and Exposure in Children (Medium)	Medium Some of this research is integral to studying mechanisms of action and multipathway exposure. Other research related specifically to differences among children in the same age group is less important at this time than differences between age groups.	Medium This is one of the strategic directions of the ORD Human Health Risk Assessment program.	Medium to Low There are efforts underway in ORD that address variability in susceptibility and exposure issues; however, this effort is minimal.	Medium This research area may serve as a catalyst to increase interest in pursuing research that addresses variability in susceptibility and exposure. Expertise for this research area will be developed and maintained through research under §§4.3.1.1, 4.3.2.1, and 4.3.3.1.	Medium to High Opportunities are high in mode-of-action research/genetic polymorphisms, which will be conducted under research programs described in §§4.3.1.1, 4.3.2.1, and 4.3.3.1. Other opportunities for collaboration in areas such as impact of preexisting disease, life styles factors, etc., exist to varying degrees.	Medium This is an area that should be largely deferred until more basic questions on causes of qualitative and quantitative differences between age groups are answered.

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4.4.5.2 Cumulative Risks to Children (Medium)	Medium Research to develop information on mechanisms of action and methods to investigate age-related differences is needed to form a basis for research into cumulative risk.	Medium to Low Methods and data for conducting cumulative risk assessments for both children and adults are currently lacking. ORD is developing guidelines for cumulative risk assessment that will provide research recommendations. As more is learned about children's risk and work proceeds under the ORD HHRA Research program, feasibility of this research will increase.	Medium Some research is being conducted under the STAR program. Intramural research capabilities should increase as cumulative risk program grows under the human health risk assessment research program.	Medium Expertise for this research area will be developed and maintained through research under §§4.3.1.1, 4.3.2.1, and 4.3.3.1. Research in this area is a next step after basic questions are answered.	Medium Collaborations exist in the area of exposure measurement with CDC (e.g., measurement of multiple chemicals in biological samples).	Medium Short-term research opportunities are in the area of exposure, mainly analysis of data from field studies where multiple chemicals have been analyzed in many media. Most of the program is long-term and should be deferred until more basic questions on methods and impacts of multiple chemicals on health outcomes have been answered.