STRATEGY FOR RESEARCH ON ENVIRONMENTAL RISKS TO CHILDREN

External Peer Review Draft

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

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TABLE OF CONTENTS

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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
DNA	Deoxyribonucleic Acid
EMAP	Environmental Monitoring and Assessment Program
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
GIS	Geographic Information System
GPRA	Government Performance and Results Act
HUD	Department of Housing and Urban Development
IEUBK	Integrated Exposure, Uptake, Biokinetic Model
ILSI	International Life Sciences Institute
IRIS	Integrated Risk Information System
NAAQS	National Ambient Air Quality Standards
NAS	National Academy of Sciences
NCEA	National Center for Environmental Assessment (EPA/ORD)
NCERQA	National Center for Environmental Research and Quality Assurance (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
NIAID	National Institute of Allergy and Infectious Diseases
NIDCR	National Institute of Dental 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
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
UF	Uncertainty Factor
WHO	World Health Organization

EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) has pledged to provide 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 (USEPA, 1996a). 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).

Research Needs

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, sub-populations, disease end points, biomarkers of disease, mechanisms of action, exposure pathways, environmental contaminants, and physiological and biological characteristics affecting doses. Figure EX-1 shows the major end points and environmental health problems addressed in the reports considered in developing this Strategy.

Figure EX-1 Children's Risk Topics

Health End Points

- 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, end points, 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 contaminants on children's health.

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. The basic questions that must be answered are the following: Are children more susceptible than adults to environmental contaminants? What are the near-term and delayed consequences of childhood exposure? Why are children more susceptible? What are the characteristics of the contaminants to which children are more susceptible? Are children more highly exposed? Why are children more highly exposed? What are the characteristics of the contaminants to which they are more highly exposed? Are EPA risk assessments protective of children? What are the methods, models, and data bases that will improve risk assessments for children? What steps can be taken to reduce exposure and 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 that rank high were those judged feasible based on the current state of scientific knowledge and ORD's capacity and capability to perform the research, and which have the greatest potential to improve EPA risk assessments or to address directly the reduction of risks specific to children. The research areas and Science Team rankings are:

- Development of data to reduce uncertainties in risk assessment
  - Mode of action research (High)
  - Epidemiology studies (Medium)
  - Exposure field studies (High)
  - Activity pattern and exposure factor studies (High)
- Development of risk assessment methods and models
  - Methods and models for assessing does-response relationships in children (High)
  - Methods and models for using exposure data in risk assessment (High)
- Experimental methods development
  - Methods for hazard identification (Medium)
  - Methods for measuring exposures and effects in children and to aid in extrapolations between animals and humans (Medium)

- Risk management and risk communication
  - Multimedia control technologies (Low)
  - Reduction of exposure buildup of contaminants indoors (High)
  - Communication of risk (High)
- Cross cutting issues
  - Variation in human susceptibility (Medium)
  - Effects of mixtures and cumulative risk (Medium)

Implementation

The Science Team developed the following guiding principles for implementing the Strategy:

- When designing a research study, Investigators should consider the impact of the results on children's risk assessments. Requests for Applications (RFAs) in the ORD Intramural Program and the Science to Achieve Results (STAR) Extramural Grants program should ask Investigators to specify the potential impact of results on the EPA risk assessment process.
- A multi-disciplinary, research program that is coordinated across the ORD Laboratories and Centers is encouraged. Requests for Applications (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.
- The development and maintenance of ORD Intramural expertise, particularly in the areas of mode-of-action research and dose-response assessment, will ensure that EPA has the ability to incorporate new scientific knowledge into its risk assessments for children. A stable in-house research program with adequate support is essential to achieve and maintain capability.
- Research across more than one end point is encouraged where possible, such as studies of biological mechanisms that can lead to multiple end points and end points affecting the same target organ, tissue, or system.
- Opportunities for risk reduction research and activities 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) has pledged to provide a safe and healthy environment for children by ensuring that all EPA regulations, standards, policies, and risk assessments consider special childhood vulnerabilities to environmental toxicants (USEPA 1996a). Many environmental health threats to children may not be recognized because we don't 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. ORD and the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) charged a team of ORD and OPPTS scientists with developing this Strategy for Research on Environmental Risks to Children (USEPA 1997a).[1]

1.1 Scope

The charge limited the scope of the Strategy to research on children from birth through adolescence. The Science Team decided that the scope should be broadened to include the prenatal period. Exposures and effects to developing humans occur on a continuum from before conception through birth and post-natal maturation.[2] Under environmental conditions, the contributions of prenatal and postnatal exposures to risk may not be easily distinguished. The emphasis, however, continues to be on the postnatal period.

The ORD Children's Health Program was started in 1998 as part of an Administrator's

[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 (USEPA 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...."

Initiative aimed at insuring 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 heightened sensitivity in children to warrant further investigations into childhood exposures and responses to environmental contaminants (ILSI 1992, ILSI 1996, NRC 1993, WHO 1986). Several interconnected factors contribute to increased vulnerability. This Section provides a brief description of some of the documented vulnerabilities of children. A more detailed description of potential post-natal 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. 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. 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 in that they suffer adverse effects not experienced by adults. And they may differ quantitatively, in that effects occur at a lower exposure level or are more severe at the same exposure level.

Children may be more vulnerable to specific environmental pollutants because of differences in absorption, metabolism and excretion (Bearer 1995). 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 (Bearer 1995). 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, 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 end points, such as spontaneous abortions, stillbirths, malformations, early postnatal mortality, reduced birth weight, mental retardation, sensory loss, and other functional or physical changes. Lead, methylmercury, polychlorinated biphenyls (PCBs), ethyl alcohol, and ionizing radiation have been implicated in human studies as causes of developmental effects (USEPA 1991), while other chemicals have been implicated in animal studies. Lead and methyl mercury exposure in children is related to a variety of neurological problems including reading and learning disabilities, IQ deficiencies, impaired hearing, reduced attention spans, antisocial behavior, and hyperactivity that do not occur in adults exposed at comparable levels. Prenatal and perinatal exposure to PCBs has been associated with delayed development and learning disabilities in children.

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.

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 again. 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, dust mites, animal dander, and especially cockroaches 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.

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 in children with asthma. Maternal smoking is considered a high risk factor for Sudden Infant Death Syndrome (USEPA 1992).

The foregoing examples show a relationship between exposure to environmental contaminants 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. One can hypothesize a chemical where the response at the target site is identical for children and adults but the child receives a much higher dose for several reasons including higher exposures, higher absorption through the lungs and gastro-intestinal tract, inactive metabolic pathways that do not detoxify the chemical, differences in partitioning in the body due to different volumes of water and lipids, and different excretion rates because of immature kidneys. 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 Goals and Objectives

This Strategy was developed within the framework established in the EPA and ORD Strategic Plans (USEPA 1997b, 1997c). 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 was developed to address 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, sub-objectives, and annual milestones for purposes of reporting under GPRA. The ORD Children's Environmental Health Program is part of the ORD Sound Science Program in Human Health Risk Assessment under Goal 8, Sub-Objective 2.1.

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 health risk assessment, and pollution prevention and new technologies for environmental protection. As called for in the ORD Strategic Plan, plans have been developed for each of the six high-priority areas.[3] Plans have also been developed for sub-topics within the high-priority research areas, including arsenic, global climate change, the Environmental Monitoring and Assessment Program (EMAP), and hazardous waste. Appendix B contains descriptions of ORD research plans and strategies. The Children's Environmental Health Program, which is the topic of this Strategy, is a sub-topic under human health risk assessment. The objectives of this Strategy are shown in Figure 1.

1.4 Organization of the Strategy

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, coordination across EPA and the Federal Government, and EPA Program and Regional activities. Section 4 summarizes research recommendations from many sources, presents research questions, and outlines a research approach. Section 5 presents guidance for implementation.

[3]Some plans are final and others are in various stages of development and peer review. Several can be found on the EPA/ORD Home Page on the Internet: www.epa.gov/ord.

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 will lead to cost effective risk reduction through more accurate, scientifically-based risk assessments for children
 # Identify research to 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 5-year research agenda that identifies research priorities for the ORD Intramural and Extramural research programs
 # Provide guiding principles for implementation

2 APPROACHES TO RISK ASSESSMENT

This Strategy was developed within the framework of the risk assessment-risk management paradigm articulated by the National Academy of Sciences (NRC 1983) and covers a wide range of topics and disciplines. Members of the audience 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 how the research outlined in this Strategy will affect EPA Programs.

Risk assessment is the process used to understand and evaluate the probability of adverse effects on human health and ecosystems resulting from environmental stressors. 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 identify the sources of exposure and quantify 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 adverse effects will occur in exposed people (NRC 1994).

2.1 The Standard Regulatory Approach

The standard regulatory risk assessment of an environmental contaminant 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.[4]

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 work place, 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. Since 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 non-threshold effect. Non-threshold effects are modeled as linear relationships between response and dose across the entire dose-response curve. Dose-response relationships

[4]EPA assessment methods are described in a series of assessment guidelines for exposure and cancer and non-cancer end points (e.g., USEPA 1996b, USEPA 1996c, USEPA 1991).

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, ERG 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 non-cancer effects, there is a safe exposure, and that no adverse effects are likely to occur at exposures below that threshold. The standard procedure is based on the highest exposure at which no toxic effect was observed in an experimental study-- the NOAEL (no 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 (UF) 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 exposure at the target tissue in humans is most often 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 end point of concern in humans 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 since 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. The 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, 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, and where there is sufficient information to infer the shape of the dose-response relationship at low doses (AIHC 1999). 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 actual disease, and biomarkers of early effects may sometimes be more specific to environmental agents. A better understanding of the pharmacokinetics of environmental agents and their toxic modes of action 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 USEPA 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 non-cancer end points.

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, which link the target-organ dose to the adverse effect (Casarett & Doull's Toxicology 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 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 non-cancer assessments and away from a consideration of end points in isolation. Carcinogenesis is now recognized to embody changes in key genes that regulate the cell replication cycle and can be influenced by mutagenic and non-mutagenic 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 non-cancer effects. For example, effects of lead exposure are manifested at existing environmental exposure levels, and no apparent NOAEL exists (ERG 1997, ERG 1998).

Thus, the current scientific data base indicates that automatic separation of dose-response relationships for cancer and non-cancer 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 non-cancer 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 end points such as the various childhood cancers. If it were found, for example, that childhood cancer cases and birth defects of a particular target organ result from similar biological processes, these cases might be combined in an epidemiology study. The higher percentage of cases in the population would increase the ability to observe any relationship 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 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 recent years, Congress, the President, and the EPA Administrator have spoken on children's health and environmental safety through legislation and policy statements. In 1996, Congress enacted two statutes requiring that EPA give special consideration to children and other susceptible subpopulations when setting health-based standards: the Food Quality Protection Act of 1996 (FQPA) and the Safe Drinking Water Act (SDWA) Amendments of 1996.

The President has also emphasized children's environmental health and safety. 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 an Agency-wide policy to explicitly take into account health risks to children and infants from environmental hazards when conducting assessments of environmental risks (USEPA 1995a). The announcement of the policy was followed by a 1996, EPA's Administrator's report, *Environmental Health Threats to Children* and EPA's *National Agenda to Protect Children's Health from Environmental Threats* (USEPA 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.

This section describes implementation of these legislative and policy directives at EPA and elsewhere in the Federal Government. Section 2.1 discusses oversight and coordination, while Section 2.2 discusses regulatory and educational programs at EPA.

3.1 Oversight and Coordination

In 1997, the EPA Administrator established the Office of Children's Health Protection (OCHP). The mission of OCHP is to make children's health a fundamental goal of public health and environmental protection in the United States. OCHP works to ensure that EPA regulations take risks to children into consideration. Encouraging research to increase understanding of children risks is one of OCHP's main activities. OCHP also sponsors outreach and education programs on children's health.

The President's Task Force on Children's Environmental Health Risks and Safety Risks, 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 the National Institutes for Health (NIH), the three Centers and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), the Food and Drug Administration (FDA), the Health Resources and Service Administration, 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. The Task Force has commissioned working groups to develop Federal-wide research initiatives for FY2000 in four areas-- asthma, developmental disorders, childhood cancer, and unintentional injury. EPA is participating in the first three initiatives with the CDC and the NIH. Research recommendations from the three working groups are listed in Appendix C.

On January 28, 1999, a joint EPA and Department of Health and Human Services initiative to fight childhood asthma through a comprehensive national strategy was announced that includes new efforts to 1) implement school-based programs to teach children how to effectively manage their asthma; 2) invest in research to determine the environmental causes of asthma and to develop new strategies to reduce children's exposure to asthma triggers; 3) provide funds to states and providers to help them implement effective disease management strategies to lower hospitalizations, emergency room visits, and deaths from asthma; and 4) conduct a new public information campaign to reduce exposure to asthma triggers.

Through the efforts of the Task Force Working Group on Developmental Disorders, EPA and the National Institute of Child Health and Human Development (NICHD), the National Institute of Dental and Craniofacial Research (NIDCR), and the National Institute of Environmental Health Sciences (NIEHS) are sponsoring a joint Request for Applications (RFA) to study genetic susceptibility and mechanisms of human congenital malformations including research on the contribution of potential genetic and environmental factors, identified at the molecular level, to the etiology, distribution and prevention of disease within families and across populations. The Working Group is also actively exploring the feasibility of establishing a longitudinal birth cohort, as a joint effort of the concerned federal agencies.

The Task Force has developed the Children’s Environmental Health and Safety Inventory of Research (CHEHSIR), which is available via the Internet (CHEHSIR 1999). CHEHSIR contains descriptions of all relevant Federal research at the project level.

3.2 Implementation of Legislation and Policy in EPA Programs and Regions

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 OPPTS program. OPPTS provides protocols for these tests and recently issued an updated set of testing guidelines that will provide better information on health effects in children, particularly reproductive and developmental effects. Previous guidance has been updated and expanded to assess chemical effects on metabolism,

developmental neurotoxicity, and reproductive and prenatal developmental toxicity (USEPA 1998a). New guidance is provided for testing for toxic effects on the immune system. In addition to testing pesticides, OPPTS is developing a Children's Health Testing Program under Section 4 of the Toxic Substances Control Act (TSCA). Under this Program, chemicals to which children are likely to be exposed and which have insufficient toxicity data to support risk assessment will be tested.

Because of the risk assessment requirements in FQPA, the 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 insure that they are protective of children. FQPA 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 408(b)(2)(C)).

OPP has developed a draft policy for use of the 10-fold Safety Factor, which is currently undergoing external review (USEPA 1999a). The draft policy identifies a core set of toxicity tests that will be accepted as a complete toxicity data base for infants and children. OPP will consider the completeness of the toxicity data as part of RfD/RfC 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 data base will be made as part of the exposure assessment. This decision will be 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, these residual uncertainties will be considered in the risk characterization stage of the assessment.

The final decision on the FQPA Safety Factor will be made by considering together the use of Uncertainty Factors to account for data base uncertainty and potential toxicity to infants and children in developing the RfD/RfC, the recommendations in the exposure assessment regarding the need to account for incompleteness in the exposure data base, and any residual uncertainties and concerns identified in the risk characterization. On the weight of the evidence, OPP may decide to

retain the 10-fold Safety Factor, or remove, reduce, or raise it[5]

ORD supported OPP in the development of recommendations for toxicity and exposure data requirements for risk assessment through leadership and participation of Agency Working Groups addressing these issues (USEPA 1999b, 1999c). The FQPA data requirements were considered in developing this Strategy.

In other activities related to children's issues, OPP has developed standard operating procedures for assessing exposure by multiple routes (Versar 1997) and methods for conducting aggregate exposure and risk assessments (USEPA 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 concern and whether to regulate contaminants. Office of Water activities are focused on protecting infants and children from contaminants such as microbials and other toxicants in drinking water and recreational water and from contaminants in fish. The Drinking Water Health Advisory Program develops guidance for short-term exposures to drinking water contaminants to protect children against non-cancer health effects.

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 while playing. OSWER is expanding its efforts through such actions as conducting consistent,

[5]There are many important issues related to the FQPA Safety Factor that can't be addressed here. It is likely that OPP will make changes in 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/pesticides/SAP/

comprehensive assessments to evaluate the impact on children of lead-contaminated hazardous waste sites and is participating in the ATSDR Children's Health Initiative at Superfund 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 APPROACH

In writing this Strategy, the Science Team followed the approach outlined in the ORD Strategic Plan (USEPA 1997c). Research recommendations of conferences, work shops, and scientific reports were considered, as well as comments and recommendations by the ORD Science Council[6] and the ORD National Laboratories and Centers. Program Office and OCHP scientists contributed through membership on the Science Team. The Science Team formulated a set of research questions and research areas to address the research questions. Criteria were developed, and the research areas were prioritized according to the criteria. Section 4.1 discusses research needs and recommendations. Section 4.2 presents the research questions. Section 4.3 summarizes current research sponsored by EPA and other Federal Agencies. Section 4.4 describes possible research areas for the EPA Program and discusses the feasibility of conducting the research at EPA and the priority of the research. Section 4.5 discusses the impact of the research on risk assessment and management, links between the research areas, and the importance of establishing and maintaining collaborations across ORD.

4.1 Research Needs and Recommendations

Over the past two decades, many groups of experts have considered how exposures to environmental contaminants affect children. Hundreds of research issues have been defined, addressing numerous age groups, disease end points, biomarkers of disease, modes of action, exposure pathways, environmental contaminants, effects of physiological and biological characteristics on biologically-relevant dose, methods of risk communication and risk reduction, and the ethics of using children as subjects in research studies. Research on children's environmental

[6]The ORD Science Council is composed of the ORD Deputy Assistant Administrator for Science, the ORD Associate Directors for Health and Ecology, and other ORD science managers.

health risks is performed by members of many disciplines, among whom are physicians, classical and molecular epidemiologists, developmental toxicologists as well as 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 by the recommendations are shown in Table 1. Appendices C and D contain more detailed discussion of the recommendations from some of these sources.

4.2 Research Questions

1. Are there adverse effects from children's exposures to environmental substances 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 substances 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. Are children more highly exposed to some environmental substances? 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. How do exposure and susceptibility vary within age groups, and how can this variability be taken into account in risk assessments?

8. How can the effects on children of exposure to mixtures be measured and assessed?

Table 1. Research Recommendations and Needs

Source	Descriptions	Topic Areas
ILSI (1992)	EPA-sponsored Work Shop conducted by International Life Sciences Institute (ILSI): "Similarities and Differences Between Children & Adults" Invited investigators	
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 Work Shop: "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 •Endrocine disruptor effects •Exposure •Risk prevention and reduction through community involvement and education
USEPA (1998b) EPA's Rule Writer's Guide to Executive Order 13045	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
USEPA (1998c)	U.S. EPA Conference on Preventable Causes of Cancer in Children Invited speakers. Break out sessions where research recommendations were developed were open to the public.	•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

Table 1. Research Recommendations and Needs

Source	Descriptions	Topic Areas
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
USEPA (1998d)	EPA Work Shop: "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
USEPA (1998e) Annual Regional Risk Assessor's Meeting	EPA meeting: Session on risk assessment issues related to children's health assessments. EPA Regional Risk Assessors and interested EPA Program 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 (USEPA, 1999a and 1999b)	Task Force initiated by EPA to consider issues related to the 10-fold safety factor required by FQPA to account for potential increased susceptibility of children and how to implement the provision	•Toxicity Working Group •Exposure Working Group •Integration Working Group (Decision-making on 10X factor based on all of toxicity and exposure considerations)
U.S. Task Force established under Executive Order 13045 (See appendix C)	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

9. How can risks to children be characterized to account for uncertainty? How can research results, data, and risks be communicated effectively to risk assessors, risk managers, and the public?

10. What are the specific toxicants and pathways of exposure where risk management research will be effective in addressing known risks to children? How can risks to children be reduced?

4.3 Current Research

ORD conducts research on exposures to environmental substances and related adverse effects in children. Several other Federal Agencies also conduct studies to document the occurrence and explain the causes of childhood developmental disorder and disease. While much of the research of other Federal Agencies is relevant to EPA's mission, only a fraction of the Federal program investigates the role of environmental agents in causing adverse effects in children. This section describes some of the large Federal programs and studies directed at children's environmental risks and gives examples of the types of research projects underway at EPA. The inventory compiled by the President's Task Force (CHEHSIR 1999) provides a list of current Federal research on children's environmental health and safety risks at the research project level.

4.3.1 National Testing Programs

Under programs administered by OPPTS (section 3.2), 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 ongoing research on improved methods of chemical testing. The National Toxicology Program (NTP) also conducts toxicity testing. NTP consists of relevant toxicology activities of NIEHS, NIOSH, and FDA. NTP develops and conducts *in vitro* and *in vivo* tests for long-term carcinogenesis, reproductive and developmental effects, genotoxicity, teratogenicity, immunotoxicity, and other disease end points. NTP is responsible for one-third of all toxicity testing performed world-wide (NIEHS 1999a). EPA is a voting member of the Interagency Testing Committee (ITC) through which chemicals are nominated and selected for NTP toxicity testing.

4.3.2 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 hazard on non-cancer human health end points, including new and refined test methods for neurotoxicity, immunotoxicity,

and reproductive toxicity, and new predictive models to improve the biological basis for human health risk assessment, including 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 1999 ORD Extramural Grants Program, Science To Achieve Results (STAR), will support 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 Ecological Effects 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. The possibility that toxicodynamic or toxicokinetic mechanisms may underlie age-dependent responses to toxicants is also under investigation.

The mission of NIEHS is closely allied with that of ORD in studying the impact of environmental contaminants on public health. Under their extramural programs, EPA and NIEHS jointly sponsor eight Centers for Children's Environmental Health and Disease Prevention Research (USEPA 1999e). 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 1999a). The role of gene-environment interactions on human development and childhood disease could be studied under the Environmental Genome Program.

The National Cancer Institute (NCI) is the primary sponsor of research on the biology of cancer. Investigations are focused on identifying and understanding the genes whose activity allow 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's many activities include launching of the Cancer Genetics Network, a program that will link centers that test, monitor, and counsel individuals for genetic susceptibility, evaluate genetic and environmental factors that contribute to cancer, and speed the application of findings for clinical use (NCI 1999).

The National Institute of Child Health and Human Development (NICHD) supports research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children and adults (NICHD 1999). The NICHD research program includes research on the effects of exposure to contaminants on human development. EPA and NICHD are jointly sponsoring a 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.

4.3.3 Studies in Human Populations

The Federal Government conducts and sponsors many surveillance, epidemiologic, and clinical 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 and devising ways to prevent or reduce exposures where necessary. ORD is participating in the Inner-City Asthma Study, a prevention trial led by the National Institute of Allergy and Infectious Diseases (NIAID) aimed at developing intervention methods to reduce asthma morbidity in inner-city children and adolescents. This study identified factors associated with asthma severity, including high levels of indoor allergens (especially cockroach allergen), high levels of smoking among family members and caretakers, and exposure to high levels of nitrogen dioxide, a respiratory irritant. ORD is studying the relationship between air pollution and children's respiratory health in four Chinese cities. A 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.

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 chemical levels in blood, breath, and urine; and activity information (questionnaire, diary and observation/video taping). Some of these studies will focus on total exposure, sources of exposure, and differences in exposure between children and adults, and some also investigate specific health end points.

An investigation of exposure of pre-elementary school children to persistent organic compounds through ingestion, inhalation, and via dermal pathways has recently begun. 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 care givers in approximately 450 households will be studied.

ORD and CDC are supporting a number of studies in which health and environmental conditions along the U.S.-Mexican border are being evaluated in the context of risk to children. The goals of one such study are to evaluate whether children are at increased risk of adverse health effects from exposure to pesticides, to identify risk factors, and to develop intervention/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.

Other current ORD studies include the following: 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 end points.

Many Federal Agencies conduct surveillance of childhood disease and sponsor population-

based studies of exposure and disease in children that produce data and results vital to EPA's risk-based programs. CDC tracks asthma emergency room visits, asthma hospitalizations, and asthma mortality on a national level and in four geographic regions. Hospitals and clinics routinely report obvious birth defects to CDC. CDC also conducts a population-based survey among 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 (CDC 1999).

CDC's National Center for Health Statistics (NCHS) is conducting the fourth National Health and Nutrition Examination Survey (NHANES IV), a population-based survey of health and nutrition in the U.S. 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 (NCHS 1999).

Through the National Center for Environmental Health (NCEH), CDC conducts surveillance and epidemiology studies of human exposure to lead, radiation, air pollution, and other toxicants. NCEH is particularly interested in studies that benefit children. NCEH also has a laboratory with expertise in analyzing biological samples for environmental contaminants. NCEH is developing improved analytical methods for blood and urine that will allow analysis of more chemicals in the smaller samples that are provided by children.

NCI conducts population-based research on environmental and genetic causes of cancer and on the role of biological, chemical, and physical agents in the initiation, promotion, or inhibition of cancer. 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 sub-group 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. The vast majority of children with cancer in the United States are enrolled in Federal programs. NCI also supports the Childhood Cancer Survivorship Study, a study of nearly 20,000 survivors of childhood cancer designed to identify the status of children successfully treated for cancer between 1970 and 1986 in

order to identify the long-term effects of successful therapy. NCI also supports grants including laboratory and epidemiological studies of pediatric cancer survivors. These studies have not focused on possible environmental causes of childhood cancer.

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 1999). NIEHS is studying the prevalence of allergy-inducing materials in house dust (NIEHS 1999b). This study will include visits to 1000 homes selected to reflect the national housing stock, and will collect environmental samples and interview occupants.

4.3.4 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 non-dietary 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 non-dietary 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 and Biokinetic (IEUBK) model (USEPA 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 clean-up levels in residences (USEPA1998f). Work is ongoing to develop a modeling framework and an integrated group of models that can be easily modified for a variety of exposure assessment and risk characterization problems for children. The models will describe transport in the microenvironment and uptake into the body by multiple routes of entry exposure and dose-response models. 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. ORD is also analyzing existing data to characterize the variability of pharmacokinetic parameters within and between age groups.

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 non-carcinogenic health effects and slope factors or unit risks for carcinogenic effects (USEPA 1999f). Information on children is included where data are available. ORD Guidance documents such as the *Exposure Factors Handbook* (USEPA 1997d) provide analyses of existing data on children and recommendations for evaluation of exposure variables for use in risk assessments. A companion project is examining the differences in exposure to environmental contaminants in children of different racial, ethnic, and socio-economic groups. ORD supports the Developmental and Reproductive Toxicology (DART) Database in collaboration with NIH and FDA. DART is an online bibliographic data base 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.

4.3.5 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 reducing the amount of a substance released to the environment using engineering controls and treatment and clean up methods. 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 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 (USEPA 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. 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 these children 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 CHEHSIR (1999).

4.4 Research Areas and Priorities

A strategy for research in children's risk must be broad enough to address diverse environmental contaminants, end points, and special groups such as farm children and urban children. Priorities may shift rapidly as more becomes known about the impact of environmental contaminants on children's health. The Science Team decided that a research strategy directed at specific environmental problems and end points 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 President'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. To address these concerns, the Strategy is organized into 5 main topic areas encompassing 13 research areas that cut across all environmental problems:

- Development of data for risk assessment
  - Mode of action research
  - Epidemiology studies
  - Exposure field studies
  - Activity pattern and exposure factor studies
- Development of risk assessment methods and models
  - Methods and models for using mode-of-action data in risk assessments
  - Methods and models for using exposure data in risk assessment

- Experimental methods development
  - Methods for hazard identification
  - Methods for measuring exposures and effects in children and to aid in extrapolations

between animals and humans

- Risk management and risk communication
  - Multimedia control technologies
  - Reduction of exposure buildup of contaminants indoors
  - Education and communication of risk and risk reduction techniques
- Cross-cutting issues
  - Variation in human susceptibility
  - Mixtures/cumulative risk

The next step was to consider which organizations could best conduct the research. The Science Team considered the following possibilities for each research area:

- ORD scientists as Principal Investigators, often in collaboration with scientists in government, academia, and private firms through interagency agreements, co-operative agreements, and contracts (the Intramural Program)
- Academic scientists as Principal Investigators under grants funded through ORD's Science to Achieve Results (STAR) Program
- Scientists at other Federal Agencies, without active ORD collaboration or support

ORD's Intramural Program is organized into three National Research Laboratories and a National Assessment Center: the National Health and Environmental Effects Research Laboratory (NHEERL), the National Exposure Research Laboratory (NERL), the National Risk Management Research Laboratory (NRMRL), and the National Environmental Assessment Center (NCEA). ORD's STAR Program is administered by the National Center for Environmental Research and Quality Assurance (NCERQA).

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 (USEPA 1997c). The ORD criteria were found to be specific to a particular health effect, a particular method or model for assessing risk, or a particular risk management technique. They are problem-specific and do not apply well 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 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 that may identify previously unknown hazards and exposures to children or change EPA's way of doing risk assessments and ultimately produce more accurate and less costly assessment procedures.

The priorities of the ORD Children's Health Program are summarized in Figure 2. This Section describes each research area and discusses how the research could be conducted in ORD. The Strategy indicates which research areas are of high priority for the Intramural Program and the STAR Program. For the high priority areas, 5-year outcomes are provided and the potential impact on EPA risk assessments is discussed. Estimates of extramural resources for the in-house contribution to the research area are provided. EPA personnel for the in-house program will come from the current staff working in these disciplines. Resources for the Extramural Program are not estimated. It is assumed that grants will be solicited through RFAs, each RFA having a funding pool of about $2 million to $10 million, and that larger RFAs will be co-sponsored by another Federal Agency.

4.4.1 Laboratory Studies and Surveys

This section describes the laboratory and field research that will provide the data base 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.

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

Description

Sound biologic data are needed to facilitate the interpretation and extrapolation of animal and human data for risk assessment. While 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. Efforts will be made 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. 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

Figure 2. Research Priorities

 # Survey, compilation, and assessment of existing data on children to identify important hazards and exposures, generate hypotheses and help design research studies, and provide age-specific data for EPA risk assessments (Section 4.4.2.1, 4.4.2.2)

#Pharmacokinetic/mode-of-action studies to elucidate transport, transformation, and biological interactions of environmental contaminants in juvenile animals and children (Section 4.4.1.1)

 # Methods and models for using biologic data in risk assessments that will allow better extrapolation between animal models and children and better use of age-specific data in risk assessment (Section 4.4.1.1, 4.4.2.1)

 # Data analysis and exposure studies to determine whether there are differences in exposure among younger age groups, and, if so, which young age groups are most highly exposed (Sections 4.4.1.3)

 # Exposure models for children and studies to provide the data for the models, including activity pattern and other data (Sections 4.4.1.4, 4.4.2.2)

 # Methods to reduce exposure to environmental contaminants within residences and other indoor environments where children are more likely to be highly exposed (Section 4.4.4.2)

 # Methods to work with communities in designing and conducting studies, communicating results, and taking action to mitigate exposures or risks where necessary (Section 4.4.4.3)

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 and Resources

ORD has the expertise to study the pharmacokinetics and modes of action that result in adverse effects in children. As discussed in Section 4.3.2, ORD supports ongoing research in both the Intramural and the STAR Program in this area. 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.

Minimum extramural resources to support an in-house program are $750-850K per year due to the high cost of equipment, reagents, and supplies. The potential for success is good provided consideration is given in designing the research program to how the data would be used to model dose-response for risk assessment (see Section 4.4.2.1).

Priority and Rationale

High. These studies and the methods and models described under Section 4.4.2.1 are critical to increasing the use of biological data in children's risk assessment, particularly in selecting appropriate animal models for children's exposures and end points and for improving extrapolations from animals to children. Current approaches in risk assessment are based 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 especially in the case of the developing child, over changing critical periods of susceptibility. 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. Moreover, it should be possible to develop testing paradigms using both *in vivo* and *in vitro* approaches that are more biologically based and address such issues as complex mixtures, varying exposure patterns, and critical periods of susceptibility. This research will require a long-term commitment of resources. Although research in this area can also be conducted under the STAR Program, it is essential to maintain and expand ORD capability through a strong in-house program to support the focused research necessary to improve EPA risk assessments.

Five-Year Outcomes

By 2005:

- # Better quantitative characterization of dose to target tissue in developing organisms with the goal of replacing default assumptions in children's risk assessments.
- # Linkage of developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels. Initial development of biologically-based predictive models.
- # Development and validation of 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.
- # Validation of *in vitro* assays (using either animal or human biological material) for inclusion in the overall risk assessment process.

4.4.1.2 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 pre- and post-natal toxicant exposure and altered development, maturation of organs/systems, and developmental disorders including childhood cancer, asthma, neurotoxic effects, reproductive effects, birth defects, and other developmental disorders. 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 potential 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 child 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/system of concern.

One such study is a case-control study of exposures 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.

Alternately, 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. 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 and Resources

Human studies of the cause-effect and dose-response relationships between environmental contaminants and adverse health end points are most feasible for ambient contaminants such as air and drinking water pollutants and 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 end points. 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 USEPA, 1998d, in Appendix D). As discussed above, the STAR Program is funding eight Centers, each of which includes an epidemiology/intervention study.

A longitudinal study is expensive and would require a long-term commitment of resources and partnerships with other Agencies. Generally, such studies have not focused on environmental contaminants, but have looked at intake of various food types, drugs/medications, nutrition, exercise, body weight, health status, smoking, and alcohol and drug use by mothers and children (Jacobson and Jacobson, 1996). Relationships between exposure to environmental contaminants and adverse health effects are usually difficult to observe. The small percentage of the population that manifests the effect at environmental exposure levels usually makes a large sample size 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 often present. The Developmental Disorders Work Group of the President's Task Force recommended that NIH, CDC, and EPA jointly evaluate the feasibility of such a study (see Appendix C).

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 use devise hypotheses that can be tested using existing databases such as NHANES.

Priority and Rationale

Medium. Human studies are crucial to understanding whether children are more susceptible to environmental contaminants than adults. However, human studies are expensive and have been limited to substances that are known or suspected to cause severe and widespread human health impacts. In addition, when adverse impacts are observed in a human population, intervention, treatment, and risk reduction are often more of a concern than risk assessment. The results of current Federal research in the causes of childhood asthma and in neurodevelopmental effects of exposure to organophosphates and PCBs will provide ORD with insights to guide the design of future studies of children.

Human epidemiologic and clinical studies are necessary to identify and 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 successful 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 part of the Children's Health Program however, is to focus on mode-of-action research and modeling and to incorporate epidemiology studies only as necessary to reach this primary goal. Thus, a human study would have a higher priority in the Intramural Program if it were part of a study that also included mode-of-action studies and had the potential to lead to improvements in extrapolation between animal models and children.

As discussed in Section 4.3, several Federal Agencies in addition to EPA support epidemiologic and surveillance programs, including CDC, NCI, NIAID, and NIEHS. A major objective of some 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 pollutants 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 the relevant Institutes of NIH are exploring the feasibility of an Inter-Agency longitudinal birth cohort to address children's environmental health and safety issues that would have a core study protocol and special studies 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 FY2002.

4.4.1.3 Multi-Media, Multi-Pathway 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, and provide the information needed to devise strategies to reduce the risk. Ideally, epidemiological and exposure studies would be combined, and sometimes they are. However, as the number of issues being studied increases, the number of measurements taken, questions asked, and time required can quickly 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 often 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 several 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.-Mexican border, and a five-county study in and around Baltimore to test temporal variability in exposure. These studies asked over 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 groups (e.g., 1 to 2 year olds) more highly exposed? If so, what are the most important contaminants and exposure pathways for these age groups?

Feasibility and Resources

ORD has experience in the Intramural and STAR Program to make these studies feasible. Extramural resources required are on the order of $500,000 to $5,000,000 for a local to regional multi-media, multi-chemical field study. Extramural resources to support an in-house program for analysis of data generated in current studies are on the order of $100,000 to $200,000 per year.

Priority and Rationale

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

- Document exposures and determine whether certain age groups are more highly exposed to certain environmental agents
- Obtain baseline data on children's exposures by age in order to assess national exposure levels, compare exposures of various age groups, evaluate status and trends, and identify and characterize highly exposed subgroups
- Provide data for assessment of exposure and risk for specific populations of children
- Provide information on total exposure via multiple pathways and to multiple chemicals and on the relative importance of the sources contributing to the exposure
- Provide a data base for developing models to estimate multi-media, multi-pathway exposures
- Provide data to evaluate exposure variables in models, such as childhood and household activities that lead to exposure

Some exposure questions may be answered for specific chemicals through an analysis of existing data or data that will be available within 2 to 3 years from NHEXAS, NHANES, and the STAR grants. As the questions are answered for specific chemicals and reduce the uncertainty for those chemicals, the information can also be generalized to other chemicals to which children might be exposed by the same pathways, reducing uncertainty for entire classes of chemicals.

Resources in the Children's Health Program are insufficient to support both an Intramural ORD field study and the other research discussed in this Strategy. 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 FQPA program and Human Health Risk Assessment Program under GPRA Goal 8.

Five-Year Outcomes

By 2005

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

4.4.1.4 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 are required to better 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 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, through dermal contact and ingestion, to pollutants in water and sediment during swimming and wading. 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 and Resources

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 dislogdable 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 small children or trespassing by adolescents on waste sites are very difficult to document. Studies to collect data on dermal exposure and non-dietary ingestion are difficult to design because of lack of validated measurements methods and models for these pathways. Extramural resources required depend on the study. A reasonable allocation would be $250,000 to $500,000 per year to support three studies.

Priority and Rationale

High. The Agency 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 for the investment than a detailed study of all pathways for one chemical. Some of these studies will need to be conducted within the ORD Intramural Program in order to obtain the data that are needed for Agency risk assessments. Some of this research 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).

Five-Year Outcomes

By 2005

- Identification of high-priority exposure variables for study through preliminary exposure analysis
- Design and completion of activity pattern survey addressing high priority activity pattern issues for children
- Completion of two studies on other high-priority exposure variables for children

4.4.2 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.

4.4.2.1 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 to relate exposures and effects that are able to make use of pharmacokinetic and mode-of-action data. 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 (Section 4.4.1.1). 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 and Resources

While some prototype models could be developed through the STAR program, the greater part of this research will need to be done intramurally so that EPA has the ability to direct the research toward its 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 an extramural expenditure of at least $500K per year 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 Section 4.4.1.1 must also be maintained.

Priority and Rationale

High. The rationale is presented in Section 4.4.1.1.

Five-Year Outcomes

By 2005

- Evaluation of the appropriateness of the assumptions in current EPA risk assessment approaches and how they may be supported or modified by biological data
- Development and refinement of PBPK models applied to the developing animal, with the intent of eventual extrapolation to embryos, fetuses, infants, and children
- Development and refinement of BBDR models applied to the developing animal with the intent of extrapolation to embryos, fetuses, infants and children
- Identification of biological pathways, environmental factors, and their interactions that are important to understanding normal and abnormal development. This should focus on the ultimate incorporation of such information into predictive models of developmental toxicology and not solely on the generation of basic information on child development.
- Incorporation of information from dose-response, pharmacokinetic, and mode-of-action studies in animals into models that more accurately predict children's risks. This will require a significant effort in defining how experimental animal models mirror child development, as well as appropriate correction factors for species differences.
- First-generation methods, guidance, and data for using mode-of-action data and pharmacokinetic data for broad application in EPA risk assessments for children

4.4.2.2 Exposure Modeling and Use of Exposure Data in Risk Assessment

Description

Models will be developed to assess pathways of exposure important to children. 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 that support regulatory decision making at EPA rely on models rather than direct measurements of exposure.

Exposure modeling, particularly the multipathway, multichemical modeling necessitated by FQPA, often requires large amounts of data, both to develop the models and to test accuracy of the models against data. The accuracy of modeling outcomes depends heavily on the quality and representativeness of the data used to evaluate the input variables. Many input variables can be evaluated using data from the literature. In addition, data from several EPA-sponsored studies of children's total exposure to a variety of chemicals, particularly pesticides will soon be available,

including studies conducted in Minnesota under NHEXAS and under the STAR program in Arizona, Minnesota, and Washington, as well as data from NHANES-III and IV. These data will be used in development of exposure models for children.

Models capable of handling data on multiple chemicals, estimating total absorbed dosed 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 when they are known. Exposure models that estimate dose by accounting for bioavailability need to be developed in concert with PBPK models (see 4.4.2.1) so that the continuum from exposure through disease can be assessed.

Feasibility and Resources

ORD has expertise and a program in exposure modeling that is turning its efforts towards 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 be able to perform exposure modeling.

A level of effort of $200K per year for data assembly and modeling and an additional $100K per year for assessments based on current data would be sufficient for the Intramural Program. The project 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 relationship between environmental measurements, biomarker measurements, human activities, and toxicological parameters. Distribution of exposure in populations including highly exposed subpopulations is also of increasing concern to risk assessors and risk managers. Computer modeling approaches and consideration of multiple pathways is thus of high priority for children's research since these approaches are required to identify and quantify risks to children.

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.

Five-Year Outcomes

By 2005:

- **#** Working multi-pathway, multi-chemical exposure model for selected pesticides
- **#** Assessment of children's pesticide exposure based on data from NHEXAS, the STAR Program, and NHANES
- **#** Analysis of the OPP Standard Operating Procedures for estimating exposure of children to pesticides, identification of important pathways, and assessment support to reduce uncertainties in the assessment

4.4.3 Methods for Studying Effects and Exposure in Humans and Animal Models

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

4.4.3.1 *In Vivo/In Vitro* Methods for Hazard Identification

Description

Research is needed in the development and validation of more sensitive and predictive test methods for identifying perturbation of normal development by environmental toxicants. The application of improved test methods will yield relevant qualitative data that is important in risk assessment. In addition, improved tests will, in many cases, reveal important information on the underlying mechanisms of toxicity. Finally, the incorporation of refined test methods in dose-response studies will provide quantitative data that is pivotal to risk assessment.

Feasibility and Resources

ORD has an ongoing program in which it develops methods of testing toxicity of pesticides and other chemicals in support of the OPPTS testing program. It is feasible to conduct this research both intramurally and through the STAR program. An appropriate level of effort is $400K per year.

Priority and Rationale

Medium. Methods development is already supported under the base Pesticides and Toxics Program. Any methods development under the Children's Health Program should take place as part of studies with additional objectives related to developing data to reduce uncertainties in risk assessment.

4.4.3.2 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 participates and tests where samples, x-rays, or other measurement are taken on the young subject.

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. An additional research area will involve the application of available techniques, such as eye-blink response and visual contrast in 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/or 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 analysis and of conducting questionnaire surveys. Analysis 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 pollutants 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 and Resources

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 Research Program. Other Agencies, such as CDC and NIEHS have an interest in the application 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. The NERL Program develops methods for survey design and implementation and methods to measure contaminant concentrations in environmental media.

Measurement methods development in NHEERL or NERL would require an annual investment of $500K.

Priority and Rationale

Medium. Given the limited resources in the Children's Health Program, methods development needs to take place within a larger study with broader objectives.

4.4.4 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.

4.4.4.1 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 contaminant 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 susceptibility 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 risks 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 children are protected and so devastating outbreaks do not occur.

Pesticides in urban settings are also of concern for children. Children are hypothesized to be particularly susceptible to pesticides, and non-point 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 non-point 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. Selected plants and/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 and Resources

ORD has expertise in the development of engineering solutions to respond to children's health problems. In order to address these issues, it is necessary to predict which sources will be of particular concern to children and the level of control that will address the risk adequately. 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 6 logs. In addition, it is anticipated that new standards for water turbidity and the matching technology to achieve these standards will be needed. Other engineering controls that may be needed to reduce children's risks include bioremediation methods for contaminated soil, treatment methods for solid waste, and controls on air releases.

Extramural resources to sustain a program directed at engineering controls addressing one environmental problem are $350K per year.

Priority and Rationale

Low for Children's Health Program. Although this research will contribute to reducing risks to children, research in control technology is too far removed from being a specific children's issue to be a high priority for this program and is more appropriately conducted as part of the program on specific risk management research for the EPA Air, Water, Hazardous Waste, and Pesticides and Toxics Programs.

4.4.4.2 Methods for Reducing Exposure Buildup of Contaminants in Indoor Environments

Description

Children spend most of their time in indoor environments. Exposures to contaminants in air and on surfaces are expected to result in significant childhood exposures. Consumer products such as pesticides that are applied indoors and other chemicals that are found in a whole range of consumer products– toys, cleaning products, building materials, floor covering, fabrics– may be released into the indoor environment and become available for exposure. These exposures can be reduced by cleaning up the contaminants after they have been released. They may also be reduced by designing consumer products that use less toxic components or don't release as much chemical during use.

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 pre-toddlers 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 or processes exist for the removal of the chemicals from the structures. High exposures can also be discovered during epidemiology and exposure studies, and it is important for ORD to 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 and Resources

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.

Extramural resources are $250K for the first year and $350K thereafter.

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, many 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. While 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. Extramural expenditures totaling $600K for 5 years should be sufficient to accomplish the objective. Methods will be extended to other pesticides besides

methyl parathion.

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 EPA Regions 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.

Five-Year Outcomes

By 2005:

- **#** Development of method and process to remove chemicals/pesticides from building debris using methyl parathion as a prototype
- **#** Development of method and process to remove chemicals/pesticides from building structures and carpets using methyl parathion as a prototype

4.4.4.3 Communication of Risks and Development of Risk Reduction Techniques through Community Participation

Description

ORD will support research into intervention and education techniques that will recruit members of the community to work 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 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 that help 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.

Resources/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 human studies, ORD should consider carefully such issues as community involvement, communication of study results to

the respondents, provision of advice about lowering exposures to respondents along with the study results, and working 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 for as part of an exposure or epidemiology study, rather than a separate research program.

Five-Year Outcomes

By 2005:

STAR program - Implementation of risk intervention programs in several communities - journal articles on effectiveness of risk intervention approaches (ongoing under Centers)

STAR program - Comparison of methods for communicating risks of pesticides on foods -- OPP will use in implementation of FQPA (ongoing grant)

4.4.5 Cross-Cutting Issues

4.4.5.1 Variability in Susceptibility and Exposure in Children

Description

Variability in susceptibility and exposure within an age group may be as important as variability between groups. Factors such as pre-existing disease, lifestyle and nutrition, genetic characteristics, sex, and ethnicity may result in great variation within a susceptible 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 be useful.

Some issues that could be explored under this research area are

Assessment of the adequacy of the uncertainty factor approach in developing RfDs and RfCs that protect children

Environmental justice issues and hypotheses related to increased susceptibility and exposures among minority and low-income children

- # Extent of variability among children in particular age ranges with respect to differences in absorption, metabolism, retention, and excretion of environmental agents and how differences affect exposure levels
- # Development of biomarkers to identify susceptible subpopulations of children
- # Interactions of genes and environmental agents that produce adverse effects in children
- # Study of the impact of existing health conditions such as respiratory problems or compromised immune system on other health end points.

Feasibility and Resources

Variability in susceptibility to environmental contaminants 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 city children. 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, the effects of 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 contaminants and genes will be important in studying mode of action and in using such data to assess risk.

Priority and Rationale

Medium. The Science Team felt that variability within and between age groups was important. However, 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 priority as other areas. Much of the research described in this area 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 this research will increase.

4.4.5.2 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 use of consumer products. Toxic

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 indoors and out.

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

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

Feasibility and Resources

Exposure research has focused on multiple chemicals for several years through NHEXAS and other studies. Research on the effects of exposure to mixtures and how such data can be used in risk assessment is less advanced and will be a major focus of ORD's Human Health Risk Assessment Program. ORD 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.

Priority and Rationale

Medium. The Science Team concluded that 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 not of as high priority for this program.

4.5 Linking and Summary of Research Areas

The preceding Sections have focused on each separate research area. This section presents an overview in Table 2 with a short description of each research area, the contribution of its research to EPA's risk assessments and risk management decisions, and its relation to other research areas.

5 GUIDANCE FOR IMPLEMENTATION

This Strategy provides direction for ORD research on children's risks over the next five years and will be implemented by ORD's three National Laboratories and two National Centers. It is assumed that resources in the ORD Children's Health Program will remain stable over the next five years. Approximately 75% of the extramural resources are expected to be dedicated to investigator-initiated grants under the ORD Extramural STAR Program. The Intramural Program will be conducted by ORD scientists supported by the remaining 25% of the extramural funding. It is also assumed that ORD Program-specific research on children, 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 (USEPA, 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

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 Organisms (§4.4.1.1) High priority		
Investigate absorption, metabolic pathways and rates, distribution and storage in the body, and elimination for 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 end points and chemicals.	Identification of more appropriate animal models for critical ages and end points. 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 (§4.4.2.1) 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 tested in human studies (§4.4.1.2). These studies may result in improved testing protocols for hazard identification that supplant or complement whole animal toxicity testing (§4.4.3.1) and contribute to methods for measuring effects in children (§4.4.3.2). This research also provides some of the basic science that will be necessary to understand the complicated issues of variability within susceptible age groups (§4.4.5.1) and exposure to multiple pollutants (§4.4.5.2).
Relationship between Exposure to Environmental Agents and Adverse Health Effects in Human Populations (§4.4.1.2) Medium Priority		
Epidemiologic and clinical studies of children. Case-control studies of children with known health effects or known exposure and collection of retrospective data on exposure. Longitudinal birth cohort enrolling children at birth and continuing through adulthood. Hypothesis-based analysis of existing data sets to investigate relationship between exposure and effects in children.	Identification of hazards or 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. Testing of intervention and risk reduction techniques. In some cases, data for dose-response assessment.	Studies in humans will be warranted by outcomes of research into the biological bases of adverse effects (§4.4.1.1) to verify predictions of response in children and to aid in developing models to extrapolate between animals and children (§4.4.2.1). Epidemiology studies and exposure field studies (§4.4.1.3) 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 not unduly sacrificed because of respondent burden. Methods of studying effects and exposure in humans (§4.4.3.2) will be used in human studies and often developed in the context of these studies. Investigators will need to work with communities and respondents to conduct epidemiology studies and will need communication methods (§4.4.4.3) and practical intervention methods to offer individuals and local public health departments to deal with problems that may be uncovered in human studies (§4.4.4.2). Human studies designed to consider multiple chemicals have the potential to provide information on variability within age groups (§4.4.5.1) and responses to complex mixtures (§4.4.5.2).

Table 2. Summary of Research Areas

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Multi-Media, Multipathway Exposures in Human Populations (§4.4.1.3) High Priority		
Measurements of exposure in various age ranges for national population and selected subgroups hypothesized to be more highly exposed. Collection of environmental concentration data, personal exposure data, biological samples, and questionnaire data.	Data to determine whether children are exposed and whether certain age groups are more highly exposed and should be subjects of risk assessment. Baseline data and data on distributions of exposure in the general population and highly exposed subgroups. Data for risk assessment for chemicals being studied and data on activity patterns and other exposure variables for direct use in agency risk assessments. Identification of important sources and pathways of exposure for risk management decisions. Data for use in model development. Data on exposure patterns (acute, intermittent, chronic) and the magnitudes of exposure for each pattern.	Information on the most highly exposed age groups and their patterns of exposure are useful in selecting relevant chemicals in pharmacokinetic and mode-of-action studies (§4.4.1.1), designing biological models compatible with actual exposure patterns (§4.4.2.1.), and designing human studies of the relationship between exposure and effect (§4.4.1.2). 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. Multi-media, multi-pathway measurement studies can often be designed to collect information on exposure variables (§4.4.1.4) and for use in designing and testing exposure models (§4.4.2.2) suitable for use in many risk assessments. The strategy recommends that methods of measuring exposure applicable to infants and toddlers (§4.4.3.2) be developed in the course of conducting these studies. Investigators will need to work with communities and respondents to conduct epidemiology studies and will need both communication methods (§4.4.4.3) and practical methods to offer help to individuals and local public health departments to deal with problems that may be uncovered in these studies (§4.4.4.2). Studies designed to consider multiple chemicals have the potential to provide information on variability within age groups (§4.4.5.1) and responses to complex mixtures (§4..4.5.2).
Analysis of Factors Contributing to Exposure (§4.4.1.4) High priority		
Development of data on distributions of values of key exposure variables within critical age groups including activity pattern data, intake rates, and other factors that bring children into greater contact with chemicals than adults. Data collected through studies focused on key variables or pathways, rather than multi-media exposures.	Variables to be studied are usually identified through conducting exposure assessments, frequently by EPA Program Offices. Studies focus on areas of greatest uncertainty and are designed to collect data that can be used directly in risk assessment.	Multi-pathway studies (§4.4.1.4) 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 (§4.4.2.2). Measurement methods are often developed (§4.4.3.2) 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 (§4.4.5.1).

Table 2. Summary of Research Areas

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Methods and Models for Using Biological Data in Risk Assessment (§4.4.2.1) High Priority		
Develop methods and models that routinely use pharmacokinetic and mode-of-action data in children's risk through an integrated biological model of the exposure-dose-response continuum. 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 age-related differences in 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 is generated through mode-of-action research (§4.4.1.1). Human studies also provide relevant data for model validation and extrapolation between animals and humans (§4.4.1.2). Exposure studies often provide relevant data on uptake, body burden, and elimination (§4.4.1.3). Exposure models (§4.4.2.2) 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 data base, probabilistic models will be useful in predicting distributions of exposure, dose, and risk within an age range, allowing for estimates of variability (§4.4.5.1).
Exposure Modeling and Use of Exposure Data in Risk Assessment (§4.4.2.2) High Priority		
Models for important pathways of childhood exposure. Models of total dose via multiple pathways. 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. Virtually every EPA exposure assessment uses models. Measurement data are rarely available or even feasible for every exposure or dose value needed. Exposure models are needed for child-specific exposures such as dermal and hand-to-mouth contact as well as for multi-pathway and multi-chemical assessments where variables are combined through probabilistic modeling techniques.	Data for model development is provided through studies of exposure variables (§4.4.1.4). Human studies (§§4.4.1.2 and 4.4.1.3) may provide data to evaluate model variables and to develop and test exposure models. Exposure models and biological models (§4.4.2.1) 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 data base, probabilistic models will be useful in predicting distributions of exposure within an age range, allowing for estimates of variability (§4.4.5.1). Probabilistic models will also be helpful in predicting distributions of dose from multiple chemicals via multiple pathways (§4.4.5.2)

Table 2. Summary of Research Areas

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
In Vivo/In Vitro Methods for Hazard Identification (§4.4.3.1) Medium Priority		
More sensitive and predictive test methods for identifying perturbation of normal development by environmental contaminants	Development of animal models and protocols for use in testing under TSCA and FIFRA for effects that could occur in children.	Predictive tests will be developed as part of a program investigating the biological basis of risk (§4.4.1.1) and provide data for extrapolation between animals and children (§4.4.2.1).
Methods for Measuring Exposures and Effects in Infants and Children and to Aid in Extrapolations between Animals and Children (§4.4.3.2) Medium Priority		
Measurement methods suitable for use in infants and toddlers, such as biological sampling methods and cognitive testing methods. 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 other human studies (§§4.4.1.2, 4.4.1.3, and 4.4.1.4)
Multimedia Control Technologies (§4.4.4.1) Low Priority		
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 non-point 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 clean up, 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 (§4.4.4.2) High Priority		
Clean up and remediation of children's environments that have unacceptable environmental concentrations. Engineering of consumer and building products to lower levels of release 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 help identify substances for which control methods are needed. Risk assessments also help identify and evaluate remediation and pollution prevention options and their efficacy. Invention methods can be used in conjunction with human studies (§§4.4.1.2 and 4.4.1.3) to assist residents and local public health departments when high exposure levels are found.

Table 2. Summary of Research Areas

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Communication of Risks and Development of Risk Reduction Techniques through Community Participation (§4.4.4.3) High Priority		
Investigation of 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 other 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 (§§4.4.1.2 and 4.4.1.3) to assist resident and local public health departments when high exposure levels are found.
Variability in Susceptibility and Exposure in Children (§4.4.5.1) Medium Priority		
Investigate impact of factors on variability in response or exposure within the critical age range. Factors include pre-existing 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 (§4.4.1.1) 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 subgroups (§§4.4.1.2, 4.4.1.3, and 4.4.1.4).
Cumulative Risks to Children (§4.4.5.2) Medium Priority		
Effects of simultaneous exposures to many chemicals on infants and children.	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 chemicals found in the child's environment.	The results of mode of action studies (§4.4.1.1) will be important in understanding impacts of mixtures. Epidemiology and exposure studies (§4.4.1.2 and §4.4.1.3) 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 multi-chemical exposures and risks.

The expertise needed for the multidisciplinary research summarized in Table 2 is distributed throughout ORD. Interdisciplinary research across a diverse and geographically dispersed organization such as ORD is a challenge. Figure 3 shows an example of a collaboration between NERL and NHEERL-- a combined exposure and epidemiology study of children in a population along the U.S.-Mexican border

Figure 3. NAFTA Pesticides in Young Children: A NERL/NHEERL Collaboratory Study

This Program assesses the relationship between health outcomes in young children along the U.S.-Mexican border subjected to 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 joint publication and peer review.

Preliminary studies included review of existing data, development of Geographic Information System (GIS) maps of the area, and a workshop to identify relevant health end points and appropriate epidemiology studies (See Appendix D below, USEPA, 1998d). Methods of screening of infants and children are now being identified and implemented in the Region. 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

Under the STAR Program, ORD scientists 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 4 shows an example of a collaboration between ORD, the Minnesota Department of Public Health, a consortium operating under NHEXAS, and a grantee under the STAR Program.

EPA has maintained coordination and collaboration with other Federal Agencies and will continue to do so in carrying out the research in the Children's Environmental Health Program. Examples of collaborations include the Children's Research Centers co-sponsored with NIEHS, sponsorship of special exposure studies in NHANES on urine levels of pesticides in children and adults, and levels of persistent organic compounds in adolescents, and collaboration with CDC, FDA, and the State of Minnesota in the NHEXAS study of children's pesticide exposures in Minneapolis-St. Paul. The Research Work Groups of the President's Task Force have recommended collaborations in several research areas (see Appendix C). From this Task Force, an EPA-NIH comprehensive

Figure 4: Pesticides and Children in Minnesota: A NHEXAS Study and a STAR Grant

Under the NHEXAS Program, NERL sponsored a study under co-operative agreement with Research Triangle Institute and the Environmental and Occupational Health Sciences Institutes where 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.

national strategy to fight childhood asthma has emerged. EPA and NIH are also planning to jointly sponsor an RFA on developmental disorders and have entered into exploratory discussions of a longitudinal birth cohort (see section 3.1).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 that are final reports or external review drafts. The OPP Home Page posts issue papers and deliberations of the OPP Science Advisory Panel (SAP) on children's risk issues. Several Agencies, including NIEHS, CDC, NCI, and the ORD STAR Program publish their current budget requests and supporting descriptions of their research programs and initiatives and provide lists of their Intramural and Extramural Research. CHEHSIR, which provides information at a project level on Federal research on children's environmental health and safety risks is on line (CHEHSIR 1999).ORD managers and scientists are encouraged to consult these sources to learn about research and activities in their areas and to provide similar information on their Home Pages.

Figure 5 summarizes principles for implementation of the Strategy.

Figure 5 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 grants programs should ask Investigators to specify the potential impact of results on the EPA risk assessment process
- A multi-disciplinary, 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.
- 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 end point is encouraged where possible, such as research on mechanisms that can lead to multiple end points and end points 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. While 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. 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 which adversely impacts cognitive function is integrated over a lifetime when applied to a child.

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. 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. 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 and neurological damage and death as a result of dermal application of hexachlorophene-contaminated talcum powder. Cases of infant poisoning and death by hexachlorobenzene have also been reported following ingestion of highly contaminated human milk. The consumption of mercury-contaminated fish by nursing mothers resulted in severe neurological disorders in their breast feed infants. The antibiotic tetracycline produces tooth discoloration and enamel hypoplasia as well as interferes 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 air borne 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. (NRC, 1993; WHO 1986). 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. Consequently, the absorption of some chemicals is greater in infants than in adults. For example, lead is absorbed better by infants than adults. The rates of activation and deactivation of chemicals are also related to the stages of maturation and development of enzyme activity (WHO 1986).

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 (WHO 1986). The EPA interim report on dermal exposure assessment (USEPA 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.

The structure and function of the kidneys are immature at birth. 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 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. Smaller proportions of absorbed lead are also excreted via the renal route in infants compared to adults (WHO 1986). Since 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 due to the prolonged presence in the body of a chemical or its active metabolite(s). Unfortunately, there is only limited information about age-related differences in elimination of environmental chemicals in experimental animals, let alone in humans.

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. Another important cell type in the neonatal liver is the hemopoietic cell, since the liver is the cite of hematopoiesis prior to birth. Biotransformation of organic chemicals via phase I and phase II metabolic reactions is generally slower in the neonate than in the adult (WHO 1986). Consequently, degradation and elimination of chemicals which are dependent on these biotransformation reactions are generally reduced in infants compared to 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. Examples of toxicities associated with the newborn's decreased

ability to conjugate and eliminate chemicals include chloramphenicol, diazepam, and hexachlorophene (NRC 1993).

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. During the first four to six months of age an infant gains weight more rapidly than during the rest of its life (WHO 1986). 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 of 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 (NRC 1993). 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.

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. 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 (NRC 1993, ILSI 1996). 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, triethyltin, polychlorinated biphenyls, and certain organochlorine pesticides (ILSI 1996, NCR 1993).

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. 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 permanently alter the sexual dimorphic pattern. Exposure to chemicals with androgenic or estrogenic activity may also alter growth and time to onset of puberty. Altered neuroendocrine function may also affect adrenal corticosterone release (WHO

1986).

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. Both innate and specific immune responses of infants and children are suboptimal compared to that of adults. For example, natural killer cell activity is at about 60% of adult levels in newborns and complement activity does not reach adult levels until about 6 months of age. As for specific immune responses, certain T helper cell functions only reach adult levels by 6 months of age. While 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. 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.

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 which 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 (NRC1993). 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 (NRC 1993). 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. Since 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.

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APPENDIX B ORD RESEARCH PLANS AND STRATEGIES

Name	Description
Final Plans and Strategies	
Ecological Research Strategy (USEPA 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.
Environmental Monitoring and Assessment Program EMAP (USEPA 1997a)	Describes ORD's role in a program to monitor the Nation's ecological resources and assess the impact of EPA's policies and programs and identify emerging issues.
Research Plan for Arsenic in Drinking Water (USEPA 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 (USEPA 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.
Waste Research Strategy (USEPA 1999)	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 due to 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.

Name	Description
Pollution Prevention Research Strategy (USEPA 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 which 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.
Final Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water (USEPA 1997b)	This research plan was developed to describe research needed to support EPA's development of drinking water regulations concerning disinfectants, disinfection by-products (DBPs) 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.
Draft Plans and Strategies	
Draft Global Change Research Strategy (USEPA 1997c)	The strategic foci of ORD's global change research program are: (1) identification and evaluation of regional ecological vulnerabilities (including associated human health impacts) to temperature and hydrologic changes associated with predicted changes in climate; and (2) identification and evaluation of adaptation strategies and cost-effective technologies to prevent or control greenhouse gas emissions.
Draft Particulate Matter Research Program Strategy (USEPA 1997d)	The Strategy describes ORD's PM research in the areas of health, exposure, risk assessment, and risk management research. 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.

Name	Description
Under Development	
Human Health Risk Assessment Research Strategy	Will provide strategic direction for the ORD Human Health Risk Assessment Program, including cross-cutting, core research in exposure, effects and dose-response research.

Source: www.epa.gov/ORD/resplans/resplans.html

USEPA (1999) Waste Research Strategy. Washington, DC: U.S. Environmental Protection Agency. EPA/600/R-98/154.

USEPA (1998a) Ecological Research Strategy. Washington, DC: U.S. Environmental Protection Agency. EPA/600/R/98-066

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USEPA (1997c) Draft Global Change Research Strategy. Washington, DC: U.S. Environmental Protection Agency.

USEPA (1997d) Draft Particulate Matter Research Program Strategy. Washington, DC: U.S. Environmental Protection Agency.

APPENDIX C INITIATIVES OF U.S. CHILDREN'S ENVIRONMENTAL HEALTH AND SAFETY TASK FORCE

In April 1998, the U.S. Task Force on Environmental Health Risks and Safety Risks to Children identified four priority areas: childhood asthma, unintentional injuries, developmental disorders, and childhood cancer; and created four work groups to report on the problem and recommendations for addressing the problem.

Three of the work groups– asthma, developmental disorders, and childhood cancer– address problems regulated by EPA. The recommendations of these work groups are summarized below.

Asthma Work Group

Recommendations:

- Conduct and fund studies to determine the causes exacerbating factors of asthma, including genetic susceptibility, early life events, effects of pollutants and allergens on immune responses, and population-based risk factors (CDC, NIH, EPA)
- Expand and accelerate research to develop and evaluate environmental strategies that will improve the quality of life for people with asthma, including studies to evaluate intervention measures, estimate allergen exposures in the U.S., continuation of the National Cooperative Inner-City Asthma Study of interventions, identification of home construction, maintenance, and occupancy practices that will reduce children's exposure to environmental agents that trigger asthma attacks, and studies of effectiveness of energy conservation strategies and technologies on reducing exposure to allergens (EPA, NIH, CDC)
- Programs to improve public health (EPA participation through Air Program)
- Surveillance of prevalence and severity of asthma and systematic determination of deaths, hospitalizations, and emergency room visits for asthma by State and major metropolitan area; integration of asthma morbidity and mortality data with ambient air monitoring data, and follow-up regional/local and population group studies (CDC)
- Conduct research and surveillance to assess disproportionate impacts on the poor and minorities (CDC, NIH, ATSDR)
- Implement programs to eliminate the disproportionate impact of asthma in minority populations and those living in poverty

Source: President's Task Force on Children's Environmental Health and Safety Risks (1998) Asthma in America: Our Children at Risk. A Plan for Environmental Action to Address Childhood Asthma. Draft Report. August 14, 1998.

Developmental Disorders Work Group

The Developmental Disorders Work Group addressed all adverse health effects on

embryos, fetuses, infants, and children except for cancer and asthma.

Research Recommendations:

- # Study susceptibility of the developing organisms through elucidation of mechanisms of normal development and mechanisms and cellular processes underlying major classes of human development that may have an environmental component to their etiology (NIH, CDC, EPA)
- # Link *in utero* exposures to developmental disorders (NIH, CDC, EPA) through identification of correlations between exposure and molecular mechanisms or cellular processes that are perturbed in different classes of developmental disorders, identification of modes of action of environmental agents that may perturb normal development, determination of body burden after exposure, and improvements of extrapolation between human and animal data
- # Investigate feasibility of a cohort study of prenatal exposure and developmental disorders (NIH, CDC, EPA)
- # National Information Database on Children's Health Risks (EPA, NIH, FDA)
- # Long-term surveillance of birth defects, genetic disorders, developmental disabilities (CDC)
- # Use of research results to develop improved risk assessment methods through incorporation of mechanistic and exposure data (EPA and other agencies)

Source: President's Task Force on Children's Environmental Health and Safety Risks. An Initiative to Prevent Developmental Disorders Associated with Environmental Factors. Draft Report. August 26, 1998.

Cancer Work Group

Areas of focus:

- # Understanding the role of the environment in childhood cancer
- # Identification of potentially preventable environmental causes of childhood cancer
- # Identification of the role of gene-environment interactions in specific childhood cancers
- # Development of strategies for reducing childhood exposure to carcinogens
- # Promote the development of toxicological research and exposure assessment associated with environmental carcinogens
- # Education and risk communication

Proposed initiatives:

- # Establishment of a National Network for Research on Cancer in Children, which will include a central registry of cases of cancer occurring among children in the United States. Registry would serve as a national resources and research platform to support research in environmental causes of cancer in children (built upon existing NCI registries with support from other agencies)
- # Establishment of a National Childhood Cancer Registry Tissue Bank. Primary purpose to

provide tissue specimens to researchers to identify causes of childhood cancers and to facilitate strategies for improved treatment (Proposed that CDC would collect and store samples)

- **#** Development and Implementation of a Model Cancer Inquiry Response System, with the objective of establishing a systematic approach to cancer surveillance by refining existing guidelines and resources for public inquiries and cancer cluster investigations (CDC and ATSDR)
- **#** Workshop to identify areas of research opportunity relating to environmental causes of childhood cancer (EPA)
- **#** Workshop on Predictive Toxicological Models for Children's Cancer (EPA and NIEHS)

Source: President's Task Force on Children's Environmental Health and Safety Risks (1998) Interim Report of the Cancer Work Group. August 25, 1998.

APPENDIX D RESEARCH RECOMMENDATIONS

NRC (1993) National Research Council. 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 with 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 other sources 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 of benchmark dose for risk assessments for infants and children
- # Use of risk distributions rather than point estimates.

ILSI (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 work shop 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.
- # Systematic collection of changes in cell proliferation rates in various tissues as a function of age in humans and relevant experimental animals
- # 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
- # Biomarkers of carcinogenicity in children as compared to adults
- # More studies of age-dependent effects of non-genotoxic compounds focusing on mechanisms
- # Focus in future epidemiology studies on methodologies designed to increase the likelihood of detecting susceptibility differences between children and adults. A better understanding of critical time periods for exposure either for certain tumor types or for certain classes of carcinogens.
- # Examination of selected well-characterized exposures associated with carcinogenesis for age-related differences in the effect. Consider feasibility of retrospective studies with data on children and adults 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, identification and characterization of 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.
Ability to connect neurobiological function with neurobiological substrates is incomplete: Major categories of effects include deficits in cognitive, sensory, autonomic, affective, and motor functions
Understanding the relationship of the neuroendocrine system to the developing nervous system

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

This three-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
- # Multi-generational studies of neurotoxicity
- # Techniques to study gene-environment interactions of neurotoxicity
- # Continue studies of neurotoxicity of mercury and PCBs using sensitive outcome measures

USEPA (1998c) U.S. EPA Conference on Preventable Causes of Cancer in Children. Conference Report. Washington, DC: U.S. Environmental Protection Agency, 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 USEPA (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
- # Community 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?

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 non-invasive, 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 (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 samples 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.

- Monitoring 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.

USEPA (1998d) EPA Workshop on the Assessment of Health Effects of Pesticide Exposure in Young Children. Draft Report. Research Triangle Park, NC: U.S. Environmental Protection Agency, 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 end points 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 pre-natal 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

Immunology and Pulmonary Work Group

End points:

- Upper respiratory infections
- Acute bronchitis
- Asthma (reactive airway disease)
- Interstitial lung disease
- Allergic diseases (allergic rhinitis, eczema, allergic broncho-pulmonary 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 end points (Hypothesis that immunopathology in adult female may contribute to adverse reproductive outcomes - No known association with OP pesticides)

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 data bases, (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 case, 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 solve 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."