LONG-TERM GOAL 3
Protect Susceptible Subpopulations

Theme Lead: John Vandenberg (NCEA)

Contributors: Roy Fortmann, Haluk Ozkaynak, James Quackenboss (NERL); Stanley Barone (NCEA); Andrew Geller, Hillel Koren (NHEERL); Nigel Fields (NCER)

Overview

Human variability in exposure and response to environmental pollutants are key uncertainties in health risk assessment. The National Research Council, in reports such as *Science and Judgment in Risk Assessment* (1994) and *Pesticides in the Diets of Infants and Children* (1993), identified variability in exposure and susceptibility as important areas where human health risk assessments could be improved. ORD's *Human Health Research Strategy* (US EPA, 2003) has identified the evaluation of risk to susceptible human subpopulations as one of three themes in its research to improve human health risk assessment. Underpinned by the 1997 Federal Executive Order 13045 "Protection of Children from Environmental Health Risks and Safety Risks", the Agency is committed to understanding why some people and groups are more highly susceptible or highly exposed than others. ORD's research to understand the exposure, susceptibility, and differential risks addresses the requirements of the Food Quality Protection Act (FQPA) of 1996 and the Safe Drinking Water Act Amendments of 1996 that EPA consider children and other potentially susceptible groups when setting health-based standards. These reports and congressional actions follow from a long history of concern in the Clean Air Act and other statutes that environmental programs consider and strive to protect those members of the population most susceptible and at risk from pollution including children, the elderly, individuals with pre-existing disease, or individuals with otherwise increased innate or acquired susceptibility.

Variation in biological susceptibility, exposure and dose depends on intrinsic factors (e.g., life stage, gender, genetic factors, physiological state) and acquired factors (e.g., preexisting disease, activity levels, nutrition, stress, licit and illicit drug use, cigarette smoking, and alcohol use). In addition, factors such as occupation, location of residence, and activity patterns that place individuals in contact with environmental agents cause variation in exposure.

Information is needed on how various susceptibility and exposure factors alter risks. Research to address this need is a key priority for EPA's susceptibility research program.

There are specific periods or windows of vulnerability during development when toxicants might permanently alter the morphology or function of a system. Children may also be more vulnerable to specific environmental pollutants because of differences in absorption, metabolism, and excretion. Children's dietary and other exposures are also often different from those of adults. The elderly may also respond differently from younger adults to environmental exposures. There may be an increased risk of cancer and degenerative diseases as a function of age. The prominence of these concerns is rapidly elevating with the largest birth cohort in the US, namely, the "baby boomers", now becoming senior citizens. Research is needed to examine the impact of life stage on responses to environmental pollutants and to develop predictive models that can be incorporated into the risk assessment process. Life stage research focusing on children is a major area of research emphasis, with research to understand later stages in life, in particular in the aging, an area of emerging emphasis.

There are a number of genetic factors that could predispose human subpopulations to adverse effects from exposure to pollutants, including genetic polymorphisms for metabolizing enzymes, differing rates of DNA repair, and different rates of compensation following toxic insult. The main scientific question for this research is whether such genetic differences significantly influence risk at realistic, low dose exposures. Information on gene-pollutant interactions as a result of long-term exposure to environmentally relevant concentrations of pollutants is needed. Research efforts on genetic factors by ORD have been relatively modest, with a new emphasis on the human genome and its relationship to variable human response being part of a new Computational Toxicology program that is complementary to this HHRA program area.

Preexisting diseases may influence the response to environmental toxicants by altering xenobiotic metabolism or otherwise altering the host's response in a synergistic, additive, or antagonistic manner. Research is needed to develop animal models of diseases having a high incidence in the human population and determine the effects of the disease on the dose-response curves for high priority environmental agents. ORD has focused most efforts on asthma, though

other disease conditions, such as cardiopulmonary disease, have been targeted for complementary research under the Particulate Matter research program.

Unique situations and populations may be evident when evaluating the range of human exposure scenarios and population subgroups. For example, the exceptional conditions surrounding the collapse of the World Trade Center towers presents a challenge to understand exposures to particles and gases in the surrounding community. The task to characterize these exposures has been directed to EPA due to the unique capabilities of the EPA research laboratories and collaborators to inform public health decisions in this difficult situation. More subtle concerns also arise as we try to understand the role of environmental agents in other populations, such as in producing neurotoxicity in children and the role of environmental agents in conditions such as autism.

ORD is uniquely poised as the research arm of EPA to conduct research that examines exposure-susceptibility-effects relationships. Multidisciplinary basic and applied research are being performed by EPA scientists and by researchers in several children's environmental health centers and investigator-initiated grants funded by ORD. Results of this research will be used by the Agency to improve risk assessment and risk management.

The Long-Term Goal for research to Protect Susceptible Subpopulations is that risk assessors and risk managers use ORD's methods and models to identify susceptible subpopulations for risk assessment, which in turn reduces risk of humans exposed to environmental stressors. The key questions guiding research in this area are:

- What at subpopulations have differential risk to environmental stressors?
- What is the basis for differential risk?
- What is the risk to susceptible subpopulations?
- How can differential risk be mitigated?

The following examples serve to highly the contributions that have been made, the current progress in relatively new research endeavors, and the expectations from new initiatives. The large scope and commitment of resources to understand and characterize susceptibility reflects the importance placed on this area in the research planning efforts, and the results demonstrate considerable progress in improving the scientific basis for health risk assessment.

Selected Examples of Research to Improve Health Risk Assessment for Susceptible and Highly Exposed Populations

Research to Understand the Exposure, Susceptibility, and Differential Risks of Children to Pesticides

In response to concerns about risks to children from pesticide exposures, ORD developed a systematic approach to address the key science questions identified above and to collect data to fill critical gaps in our understanding of children's exposures, susceptibility, and differential risk. Key research outputs were identified and include: (1) tools for identifying highly exposed populations, (2) tools for characterizing exposures and risks for subpopulations, (3) tools for describing the biological basis for differential sensitivity, and (4) tools that lead to reduced exposure. The quality and quantity of the available scientific data regarding exposure and response was assessed, the existing data gaps were evaluated, and a conceptual model was developed that was used to identify and prioritize research needs.

A set of highly focused research studies were then developed by ORD researchers to fill critical data gaps. In the area of children's exposure measurements, ORD researchers focused on four priority areas: pesticide use patterns, spatial and temporal distribution of pesticides in indoor environments, dermal and non-dietary ingestion exposure pathways, and dietary exposures. For example, to develop a better understanding of dermal exposure factors, laboratory studies were developed using fluorescent tracers as surrogates for pesticides and a dosimeter method was developed. Pilot studies were designed to evaluate aggregate exposure measurement methods and a draft protocol for measuring children's exposures to pesticides was developed. To understand the basis for differential risk, basic research within ORD was initiated to evaluate differential responses to pesticide exposures to determine the magnitude and biological basis for the differences. The research involved characterizing the differential response of the young to the neurobehavioral and neurochemical effects of cholinesterase-inhibiting pesticides (carbamates and organophosphates) and determining the biological mechanisms for these differences.

For extramural research, ORD was able to leverage research dollars through partnering with the National Institute of Environmental Health Sciences to award grants to eight Centers of

Excellence in Children's Environmental Health and Disease Prevention Research. The research efforts of these Centers address the continuum from exposure, susceptibility, and effects through environmental epidemiology studies, incorporating a variety of tools including pesticide and metabolite concentrations in environmental and biological samples. Research performed by the Centers complements the basic and applied research performed by ORD scientists. The integrated, multidisciplinary approach by ORD has facilitated collection of data that comprehensively addresses the exposure, susceptibility, and risk of children to pesticides.

Source-to-Effects Modeling for Susceptible (Children) Populations

Assessment of chemical-specific risk for children requires several types of information on exposures and effects occurring during early life stages. The main goal of this research program is to develop methods, techniques and models to identify and quantify routes and pathways of exposures of concern for children as well as to develop new tools that can describe the biological basis for differential sensitivity in children. This information is provided to risk assessors and managers both within the Agency and elsewhere, so that appropriate source and exposure mitigation strategies can be considered, in order to reduce risks of children exposed to environmental stressors.

In order to understand potential health risks to children from exposures to environmental chemicals of concern, it is necessary to investigate quantitative relationships between exposure, absorbed dose and the biologically effective dose. ORD has been developing a state-of-the-art aggregate exposure and dose model, the Stochastic Human Exposure and Dose Simulation (SHEDS) model, to examine children's exposure to a variety of multi-media multi-pathway pollutants, such as organophosphate pesticides and arsenic from contact with CCA-treated wood. The SHEDS model is designed to interface with more sophisticated source-to-concentration (e.g., the indoor fugacity model for pesticides) and exposure-to-dose (e.g., ERDEM or the Exposure Related Dose Estimation Model) models. In the development, evaluation and dissemination of the exposure and dose models, ORD has been collaborating with various academic partners (e.g. Rutgers and Harvard University) and with several private and public organizations, for example, the International life Sciences Institute (ILSI), the Cumulative and

Aggregate Risk Evaluation System (CARES) model group, and the World Health Organization's International Program on Chemical Safety (WHO/IPCS).

Physiologically-based toxicokinetic and toxicodynamic models provide useful approaches for developing and testing mechanistic hypotheses and identification of vulnerable developmental periods and susceptible individuals. Physiologically based pharmacokinetic (PBPK) models are often relied upon for simulating biologic processes, such as absorption, metabolism, distribution and elimination based on results of animal or clinical human studies. However, understanding the mechanisms of action of different chemicals by specific life-stage is quite important for accurately describing the relationship between exposures and dose using the PBPK models, as well as the relationships between dose and effects. In formulating appropriate PBPK models for children, ORD has been evaluating both human and animal data sets that are relevant to chemicals and exposure scenarios of concern for children. Two major approaches are being used for evaluating potential risks from early life exposures, each of which has strengths and limitations. The first approach is to extrapolate from adults to children based upon quantifiable differences in exposure, pharmacokinetics, and pharmacodynamics leading to potential pharmacological activity or toxicity. The second approach is to extrapolate across species from animal toxicity studies that involve exposures at early life stages. Such studies include developmental toxicity studies (in utero exposure), one- or two-generation reproductive, developmental toxicity and neurotoxicity studies.

ORD researchers have been conducting research using the first approach for evaluating and incorporating child/adult toxicokinetic differences in assessing risk to several environmental toxicants. Specific research questions addressed under this research are: 1) are there differences in toxicokinetics (TK) of xenobiotics between children and adults due to physiological changes and the immaturity of enzyme systems and clearance mechanisms? and 2) how can these differences be incorporated into PBTK models that simulate fate of environmental toxicants in both children and adults?

While there are very little PBTK data for environmental agents in children, there are bundant data for therapeutic drugs used in pediatric practice. Using published literature, a

children's PK database has been compiled by ORD-sponsored research that compares PK parameters between children and adults for 45 pharmaceutical agents.

The latter approach evaluates risks at early ages by conducting cross-species extrapolation from animal studies that involve exposures at early life-stages. A major challenge for modeling these life stages is how to obtain datasets for model parameterization (i.e. choices of physiological and chemical-specific parameters), calibration (i.e. assignment of values to the parameters), and testing (i.e. using an independent dataset to evaluate the success of the model beyond the original data). Pregnancy and very limited lactational models have been developed previously. Therefore, the postnatal development period has been the major focus of recent ORD research. Physiological parameters for growing rats have been compiled in an electronic database; this has been contributed to an ORD sponsored and ILSI-organized a collaborative effort among government Agencies, academics, and industry to evaluate the state of knowledge for physiological parameters for modeling growing mice, rats, and humans. Chemical-specific parameters can be estimated using *in vitro* or *in vivo* studies. In collaboration with ORD and the Air Force Research Laboratory, the age-dependency of partition coefficients for volatile organic compounds with a range of physicochemical properties are being determined in rat and human blood and tissues.

National Children's Study (NCS) for Susceptible (Children) Populations

The Children's Health Act of 2000 (Public Law 106-310) lays the groundwork for a major national study of the impact of the environment on child health. The act authorized the National Institute of Child Health and Human Development (NICHD) "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development." It directed NICHD to establish a consortium of representatives from appropriate Federal agencies, including the US Environmental Protection Agency, to: " 1) plan, develop, and implement a prospective cohort study from birth to adulthood, to evaluate the effect of both chronic and intermittent exposures on child health and human development; and 2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes." The goal of the National Children's Study, created in response to

these directives, is to develop information that will ultimately lead to improvement in the health, development, and well being of children. The primary aim of the NCS is to investigate the separate and combined effects of environmental exposures (chemical, biological, physical, psychosocial) as well as gene-environment interactions on pregnancy outcomes, child health and development, and precursors of adult disease.

ORD scientists have worked closely with their colleagues in other Agencies to build a foundation for the National Children's Study. Beginning in 2000, these efforts collectively known as "pilot studies," were conducted in three general areas, including design studies to explore different ways to conduct the Study, health-related studies to evaluate and recommend specific testing and measurement techniques, and exposure studies to identify methods and approaches to measure or assess environmental exposures and to identify the different pathways of these exposures. Planning and protocol development for the National Children's Study is well underway, and the Study is expected to be launched in late 2005. ORD researchers are working closely with scientists from the other lead Agencies in the planning and design of the study, and in developing and testing methods for data collection. ORD is also engaging the extramural scientific community to develop and test methods for data collection, biological markers and other tools, such as questionnaire or environmental information for the NCS.

Susceptibility: Aging

Demographics of the US are changing rapidly. By the year 2030, one of every five Americans will be over 65 years, twice the current population, with the population older than 85 years growing even more rapidly. This growth in the number of older Americans has major implications from both human and ecological health perspectives. In October, 2002, the EPA Administrator launched an Aging Initiative to address these issues, recognizing that EPA has a legislative mandate (through the Safe Drinking Water Act and Clean Air Act) to protect America's most susceptible sub-populations as defined by lifestage. As with the Agency's well-established programs to assess risk to children, a program focused on the aging population must consider the exposure, toxicokinetic (TK), and toxicodynamic (TD) factors associated with this lifestage. ORD is uniquely positioned to address these issues because of its strong research programs in human activity, exposure, TK, and TD as well as ecology and land-use planning.

EPA's particulate matter research program, for example, has established a strong record for investigating the susceptibility of older adults using teams from across ORD's labs and centers; one goal of the research program on aging is to expand this understanding to other environmental contaminants.

Health risk increases with age; EPA needs to understand the contributions of environmental exposures and conditions to mitigate human health risk as individuals enter the later stages of life. The nascent ORD research program on aging and environmental health addresses the following questions: Are older adults more susceptible to health effects of environmental exposures than younger adults? Which older adults? What are the high priority exposure and health effects for this sub-population? How do aging-related alterations in toxicokinetics and toxicodynamics affect the susceptibility of older adults? Equally important will be the need to understand the impact on ecological resources associated with needs of this population. Prominent questions include: As the population ages, how will the changes in, e.g., housing, recreation and transportation needs and waste handling and health care requirements affect natural resource utilization, land-use planning, and environmental quality? What are the environmental stressors associated with retirement in-place versus relocation to communities at the far edges of existing communities, expanding into rural areas and otherwise pristine areas?

In recognition of these issues, ORD has embarked on a research program to better: (1) delineate the special susceptibilities associated with the aged compared to the healthy younger adult population; (2) identify gaps in knowledge; and (3) establish research priorities. The data needed to address the problem of environmental public health for older adults can be arrayed along an environmental public health paradigm to identify the critical relationships between external pollution sources → human exposures → internal dose → early biological effect → and adverse health effects. EPA's approach is to generate models and data about aging-related changes in exposure, toxicokinetic (TK), and toxicodynamic (TD) factors to identify processes that may make older adults more vulnerable in the course of normal aging or in conjunction with changes in health status associated with aging. Data are needed regarding 1) behavior/activity patterns and exposure to the pollutants in the microenvironments of older adults; 2) changes in absorption, distribution, metabolism, and excretion with aging; 3) alterations in reserve capacity that alter the body's ability to compensate for the effects of environmental exposures; and 4)

strategies for effective communication of risk and risk reduction methods to older individuals and communities.

Asthma

In 2001, 20.3 million Americans had asthma, and 12 million had had an asthma attack in the previous year. In 1980, 3.6% of children had asthma. By 1995, the prevalence had increased to 7.5%, or approximately 5 million children. Because of its epidemic proportions, the US government has identified asthma as a top priority for research. Healthy People 2010, a guiding document for the Department of Health and Human Services, identified asthma as a "serious and growing health problem" in need of action, and the President's Task Force on Environmental Health and Safety Risks to Children selected asthma as one of four childhood diseases to target. In response, ORD has developed a targeted asthma research program, outlined by a peer-reviewed 2002 Asthma Research Strategy (US EPA, 2002). ORD is unique in that it has capabilities for toxicological, clinical, and epidemiological research combined with extensive capabilities of measuring air pollutants by personal monitoring, monitoring in and around buildings, and fixed site community monitoring. Monitoring and health effects data are used to assist ORD in performing risk assessment and identifying risk management and intervention strategies that relate to asthmatics and their environment. The intended beneficiaries of this research program are primarily EPA's program offices and other federal programs, including: the Office of Air and Radiation, Office of Prevention Pesticides and Toxic substances (OPPTS), Regional Offices, National Center for Environmental Assessment, Department of Housing and Urban Development, and the General Services Administration.

ORD has developed a targeted asthma research program, focused on understanding how pollutants and allergens affect the incidence and severity of asthma and the underlying mechanisms, understanding the factors responsible for susceptibility of asthmatics to pollutants, and identifying effective risk management strategies to reduce the burden of asthma to the population. To address these questions, ORD is currently conducting both intramural and extramural research focusing on combustion-related particles (CRP) and bioaerosols. Research issues are addressed by using an interdisciplinary approach that includes epidemiology, clinical and experimental toxicology, exposure assessment, and risk management. Population studies

assess real world exposures of asthmatics to different pollutants (or their mixtures) at different concentrations. Controlled (animal and clinical) studies are aimed at better understanding the underlying mechanisms responsible for the onset and exacerbation of asthma. EPA is coordinating with other agencies involved in asthma research including the National Heart Lung and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Environmental Health Sciences (NIEHS), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control. National Center for Environmental Health (CDC/NCEH), and the National Center for Health Statistics (NCHS). EPA scientists are working closely with some of these organizations to ensure that EPA research complements and expands current research efforts. Examples of joint inter-agency collaborations include ORD support of an air pollution extension to the Inner-City Asthma Study (ICAS) and the EPA/NIAID/NIEHS funded Centers of Excellence in Children's Environmental Health and Disease Prevention Research.

Applications of Risk Assessment and Risk Management Principles and Practices to Susceptible Populations

In 1993, the National Academy of Science report *Pesticides in the Diet of Infants and Children* (NRC, 1993) recommended placing special emphasis on age-related sensitivity and the possible susceptibility of developing humans to environmental contaminants in risk assessment. In response to this report, the Administrator of the EPA established a policy for "Evaluating Health Risks to Children" (US EPA, 1995), which stated that the Agency will consider risks to infants and children consistently and explicitly as a part of risk assessments generated during its decision making process, including the setting of standards to protect public health and the environment. The ORD labs and centers and ORD sponsored extramural research are uniquely positioned to implement a research program to improve children's health risk assessment. In order to better characterize the risk of exposure to environmental stressors on susceptible populations, improved hazard characterization, dose-response assessment and exposure assessment are essential. It is critically important to have an interdisciplinary team that can conduct, incorporate and synthesize the research data /information produced by the intramural

and extramural programs into applications for improving risk assessment approaches for susceptible populations.

The effort here is to use information derived from methods, models and guidance provided by ORD research on susceptible populations, much of which is described in the research themes above, to make more informed scientifically sound risk assessment and risk management decisions and more informative risk communication to the public about susceptibility of children. The results improve the consistency of considerations of children's health in the form of better health assessments for specific chemicals in the *Integrated Risk Information System (IRIS)* which is used by the Agency offices and regions and by organizations outside the Agency (states, tribes other governmental bodies). The intended recipients of this effort are the EPA regulatory programs and regions, the EPA Office of Children's Health Protection, states, tribes and communities.

Uniquely Vulnerable Populations: Research in Targeted At Risk Populations

Protecting human health from known and potential environmental threats requires a broad understanding of human biological function and behavior, the characteristics of toxic agents, and the nature of diverse environmental settings. In each of these arenas ORD investigates multiple aspects of the basic relationships between chemical source and media transport, exposure and health effects, as well as intervention and outcomes. Even so, health risks from environmental toxics are not evenly distributed throughout the general population and cannot be managed commensurably.

There are many reasons for differential risk. For example, environmental conditions vary considerably within and between the seasons and geographical settings, modifying toxic agents' transport and impact. There are multiple cultural, behavioral and social factors that influence risk, as does preexisting disease, genetic predispositions and unexpected catastrophic events. With this awareness ORD has systematically fashioned a research program designed to employ cutting edge technologies and novel scientific methods to specifically address the health and wellness concerns of populations with unique exposures or vulnerabilities. Encouraged to focus on sensitive sub-populations by authorizations such as the Food Quality Protection Act and Presidential Executive Orders such as the E.O. 12928–Environmental Justice, ORD seeks to,

first, understand why some people and groups are more susceptible or highly exposed than others, considering genetic factors, health status and life stages. Secondly, ORD investigators aim to hone risk management and intervention methods to promote improved health outcomes in communities at risk.

With an integrated approach, ORD is singular in its capacity to understand the complex constituents of risk. With a collection of laboratories and research centers modeled in parallel to the risk paradigm, ORD coalesces specific research on exposure, biological effects, and intervention in a targeted manner. ORD collaborates with the Centers for Disease Control and Prevention, National Institutes of Health, state agencies and research institutions to identify specific high risk populations and to garner community-level involvement in research activities. This approach provides a direct mechanism to translate results to the audiences of concern: the targeted populations. Just as importantly, the novel methods and raw data have important secondary applications, which are often translated for EPA's Office of Pesticide Programs, Office of Children's Health Protection, Office of Air and Radiation, Office of Solid Waste and Emergency Response, and EPA Regional Offices.

ORD has developed a cross-disciplinary approach to investigate unique populations congruent with the *Human Health Research Strategy* (USEPA, 2003). One of the primary goals outlined in the Human Health Strategy is to support and conduct research, which seeks to understand how and why some populations are more susceptible or more highly exposed than others. ORD employs hypothesis-driven and observational research in working to understand the basis for human biological and environmental variation. Exposure research and epidemiological studies are often coordinated between ORD laboratories and centers to investigate disproportional risk in a community setting. The use of biological markers in human studies provides a common "language" that can be used between research teams of different disciplines. ORD has increasingly placed an emphasis on the development, validation and use of biomarkers because they can provide a direct link between exposure, susceptibility and effect. For example, two separate human studies along the US/ Mexico Border and in lower Manhattan where pesticides and air toxics respectively are of concern, involve NHEERL, NCER, NERL and NCEA in a way tailored to connect susceptibility and high exposure to effect on a molecular basis by analyzing DNA and urinary metabolites.

At times ORD recognizes the appropriateness of fostering community capacity building and supporting targeted populations in (a) conducting their own studies, (b) analyzing potentially sensitive biological and cultural data while (c) developing interventions designed specifically to their situation. With many populations who have traditionally been difficult to recruit and retain, the STAR extramural research program provides an open door between the resources and experiences of EPA scientists and extends the reach and direction of ORD efforts across the country. This is particularly the case for Native Americans, migrant workers, immigrant groups and low-income urban populations where the investigation of exposures and susceptibility factors are a top concern of EPA as is ensuring the trust of study participants in the quality and benefit of the science.

ORD does not work with unique populations in isolation, but rather in cooperation with invaluable partners, e.g. the Center for Environmental Health at the Centers for Disease Control and Prevention, who provide technical expertise in analytical chemistry, chemical exposures, health tracking and surveillance. Experience in addressing toxics in tribal country is offered by tribal scientists and health professionals at the Agency for Toxic Substances and Disease Registry. The National Institute of Environmental Health Sciences is a longstanding ORD partner in supporting the science of environmental justice and community-based participatory research via co-funding extramural research. Regional scientists and university researchers are integral in developing and maintaining relationships with targeted communities, building trust and ensuring benefits of sound, action-oriented science.

Summary

As mentioned in the Overview Section of this theme narrative, there are many intrinsic and extrinsic factors that could lead to differential sensitivity or vulnerability to environmental stressors. In the past, specific recommendations from the NRC and EPA Administrator priorities have focused ORD research on issues related to children.
Emerging demographic trends are now focusing on potential differential sensitivity of older people.

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Poster LTG3-01
Overview of ORD's Research to Understand the Exposure, Susceptibility, and Differential Risks of Children to Pesticides

Presenter: Roy Fortmann (NERL)
Contributors: Kacee Deener (NCER); Virgina Moser (NHEERL); Dan Stout and Nicolle Tulve (NERL), Gertrud Berkowitz and Mary Wolff (Mount Sinai School of Medicine), Brenda Eskenazi and Asa Bradman (University of California at Berkeley), Richard Fenske and Elaine Faustman (University of Washington), and Robin Whyatt (Columbia University)

Science Question:

This research addresses the following science questions:

- What subpopulations have differential risk to pesticides?
- What is the basis for differential risk?
- What is the risk to susceptible subpopulations?
- How can differential risk be mitigated?

The Research:

One of the goals of the Office of Research and Development's (ORD) human health research is to provide the scientific basis to understand and protect subpopulations that have differential risks. Understanding the exposure, susceptibility, and differential risks of children to pesticides is integral to ORD's effort to provide scientific support for conducting risk assessments that consider the vulnerabilities of susceptible and highly exposed life stages and subpopulations. The research on children's exposure to pesticides addresses the requirements of the Food Quality Protection Act of 1996 and the Safe Drinking Water Act Amendments of 1996 that EPA consider children and other potentially susceptible groups when setting health-based standards. In response to these requirements, ORD developed a systematic approach to address the key science questions identified in its research strategy documents and to collect data to fill critical gaps in our understanding of children's exposures, susceptibility, and differential risk. Key research outputs that were identified included *(1)* tools for identifying highly exposed populations, *(2)* tools for characterizing exposures and risks for subpopulations, *(3)* tools for describing the biological basis for differential sensitivity, and *(4)* tools that lead to reduced exposure (see ORD's logic diagrams). The quality and quantity of the available scientific data regarding exposure and response and the existing data gaps were evaluated and a conceptual model was developed that was used to identify and prioritize research needs. A set of highly focused research studies were then performed by ORD researchers and their collaborators to collect high quality data to fill critical data gaps. To evaluate exposure, the studies developed innovative tools for assessing children's exposures (see Tulve et al. poster), collected data on the pesticides to which children are currently exposed (see Fortmann et al poster), and developed data on the factors that impact children's exposures (see Stout et al. poster). Basic research within ORD was initiated to evaluate differential responses to those pesticide exposures (see Moser et al. poster) to determine the magnitude and biological basis for the differences. ORD

also awarded STAR Grants to eight Centers of Excellence in Children's Environmental Health and Disease Prevention Research, where research has been, and continues to be, performed that has contributed substantially to developing the tools described above, as well as to developing and implementing effective intervention strategies (see Deener et al. posters). The Center's research efforts address the continuum from exposure, susceptibility, and effects through environmental epidemiology studies, incorporating a variety of tools including pesticide and metabolite concentrations in environmental and biological samples.

This poster provides an overview of ORD's approach to developing the critical research tools, the accomplishments of this research program, and the future directions.

Impact and Outcomes:

This research reduces uncertainty in risk assessment by:

- Implementing research that contributes to a substantially improved understanding of the exposures, susceptibility, and risk of children to pesticides
- Collaborating with the EPA Program Offices, other Federal Agencies, industry and academia to implement research addressing high priority children's research needs
- Providing validated data through web-based databases that are being used by ORD, the Office of Pesticide Programs, the Office of Children's Health Protection, industry, and others to improve exposure and risk assessments for children
- Providing validated exposure, effects, assessment, and risk management data and methods that will assist the Agency in meeting the mandates of the Food Quality Protection Act of 1996
- Providing real-world data for the development and evaluation of sophisticated models assessing exposure, effects, and risk
- Providing results that will likely inform the planning and implementation of the National Children's Study (NCS), through both publications and the involvement of the center investigators in the NCS workgroups
- Providing real-world data that are being used to develop risk intervention and source management strategies.

Poster LTG3-02
Innovative Tools and Methods for Assessing Children's Pesticide Exposures

Presenter: Nicolle Tulve (NERL)
Contributors: Kacee Deener and Chris Saint (NCER); and Elaine Cohen Hubal, Lisa Melnyk, Linda Sheldon, and Daniel Stout (NERL)

Science Question:

The research addresses the following science question:

- What are the innovative tools and methods needed to provide the scientific basis to protect subpopulations that have differential risks?

The Research:

A goal of the Office of Research and Development's (ORD) human health research program is to provide the scientific basis to protect subpopulations that have differential risks. Children's exposures to environmental contaminants are different than adults due, in part, to differences in physiologic function, surface-to-volume ratio, and the way in which children interact with their environment (i.e., sitting on the floor, eating off the floor, hand-to-mouth activity). Therefore, the tools and methods used to assess exposure for adults cannot be directly applied to children. Research on children's exposure to environmental contaminants is being performed within EPA, academia, industry, and other research organizations. However, the protocols and methods that have been previously developed and implemented by individual researchers for specific studies do not always collect all of the data, and with documentation addressing data quality, that are required for reliable exposure assessments. As a result of these shortfalls, the data collected can not always be interpreted for assessing exposures and risks. Prior to the ORD research summarized herein, standardized protocols for conducting exposure field studies that provided useful data for measurement-based exposure assessments did not exist. Likewise, protocols for developing exposure factor data to be used for modeling assessments were not available. The development of innovative tools and methods for assessing children's pesticide exposures are integral to ORD's human health research program. In order to evaluate whether a subpopulation can be considered to have differential risks, tools and methods that are capable of measuring differential risks must be developed and tested.

Numerous tools and methods have been developed by ORD to characterize children's pesticide exposures. These tools and methods include: *(1)* a *Protocol* for evaluating children's aggregate exposures to chemicals, *(2)* methods for collecting urine samples using commercially-available disposable diapers, *(3)* a non-invasive saliva biomonitoring method, *(4)* improved methods for collecting and analyzing dust samples, *(5)* a glove protocol method to assess pesticide exposures from pets, *(6)* improved methods for collecting time/activity information, including a visual child activity diary and a novel global positioning system technology to characterize child activity patterns, *(7)* methods for using cotton garments to estimate dermal exposure, *(8)* development of a less burdensome "lunchbox" sampler for air sampling, *(9)* multi-residue analysis methods for

pyrethroid pesticides, and *(10)* methods for sampling surfaces using wipes. The validated results of these methods development studies are being compiled in web-accessible databases and provided to the scientific community. The data are being analyzed with the results used to fill critical exposure/exposure factor data gaps and to reduce default assumptions in the risk assessment process. These results are also being used to update the ORD Exposure Factors Handbooks.

The research supporting the development of these innovative tools and methods demonstrates ORD leadership within the international exposure and risk assessment fields. By working closely with and sharing these improved methods and protocols with community stakeholders, industry partners, and academia, ORD is promoting the consistent collection of high quality data needed to reduce uncertainties in risk assessment and ultimately reduce children's health risks. This poster highlights the innovative tools and methods that have been developed and used by ORD in its research program.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing and validating numerous innovative tools and methods for characterizing children's exposures that have been shared with other groups (EPA's Program Offices, other Federal Agencies, and researchers in academia and industry). For example, the glove protocol for measuring pesticides on pet fur has been incorporated into the revised pesticide exposure guidelines for use in the pesticide registration process. The improved methods for collecting and analyzing dust samples will be incorporated into future pesticide exposure assessment guidelines
- Providing data and tools for generating high quality data that will be used to meet the mandates of the Food Quality Protection Act of 1996
- Collaborating with ORD and other stakeholders to ensure the validated methods and protocols are being employed in future children's exposure and environmental epidemiology research studies to generate the high quality data for risk assessment
- Providing research results that have resulted in environmental health policy changes in Washington, California, and Minnesota. The methods developed and validated by ORD researchers are being used in a number of on-going exposure and environmental epidemiology studies.

Poster LTG3-03
Measurement Studies to Assess Children's Exposures to Pesticides

Presenter: Roy Fortmann (NERL)
Contributors: Kacee Deener and Chris Saint (NCER); Elaine Cohen Hubal, Lisa Melnyk, Marsha Morgan, Linda Sheldon, Dan Stout, and Nicolle Tulve (NERL), Gertrud Berkowitz and Mary Wolff (Mount Sinai School of Medicine), Brenda Eskenazi and Asa Bradman (University of California at Berkeley), Richard Fenske and Elaine Faustman (University of Washington), and Robin Whyatt (Columbia University)

Science Questions:

This research addresses the following science questions:

- What subpopulations have differential risk to pesticides?
- Are some susceptible subpopulations and age groups of children exposed to higher levels of pesticides or more toxic pesticides than other subpopulations?
- If some susceptible subpopulations of children are more highly exposed to pesticides, how and why are these children exposed?

The Research:

EPA is committed to protecting children's health through identifying, assessing, and reducing the risks from exposures to pesticides and other chemicals present in the air they breath, food they eat, water they drink, and surfaces they touch. The Agency is committed to understanding why some people and groups are more highly susceptible or highly exposed than others. This research focuses on the latter. The Office of Research and Development (ORD) has performed and funded several children's pesticide exposure studies to collect data that has improved our understanding of what pesticides children are exposed to; the levels of the pesticides in food, beverages, and environmental media; and the key factors that impact children's exposures. Many of these studies have also involved the collection of biological samples from the children. ORD-sponsored studies, both intramural and STAR Grant studies, have addressed exposures for a wide range of children's ages, under different socioeconomic conditions, in different environments (e.g., homes and child care centers), for many different pesticides. The scope of these studies has varied, with a number of them being relatively large. The objectives have also varied. However, as shown in this poster, the studies complement each other, providing the EPA with a comprehensive picture, filling in gaps, and substantially improved understanding of the exposures of this susceptible subpopulation to pesticides.

Examples of these studies include the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP), which measured exposures of 260 children (ages 2 to 5 years) to persistent and non-persistent pesticides in homes and child care centers in North Carolina and Ohio. The EPA-sponsored STAR Grant study of Exposures and Health of Farm Worker Children in California collected exposure samples from a cohort of 550 pregnant women and followed their newborn children for 3 years to address exposures to agricultural pesticides.

Research by the Columbia University Children's Center has examined exposures of children of minority communities in the inner city areas of North Manhattan and South Bronx, New York, to determine the validity of exposure markers and their relationship to outcome measures. Exposures of a very different subpopulation (urban and rural children, ages 3 to 13 years) were measured in the Minnesota Children's Pesticide Exposure Study.

The validated results of these studies are being compiled in web-accessible databases. The data are being analyzed with the results used to fill critical exposure/exposure factor data gaps and to reduce default assumptions in the risk assessment process. The results are also being used to update the ORD Exposure Factors Handbooks.

ORD's measurement studies are in various stages of completion. CTEPP and MNPCES, for example, have been completed. Work at the ORD funded children's centers is also continuing. ORD will be collecting additional data on exposures of children ages 3 months to 3 years in the Children's Environmental Exposure Research Study, scheduled to begin in summer 2005.

This poster presents information for a number of ORD-sponsored children's exposure studies, including descriptions of the age groups, the environments monitored, samples collected, and important findings that have furthered our understanding of children's exposures to pesticides.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Demonstrating the value of employing the innovative methods in field studies to consistently collect high quality exposure and exposure factor data
- Conducting numerous children's exposure studies that have collected a large volume of high quality exposure/exposure factor data that has contributed to a substantially improved understanding of the exposures of children to pesticides in their homes and child care environments that will be used by the Agency to meet the mandates of the Food Quality Protection Act of 1996 and to reduce children's risk
- Generating data for age groups (especially very young children) that have not been studied extensively in previous exposure measurement studies
- Conducting studies that characterize real-world concentrations of pesticides to which the children are exposed and the key factors affecting exposures of children
- Using these data to update and further refine exposure factors used in risk assessments being performed by the EPA Office of Pesticide Programs, industry, and others to improve exposure and risk assessments for children
- Providing a rich database to develop and test hypotheses for determining which populations are more highly-exposed and for the development and evaluation of models
- Providing results that will likely inform the planning and implementation of the National Children's Study (NCS), through both publications and the involvement of the center investigators in the NCS workgroups
- Providing validated data that are also being used to develop risk intervention and source management strategies.

Poster LTG3-04
Understanding the Factors Affecting Children's Residential Pesticide Exposures

Presenter: Daniel Stout (NERL)
Contributors: Elaine Cohen Hubal, Lisa Melnyk, Linda Sheldon, and Nicolle Tulve (NERL); Kathleen Deener (NCER); and Mark Mason (NRMRL)

Science Questions:

This research addresses the following science questions:

- What is the basis for differential risks of children exposed to pesticides?
- What are the factors that influence children's exposure in homes and living areas?
- What are the important exposure pathways?
- How can the uncertainties in exposure and risk assessments be reduced?

The Research:

The Office of Research and Development (ORD) has recognized the importance of understanding the routes and pathways by which children can be exposed to pesticides in their homes and daycares. Children's exposure to pesticides occurs via multiple routes and pathways, including dietary ingestion (from foods and drinking water) and non-dietary routes (e.g., inhalation of pesticide residues from air, dermal contact with pesticide residues on indoor or outdoor surfaces, or ingestion of residues transferred from children's hand to mouth or object to mouth activities). ORD's research is designed to collect data that will improve our understanding of the relative importance of these routes of exposure and identify the key factors affecting children's exposures to pesticides.

A research strategy has been developed and implemented to collect information on pesticide use patterns, spatial and temporal distribution of pesticides in non-occupational environments, dietary ingestion, dermal and non-dietary exposure assessment methods, and exposure factors. Data on spatial and temporal distributions of pesticides applied in homes have been collected in both field measurement studies and under controlled conditions in the US EPA Indoor Air Quality Research House. During tests at the research house, chlorpyrifos residues were monitored over a 21 day period on various surfaces located throughout the home after a professional crack-and-crevice application of chlorpyrifos in the kitchen. Chlorpyrifos residue levels were detected in all the samples in every room for the entire 21 day study, although the concentrations decreased by ~70% over the study duration. In another study, factors affecting exposure associated with repeated dermal contacts with surfaces (mimicking hand contact) have been addressed in laboratory tests using a non-toxic tracer (riboflavin) in conjunction with a novel fluorescent imaging system. These tests demonstrated that repeated contacts do not result in a linear increase in the amount of residue on the skin and that surface parameters, such as moisture on the skin, were more important than the loading on the surface being contacted. Another ORD research activity has addressed potential exposures to pesticides from food contaminated through normal activities in the home such as processing the food in the home or a

child dropping a food item onto pesticide treated surfaces. The results of measurements in homes with recent pesticide applications indicate that children's handling and processing of the food at home result in increased food residue concentrations, and therefore are potentially significant route of exposure that are not considered in current risk assessments. Pets have been identified as potentially important vehicles for translocating residues from outdoors to indoors. A number of studies have addressed the importance of children's activities on their exposures. Analyses of data on children's mouthing behavior, for example, showed differences in mouthing frequency related to age, but not to gender.

This poster summarizes the study results and demonstrates how ORD is conducting research to provide improved understandings of the key factors that may impact children's exposures to pesticides.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing children's pesticide exposure and exposure factor data that will be used to meet the mandates of the Food Quality Protection Act (FQPA) of 1996
- Conducting innovative research resulting in improved understanding of key factors influencing children's exposures to pesticides
- Providing updated exposure factor data that will be used to reduce uncertainty in exposure assessments and for the development and evaluation of multi-media, multi-pathway exposure models
- Filling data gaps and providing exposure/exposure factor data for updating ORD's Exposure Factors Handbooks. For example, data on the frequency of mouthing activity will be replace or refine default assumptions currently used by OPP and OPPT in exposure and risk assessments for pesticides. These data will also be available to industry and other private sector researchers for use in exposure and risk assessments.

Poster LTG3-05
Differential Sensitivity of the Young to Cholinesterase-Inhibiting Pesticides

Presenter: Virginia C. Moser (NHEERL)
Contributors: Stephanie Padilla (NHEERL); William Sette, Kathleen Raffaele, and Susan Makris (OPP/OPPTS)

Science Questions:

This research addresses the following science questions:

- What subpopulations have differential risk to pesticide toxicity?
- Specifically, are children and infants more sensitive to the neurotoxic effects of cholinesterase-inhibiting pesticides, and, if so, what is the biological basis for this differential sensitivity?

The Research:

This research addressed concerns that risk assessment approaches may not adequately protect the young, as was suggested in the National Research Council monograph, "Pesticides in the Diets of Infants and Children". The 1996 Food Quality Protection Act (FQPA) required a determination of "reasonable certainty of no harm" for children. The Office of Pesticide Programs (OPP) needed sound scientific data to understand better the differential sensitivity of this subpopulation, so they can make informed decisions regarding the assessment of risks for individual chemicals and cumulative exposures.

The overall goal of this research was to characterize the differential response of the young to the neurobehavioral and neurochemical effects of cholinesterase-inhibiting pesticides (carbamates and organophosphates), and to determine the biological mechanisms for these differences. We systematically compared dose-response data in young (preweaning) and adult rats. We then identified and tested hypotheses to establish mechanisms, which would allow better extrapolation to the human population. We showed that the magnitude of differences in sensitivity at maximum-tolerated doses (MTDs) can vary as much as 9-fold, depending on the pesticide, and that differences in sensitivity to cholinesterase inhibition correlated well with the MTDs. Furthermore, age-related differences in behavioral, or functional, responses depend on the specific endpoint as well as the specific pesticide. We found that the sensitivity of the target enzyme to inhibition by the pesticides is not different in the young, and that some age-dependent metabolic differences could not account for the increased sensitivity. We postulated that differences in detoxification via non-target esterases may be a key kinetic parameter mediating this sensitivity, due to markedly lower activity of these detoxification enzymes in the young organism. The detoxification of pesticides was simulated in *in vitro* assays using rat blood and liver. This *in vitro* model verified our conclusions. We concluded that pesticides which depend to a great degree on detoxification via specific esterases will be more potent in producing neurotoxicity in the young.

The research is near completion and has provided data for developing future research hypotheses.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Identifying pesticides for which the young are uniquely sensitive
- Generating effects data that have directly influenced regulatory actions and risk assessment decisions for carbamates and OP pesticides, as directed by FQPA. OPP has used these results in their decision to cancel or reduce household and agricultural uses of selected cholinesterase-inhibiting pesticides to decrease potential for exposure in the young. In addition, a Data Call-In (DCI) was issued for all registered organophosphates (~30) to collect data on comparative sensitivity of the young. ORD data were instrumental in developing the testing paradigm required by OPP of pesticide registrants for this evaluation. This DCI has provided information used by the Agency to evaluate the risk to infants and children
- Improving the understanding of the influence of detoxification enzymes, science that is directly relevant to human exposures, because, like young rats, infants and young children have less detoxification enzymes than adults. This result could also impact future risk assessments of other chemical classes that may be metabolized by these enzymes, or others that have different maturation profiles
- Conducting high quality research that has directly contributed to lowered risk of adverse health outcomes from pesticide exposure in infants and children.

LTG3-06
Children and Pesticides: Investigating Exposure, Susceptibility, and Effects through Epidemiology

Presenter: Kacee Deener (NCER
Contributors: Chris Saint and Nigel Fields (NCER)

Science Questions:

This research addresses the following science questions:

- What is the basis for differential risk?
- What is the risk to each subpopulation?

The Research:

EPA is committed to protecting human health through identifying, assessing, and reducing the risks presented by the thousands of chemicals upon which our society has come to depend. Underpinned by Federal Executive Order 13045 (April 1997), "Protection of Children from Environmental Health Risks and Safety Risks", the Agency is committed to understanding why some people and groups are more highly susceptible or highly exposed than others. Life stage and genetic predisposition, along with a myriad of other factors, create complex interactions that are best teased out through a carefully designed epidemiological study. The Office of Research and Development (ORD) is uniquely poised as the research arm of EPA to conduct research that examines exposure-susceptibility-effects relationships. ORD has funded several children's environmental health centers that have developed multidisciplinary basic and applied research to support studies on the causes and mechanisms of children's environmentally induced diseases, and to identify relevant environmental exposures of concern. Several of these Centers focus on health effects resulting from exposure to pesticides. Several significant findings have resulted from this EPA supported research. Epidemiologic evidence from one of the centers suggests that recent EPA restrictions on the use of certain organophosphate (OP) pesticides in the home have reduced the exposure of both mothers and infants to these pesticides, and that since these insecticide exposure levels have been reduced substantially, there is no longer a detectable impact on fetal growth. Another EPA-funded center, in cooperation with EPA Region 9, has assessed the potential risk levels associated with EPA reference values related to children's risks from pesticide exposure, and the findings have called into question the currently used assumption that established RfD and RfC values represent negligibly small risk levels (EHP, 111(13):1640-1648, 2003). Other results include: the discovery of an apparent gene-environment interaction for OP pesticide exposure and paraoxanase (PON1) polymorphisms; demonstrated substantially lower expression levels of PON1 in human infants than adults; and the discovery that higher levels of pesticide are found in the dust in vehicles used by farmworkers.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Disseminating the ORD study research results throughout the scientific community and to community groups and local health departments
- Providing opportunities for research collaboration between the academic community, EPA Program Offices and research laboratories and centers (to develop the visual child activity diary), and regional scientists (to conduct a study of pesticides in vehicle dust). These collaborations provide needed expertise, skills, and capabilities that enhance ORD's research capability and capacity to address key issues associated with children's risks to pesticides
- Conducting research that showed a correlation between a reduction in levels of insecticide exposure and an improvement in a health endpoint (fetal growth), demonstrating that a public health benefit resulting from a regulatory decision (Food Quality Protection Act of 1996)
- Producing scientific data and evidence that has called into question the assumption that RfD and RfC values represent negligibly small risk, leading to a re-evaluation of the current RfD and RfC values for certain organophosphate pesticides
- Providing results that will likely inform the planning and implementation of the National Children's Study (NCS), through both publications and the involvement of the center investigators in the NCS workgroups.

Poster LTG3-07
Children and Pesticides: Approaches to Reducing Health Risks through Intervention, Source Management, and Community Partnerships

Presenter: Kacee Deener (NCER)
Contributors: Chris Saint and Nigel Fields (NCER)

Science Question:

- How can differential risk be mitigated?

The Research:

EPA has made it a priority to conduct and fund high quality children's environmental health research. Through it's extramural grants program, EPA, in cooperation with NIEHS, has funded several children's environmental health centers that are conducting basic and applied research into the causes and mechanisms of children's environmentally induced diseases, with one unique component being the inclusion of community-based intervention projects designed to mitigate risk by reducing hazardous exposures and their potential health effects. Through this effort, EPA has developed a portfolio of research that examines ways to reduce health risks from exposure to pesticides through source management, intervention, and community partnerships. Source management efforts often begin with the identification of relevant exposure pathways, and intervention methods are then tailored for specific situations. In-home and community level intervention programs have been developed for both urban and rural settings to reduce children's pesticide exposures. In-home interventions include the development of home-based educational strategies and the implementation of integrated pest management (IPM), which incorporates professional house cleaning, sealing of cracks and crevices to reduce cockroach populations, and encouraging the use of lower toxicity pesticides in the home. Home-based interventions are enhanced and taken to a broader audience through the development of community level programs, including health fairs, family parties, and educational programs. Interventions are bolstered through partnerships with various community organizations, including multi-lingual community health organizations, state-funded health programs, and agricultural associations. Results from the research thus far have shown that interventions are effective in reducing environmental exposures. Based on exposure assessment research, one center determined that a major exposure pathway for children in an agricultural setting can be attributed to a farmworker parent "taking home" pesticide residues. Source management efforts were designed to break that take-home pathway by providing a place for the parent to change out of clothes worn in the field before beginning the trip home. Two children's centers have demonstrated that IPM is more effective at reducing cockroach populations than traditional pest control practices. Another center has discovered that many farmworkers, because of cultural beliefs that cold water causes arthritis, do not wash their hands in the field where only cold water is provided for hand washing.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Conducting collaborative research to develop and test innovative IPM intervention strategies for reducing children's pesticides exposures
- Disseminating the research results and facilitating the implementation of these intervention strategies. The Central Coast Grower Shipper Association has agreed to provide warm hand washing water and protective clothing based on research findings from the children's center at the University of Berkeley. This center has also developed a prenatal environmental health education program for pregnant women enrolled in the California Comprehensive Perinatal Services Program (a state-funded service that provides prenatal care to 150,000 low-income women in California each year). The Columbia University children's center is working with the New York City Department of Health and Mental Hygiene and the New York City Housing Authority to consider the use of IPM in public housing
- Providing data and scientific understanding to generate new hypotheses and implement additional risk management research.

Poster LTG3-08
Overview of Source-to-Effects Modeling Research for Susceptible-(Children) Populations

Presenter: Halûk Özkaynak (NERL)
Contributors: Hugh Barton (NHEERL); Bob Sonawane (NCEA)

Science Questions:

This research addresses the following science questions:

- How can we improve the linkage among emissions, exposure and dose estimations for predicting target tissue(s) or biologically effective dose(s) for children?
- What are the best approaches for developing pharmacokinetics modeling and evaluating potential heath risks to children, either using human studies data or by extrapolating across species using animal toxicity data that involve exposures at early life stages?

The Research:

The Office of Research and Development's (ORD) source-to-effects modeling research for susceptible populations is designed to develop, evaluate, and apply a scientifically robust human exposure and risk analysis framework that incorporates models, databases, and analytical tools for realistically estimating exposures, dose, and health risks to children by predicting the complex relationships between sources, exposures, dose, and health effects. ORD research has developed state-of-the-art source, exposure, and dose models. Sophisticated emission or source-to-concentration models, including an indoor fugacity model for pesticides, have been developed. The Stochastic Human Exposure and Dose Simulation (SHEDS) model examines children's aggregate exposure to a variety of multi-media, multi-pathway pollutants. The Exposure Related Dose Estimation Model (ERDEM) estimates selected tissue doses from exposure data. SHEDS is designed to interface with these sophisticated source emissions and exposure-to-dose models. The development and evaluation of these models is described in the Aggregate/Cumulative Risk session.

To better understand potential health risks to children from exposures to environmental chemicals of concern, it is necessary to investigate quantitative relationships between exposure, absorbed dose and the biologically effective dose. Physiologically-based pharmacokinetic (PBPK) models are often relied upon for simulating biologic processes (absorption, metabolism, distribution and elimination) based on results of animal or clinical human studies. Understanding the mechanisms of action of different chemicals by life-stage is important for accurately describing the relationship between children's exposures and dose with PBPK models, as well as the relationships between dose and effects.

In formulating appropriate pharmacokinetic models for children, ORD has been evaluating both human and animal data that are relevant to chemicals and exposure scenarios of concern for children. ORD researchers have been examining results from human pharmaceuticals studies and developing PBPK models for children's exposure to caffeine and malathion. ORD scientists have been evaluating risks at early ages and conducting cross-species extrapolation from animal studies that involve exposures at early life-stages. This later approach requires extrapolation based on differences in exposure and pharmacokinetics, but also involves extrapolations from animal toxicity test species to humans. The animal toxicity studies that are available include developmental (in-utero) and one- or two-generation reproductive and developmental toxicity studies (in-utero, lactational and post-weaning). On-going and future ORD exposure, PBPK, and computational toxicology modeling research programs will produce results that will be used to improve the cross-species extrapolation of effects and the prediction of health risks to children that result from exposures to chemicals of concern.

Impact and Outcomes:

This research program will reduce uncertainty in risk assessment by:

- Producing improved source, exposure, and dose models that facilitate making risk projections for children during critical developmental stages
- Identifying modeling data needs and promoting the collection of field and laboratory data on different species needed for advancing the early life pharmacokinetic modeling
- Providing a more reliable source-to-effects modeling framework that will allow the Agency to reduce or replace default uncertainty factors typically used in its current risk assessments for children. The models, modeling framework, and resulting guidance will move toward more data-derived approaches
- Designing and implementing more effective risk management programs.

Poster LTG3-09
Evaluation and Incorporation of Child/Adult Toxicokinetic Differences in Assessing Risks to Toxicants

Presenter: Bob Sonawane (NCEA)
Contributors: Hugh Barton and Marina Evans (NHEERL)

Science Questions:

This research addresses the following science questions:

- Are there differences in toxicokinetics (TK) of xenobiotics between children and adults due to physiological changes and the immaturity of enzyme systems and clearance mechanisms?
- How can these differences be incorporated into physiologically-based pharmacokinetic models that simulate the fate of environmental toxicants in both children and adults?
- What are the implications of assessing children's risks from environmental agents?

The Research:

Children's risks from environmental toxicant exposures can be modified by toxicokinetic factors that affect the internal dose of the parent chemical and/or active metabolite(s). Numerous physiologic differences between children and adults affect toxicokinetics, including: size of lipid; tissue compartments; blood flows; protein binding capacity; and immature function of hepatic and extrahepatic organ systems. Physiologically-based toxicokinetic (PBTK) models can be used to simulate the absorption, distribution, metabolism, and excretion of xenobiotics in both children and adults and also allow for a direct comparison of internal dose and potential risk across species and age groups.

While there is very little PBTK data for environmental agents in children, there is a wealth of comparable children's data for therapeutic drugs used in pediatric practice. Using published literature data, ORD has compiled a children's TK database that compares TK parameters between children and adults for 45 drugs. This database has enabled ORD researchers to compare child and adult TK function across a number of cytochrome P450 (CYP) pathways, as well as certain Phase II conjugation reactions and renal elimination. These comparisons indicate that premature and full-term neonates tend to have 3 to 9 times longer half-life than adults for the drugs included in the database. Equally important, this difference disappears starting at 2-6 months of age and beyond. The research also has shown that the half-life can be shorter for children than adults for specific drugs and pathways. These findings present a TK developmental profile that is relevant to environmental toxicants metabolized and cleared by the pathways represented in the database.

Furthermore, the database provides an opportunity for calibrating and validating PBTK models for theophylline and caffeine. These drugs are particularly useful case studies because the

clearance mechanism in neonates and infants is considerably different (slower) than adults. ORD is performing a PBPK modeling case study on malathion exposures for children (see Aggregate/Cumulative Session).

Chemical dosimetry will likely differ across children's developmental stages, and in general between children and adults. Future Agency risk assessments can begin to describe the implications of these child/adult differences by appreciating how toxicokinetics can affect toxicant action and elimination, and by considering the functional status of these dynamic mechanisms in early life. PBTK models for environmental toxicants are needed for quantitative evaluation of dosimetry differences across age groups based on better understanding of physiological development and enzyme maturation processes. The application of these innovative approaches will be critical in demonstrating whether the traditional uncertainty factors used in adult-based assessments are appropriate to account for sources of variability introduced by life-stages, species, route, and dose extrapolations.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Producing critical tools to enhance the understanding of toxicokinetic/ toxicodynamic differences across life-stages and to better characterize uncertainties in risk assessments of children and other sensitive subgroups
- Applying innovative tools/approaches and demonstrating whether traditional uncertainty factors used in adult-based assessments are appropriate to account for sources of variability introduced by life-stages, species, route, and dose extrapolations
- Providing the research results and guidance to the EPA Program Offices and external stakeholders for their use for estimating internal target dose and evaluating risk to children from environmental agents
- Informing risk assessors regarding child/adult differences in toxicokinetics by lifestage and how these should be considered in risk assessment
- Communicating these results at national and international meetings and published the findings in peer-reviewed scientific literature.

Poster LTG3-10
Species Extrapolation of Pharmacokinetics during Early Life Stages

Presenter: Hugh A. Barton (NHEERL)
Contributors: John Lipscomb (NCEA); Justin Teeguarden (Pacific Northwest National Laboratory)

Science Questions:

This research addresses the following science questions:

- Can cross-species extrapolation of toxicological studies in rodents involving early life stages (e.g. two-generation reproductive/developmental studies) be improved through the use of pharmacokinetic modeling?
- What approaches can be used to compile or obtain appropriate physiological and chemical-specific information for this modeling?

The Research:

Three approaches exist for evaluating potential early life hazards: 1) using data from children available from epidemiological studies, 2) animal toxicity testing during early development, and 3) assuming toxicity observed in adults would occur with some differential incidence (or severity) if early life dosimetry were accounted for. Each of these approaches involves the estimation of exposure and internal doses and, in the latter two cases, extrapolations from animals or adults to children. Computer simulation models, such as physiologically-based pharmacokinetic (PBPK) models, provide a rigorous and internally logical methodology for describing the numerous factors that can be important in extrapolating tissue dose from animals or adults to human children. The goal of this research is to develop PBPK models for the *in utero* and postnatal lactational and weaning periods in rodents, such that developmental studies can be simulated to obtain estimates of internal dose for a diverse range of chemicals. Simulations of two-generation studies in rats would be particularly valuable as these involve all of these early life stages and are frequently used as the basis of dose-response analyses for chemicals.

PBPK models rely upon two kinds of parameters, physiological and chemical-specific, so these are the focus of data compilation and collection. Pregnancy and very limited lactational models have been developed previously. Therefore, the growing rat pup has been the major focus. Physiological parameters for growing rats have been compiled in an electronic database. This database has been contributed to a ILSI-organized collaborative effort among government Agencies, academics, and industry to organize and evaluate the state of knowledge for physiological parameters for modeling growing mice, rats, and humans. Chemical-specific parameters can be estimated using *in vitro* or *in vivo* studies. In collaborative ORD and the Air Force Research Laboratory research activities, the age-dependency of partition coefficients for volatile organic compounds with a range of physicochemical properties are being determined in rat and human blood and tissues. These data demonstrate only minor differences across ages. By contrast, modeling of serum protein binding for estrogenic compounds demonstrates

substantial differences across ages and species due to high affinity binding to alpha-fetoprotein (rats) and serum hormone binding globulin (humans), while lower affinity albumin binding is age, but not species, dependent. Thus, determinants of tissue distribution must be carefully considered.
Conazole fungicides are the subject of an integrated pharmacokinetic and toxicity research effort (see Harmonization Session). Blood dosimetry for the one-generation toxicity studies in rats will be predicted using a model based upon *in vivo* pharmacokinetic studies in adult rats and *in vitro* studies of changes in liver metabolism at different ages with and without exposure. Additional validation studies will be undertaken, if necessary.

Future research will build on science learned through these on-going research activities and the additional hypotheses and data gaps discovered.

Impact and Outcomes:

This research program is reducing uncertainty in risk assessment by:

- Conducting on-going collaborative research with other human health research institutions (*e.g.*, Air Force Research laboratory, ILSI) to improve the understanding for how to use animal toxicology study data for supporting cross-species extrapolations
- Generating information and developing methods needed to support early life pharmacokinetic modeling
- Communicating the research results and issues through workshops (2005 Society of Toxicology Annual Meeting) and throughout the broader toxicology community
- Producing state-of-the-science modeling tools for use by the US EPA Program Offices in future risk assessments that based upon early life stage toxicological studies to supplement or replace current approaches based upon the maternal exposure.

Poster LTG3-11
The National Children's Study of Environmental Effects on Child Health and Development

Presenter: J. Quackenboss (NERL)
Contributors:P. Mendola (NHEERL); P. Scheidt (NIH/NICHD); K. Deener (NCER); R. Brown, T. Thomas, S. Selevan, C. Kimmel (NCEA)

Science Question:

The research addresses the following science questions:

- What is the contribution of environmental exposures to child health and development?
- Are there long-term health effects from early life exposures?
- Are certain population sub-groups more susceptible to environmental contaminants than others, and which factors alter susceptibility (e.g., specific genetic polymorphisms, immune deficiencies)?
- What factors account for disparities in health outcomes (e.g., race, ethnicity, poverty, environmental quality, housing, income, nutrition)?
- What are the effects of aggregate or cumulative exposures?
- Are uncertainty factors and defaults in risk assessment sufficient to protect children's health?

The Research:

The Children's Health Act of 2000 authorized a consortium of Federal agencies, including EPA, to develop and implement a prospective cohort study to: 1) evaluate the effects of both chronic and intermittent exposures on child health and human development, and 2) investigate basic mechanisms of developmental disorders and environmental factors that influence health and developmental processes. The National Children's Study (NCS) is the result of a multi-agency collaborative research effort, lead by the National Institute of Children's Health and Human Development (NICHD), aimed at addressing these science issues. The NCS will enroll women as early as possible in pregnancy, including some before conception, and will follow their children into adulthood (approximately 21 years of age). Outcomes of interest include: pregnancy outcomes, growth and neurobehavioral development, asthma, injuries, obesity and physical development. Environmental factors to be studied include chemical, physical, biological, behavioral, and social factors, as well as genetic factors and their interactions with the environment. The size of the study (100,000 newborn children) will provide a data base to answer many questions about the effects of children's exposures to environmental contaminants, including those where only a small percentage of the population experiences an effect, and to detect combined effects of low-level exposures.

Findings from the NCS will help determine, for example: if early life exposures to chemicals such as pesticides increase the risk of conditions such as autism and other developmental disabilities; the effects of prenatal and early childhood exposures with potential immune-modulating effects on the incidence and severity of asthma; or how individual, family, and

community factors affect the incidence, severity, and outcome of childhood injuries. The study will serve as a national resource for future studies of child health and development by providing a rich database and repository of environmental and biological samples and information that can be used to address future questions and hypotheses. This value is enhanced by unique features of the design, including a national probability-based sample for selection of geographic areas and participants, and pre-pregnancy enrollment to collect measures of early pregnancy exposures for a portion of study participants.

Planning and protocol development for the NCS is well underway with the initial study centers expected to be established in late 2005. ORD scientists are working closely with scientists from the other lead Agencies in the study planning and design, and in developing and testing methods for data collection. ORD is also engaging the extramural scientific community while developing and testing methods for data collection, biological markers and other tools, such as questionnaire or environmental information for the NCS.

Impact and Outcomes:

This research program is reducing uncertainty in risk assessment by:

- Providing ORD's exposure, effects, and assessment scientific expertise and state-of-the-science tools, approaches, and designs in support of the NCS
- Collaborating in studies, literature reviews, white papers, and workshops supporting the development of new methods, tools, approaches with the results of these activities being used to develop the NCS Study Plan
- Through continued collaboration, using the study platform and results to extend ORD's children's human health program and improving the understanding key factors influencing children's risk by lifestage, identifying data gaps, developing research hypotheses, generating improved tools for characterizing children's risk, and providing data and tools to improve Agency risk assessments for reducing children's risk.

Poster LTG3-12
Design Development Projects for the National Children's Study (NCS)

Presenter: Sherry G. Selevan (NCEA)
Contributors: Carole A. Kimmel (formerly NCEA); Pauline Mendola (NHEERL); James Quackenboss (NERL); Nigel Fields (NCER); Rebecca Brown (NCEA, formerly ASPH); Tracey W. Thomas (formerly AAAS); and Peter Scheidt, (Director, NCS, NICHD/NIH).

Science Questions:

This research addresses the following science questions:

- What lessons can we learn from other projects to assist in planning and executing the NCS?
- How can the sample best be selected to answer the diversity of questions in the NCS?
- How can innovations in technology be used to reduce respondent burden and increase data quality?

The Research:

ORD scientists have led several projects that impact the design of the NCS. These include the examination of the experiences of others in the field, such as scientists from the NIEHS/EPA Children's Environmental Health Centers who have much experience in conducting long-term birth and school-age cohort studies. ORD scientists have worked with the Center scientists to develop publications highlighting lessons learned with regard to study design, community-based participatory research, pesticide and air pollution exposure assessment, asthma, and neurobehavioral development.

One critical question is the sample design for the selection of study areas and participants. Different questions within the NCS have different design requirements to obtain valid results. ORD scientists played major roles, along with scientists at the other lead Agencies and the NCS Advisory Committee, in exploring the strengths and limitations of design options through white papers, an expert workshop, and other discussions. ORD scientists are currently working with the National Center for Health Statistics to implement the sampling strategy.

Given the depth and length of data collection in the NCS, planners are concerned about the study being overly burdensome to the participants. ORD scientists, along with those from the other lead Agencies, have been exploring alternative ways to collect data from respondents that are less burdensome, allow for the collection of information between clinical visits, increase data accuracy, and support data analysis in a more timely fashion. This has included the development of an annotated bibliography of available technologies, a workshop on innovative technologies for remote collection of data (questionnaire, health and exposure data), and white papers.

Finally, ORD is leading an interagency effort to initiate an early cohort in North Carolina that will have sufficient power to answer some research questions of interest to the NCS. Just as

important, this initial project will provide a real world opportunity to examine the implementation of the methods and approaches that are identified for the larger study and assess their suitability for use in the larger study, and where needed improve and/or replace the methods and approaches.

The National Children's Study will greatly contribute to a better understanding the role environment plays in healthy growth and development. The longitudinal study design and large number of families followed will allow the examination of a range of exposures not possible in smaller studies. These data will contribute to risk assessments, by providing quantitative exposure measures at different points in development, and directly linking them to health outcomes of importance.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing leadership, critical expertise and collaborative research needed for the design and implementation of the NCS, and the ability of this study to identify children's environmental risk factors for disease
- Drawing from previous experiences in developing the study plan and protocol for the NCS, and designing other projects studying children's environmental health
- Using information gleaned from a North Carolina cohort to inform the design and execution of the national study and to provide key data supporting the NCS objectives
- Identifying technologies to reduce participant burden, enhance data capture, and decrease overall costs for this large cohort study
- Influencing the sampling design decisions for the NCS (a nationally representative probability sample)
- Using the NCS to inform future ORD research hypotheses and contribute data that informs and enhances future risk assessments (quantitative exposure measures at different points in development that are directly linked to health outcomes of importance).

Poster LTG3-13
Exposure Projects to Support the National Children's Study

Presenter: James Quackenboss (NERL)
Contributors: Gary Robertson and Roy Fortmann (NERL); Nigel Fields (NCER); and Haluk Ozkaynak (ORD)

Science Questions:

This research addresses the following science questions:

- How well do data collection methods that impose a minimal burden on the study participants perform?
- How can exposure assessment methods be employed in a cost-effective manner to support testing of the NCS hypotheses?

The Research:

The National Children's Study (NCS) is a long term study based on a national probability sample of geographic locations and households, and includes assessment of pre- and early-pregnancy exposures. Several exposure assessment projects were initiated by the Office of Research and Development (ORD) scientists early in the development of the NCS, with examples provided in this poster. These projects utilize ORD's unique capabilities for integrating exposure methods and measurement approaches with large scale study designs. They were selected based on their relevance to the NCS needs for assessing children's exposures in the context of evaluating the NCS's hypotheses. In addition to the projects identified below, ORD scientists have provided leadership through collaborations with other Federal and non-Federal scientists and through serving on the NCS's Exposure to Chemical Agents Working Group to develop a white paper and manuscripts on potential exposure assessment approaches for the NCS**.**

Development of Exposure Assessment Study Design Options for the NCS. The large sample size and longitudinal nature of the NCS introduce unique statistical issues to address in developing a cost-effective sampling design. A very important issue is how to obtain enough samples to provide adequate statistical power to detect health effects attributable to environmental and personal exposures, and at the same time minimize participant burden and costs.

Demonstration of Low Cost, Low Burden, Exposure Monitoring Strategies for Use in the NCS. Three pilot studies have been undertaken involving nine participants in three cohorts: parents and their children ages 0-1 years, 3-5 years, and 6-8 years old. These demonstration studies were designed to address some of the concerns anticipated in carrying out the NCS, and to assess the feasibility of having study participants use readily available, easy to use, state-of-the-art methods, instruments, and techniques to collect environmental samples, biological samples, and survey information.

Synthesis of Applied Exposure Methods and Lessons Learned for the NCS. The EPA/NIEHS Children's Environmental Health Centers began in 1998 and have specialized in pediatric exposure, epidemiology and intervention research. ORD scientists have worked with investigators from these Centers to develop publications highlighting their experiences in conducting studies in birth cohorts and school age children. The exposure papers summarize their shared experiences in sampling, analyzing and translating air pollutant and pesticide exposures in the urban and rural environments. The papers evaluate alternative biological and environmental measures, hierarchical designs, interpersonal variability, and analytical challenges for future studies.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing leadership to address key NCS exposure assessment and sampling design issues
- Providing guidance and exposure assessment study design options that will enable NCS researchers to develop statistically valid designs for validation sub-studies to assess exposure measurement error within the NCS and to incorporate these results into testing of study hypotheses
- Developing, testing and evaluating low cost, low burden exposure monitoring methods and strategies that will provide NCS researchers with low-cost alternatives to having technicians administer questionnaires and collect samples
- Developing guidance and recommendations for improving participant success in the less burdensome procedures
- Providing insights from lessons learned through past studies that will be used to guide the methods and study plan (protocol) of the NCS and potentially other long-term cohort studies where environmental conditions or stresses are of concern
- Employing the methods and approaches to assist EPA address the Food Quality Protection Act mandates and other science programs concerned with the effect of environmental contaminants on human health.

Poster LTG3-14
Health-Related Methods Development Projects for the National Children's Study

Presenter: Pauline Mendola (NHEERL)
Contributors: Jane Gallagher, John Rockett, Suzanne Fenton, Danelle Lobdell, Suzanne McMaster, Robert MacPhail, and Tara Lyons-Darden (NHEERL); Stan Barone (NCEA)

Science Questions:

This research addresses the following science questions:

- Can we identify and validate comparable biologic markers in both test animals and humans that can be used to investigate the risk and mechanism of environmental exposures associated with functional impairments of the reproductive and nervous systems?
- Can we determine the key genetic and physiologic factors that modify associations between exposures and outcomes in a similar fashion in both animal and humans?

The Research:

A variety of health outcome markers are being investigated for potential use in the National Children's Study (NCS). We anticipate these efforts will yield substantial improvements in measuring NCS priority health outcomes as well as increasing our understanding of the exposure-outcome relationships observed. Key concepts for this research program are to: (1) Maximize human-animal extrapolation by identifying and validating common biomarkers from observational human studies and experimental animal studies; and (2) Focus on samples that could be obtained with minimal invasiveness from human subjects, including children, infants and pregnant women.

Considerable effort has gone into gene expression profiling of surrogate tissues. Our goals are to compare animal and human data on surrogate biospecimens (blood, hair follicles, semen, urine), and evaluate the relationships with target tissues in animal models. We have found that blood may be a useful surrogate for gene expression in uterine tissue, and that commercial systems for RNA isolation from blood which "freeze" the transcriptome can yield good quality RNA, although each system has certain advantages and disadvantages. Good quality RNA can be extracted from hair follicles and sperm, but urine is not a good source of RNA for gene expression analysis. Obtaining biological specimens from newborn humans is a particular challenge. We developed methods to use non-invasive samples that can reflect *in utero* exposures, such as fingernail specimens. We validated the usefulness of fingernail DNA for assessing relevant metabolic and detoxification genetic polymorphisms, comparing nail results to blood and buccal cell samples, and found that a MALDI TOF high throughput technique could be used in place of standard genetic analysis.

Our nervous system studies focus on behavioral indicators. We began by looking at analogous measures of cognitive function between human infants and laboratory animals. Building on a

published review, we are piloting a study of activity assessment in human infants and a parallel study with a comparable animal model. We are developing methods in animal and human tissues that examine neurotrophic factors, evaluating peripheral blood as a surrogate for brain tissue using methyl mercury as a positive control toxicant.

Work is also being conducted to develop fractionation and freezing protocols for breast milk samples. This will facilitate the development of reliable assays to measure endogenous and exogenous constituents of fresh and frozen breast milk, and to evaluate whether blood, saliva, and urine are useful surrogate mediums for the analysis of some constituents of milk.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Influencing the selection of biomarkers and methods to be used for health assessment in the NCS
- Evaluating the utility of non-invasive sample matrices, methods and techniques essential to the long term success of this study, especially supporting the use of developing science fields as gene expression
- Providing improved understandings of the data needs relevant to risk assessment implementation, such as comparable animal and human biological markers
- Employing lessons learned through the NCS to provide important guidance for the measurement of NCS outcome variables.

Poster LTG3-15
Development of Child-Specific Guidance for Exposure Assessment and Use in Risk Assessment

Presenter: Gary Bangs (NCEA)
Co-authors: Elaine Cohen-Hubal (NERL), Michael Firestone (OCHP), Jacqueline Moya (NCEA), Valerie Zartarian (NERL).

Science Question:

- What are the critical data needed to define exposure parameters in order to conduct exposure and risk assessments for children?

The Research:

Research to answer this question has focused on the exposure factors that make children's exposure different from adults. In the process of conducting risk assessments, parameters have been identified that are child-specific. Children are often more heavily exposed to environmental contaminants than adults on a weight/weight basis. Children's activities and behaviors also put them at higher risk from environmental contaminants.

The Child-Specific Exposure Factors Handbook (CSEFH, 2000 interim final) provides a summary of statistical data on various exposure factors used in assessing children exposures. This Handbook serves as a resource for exposure assessors inside and outside the Agency who need to obtain data on exposure factors to calculate children exposures. Some of these factors include: drinking water consumption; soil ingestion and mouthing behavior; inhalation rates; dermal factors including skin surface area and soil adherence factors; consumption of retail and home-grown foods; breast milk intake; and activity pattern data. Data gaps in the current database were identified for numerous areas of exposure factors. Research is being conducted in NCEA and NERL that will generate data to fill some of the areas where data is limited. A colloquium was held in June 2004 to bring together representatives of all of the Agency constituents and prioritize the research needs.

Many experienced EPA risk assessors noted that guidance was needed on the appropriate age groups to consider when assessing childhood exposure and potential dose to environmental contaminants. In July 2000, the Risk Assessment Forum held a workshop to examine developmental factors and how they influence the assessment of childhood exposure. Workshop participants included experts in the fields of pediatric medicine, toxicology, risk assessment, and public health a peer consultation. The report was called a *Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children.* The participants concluded that age groupings (or bins) can be useful as guides for the development of environmental exposure scenarios. Recommendations included not only suggested groupings but also research needs to fill in the substantial data gaps. A technical issue paper completed in October 2001 reviewed and re-evaluated the data supporting the age groups from the CSEFH (2000) and made

recommendations for short-term analyses and longer term research to improve the database for childhood exposure. A draft *Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants* was released for public comment in September 2003, and an external peer review was completed in March 2004.

Future Research

Data from the interim final Child-Specific Exposure Factors Handbook is being reanalyzed to ensure consistency with the recommended age groups from the draft Guidance (2003). An Agency-wide exposure factors advisory group was established to identify research needs and set priorities on exposure factors research. A soil ingestion workshop is planned in the spring of 2005 to discuss the state of the science and develop research needs in this area.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Producing and publishing key exposure and exposure factor data (Exposure Factors Handbook (EFH) and the Child-Specific Exposure Factors Handbook) that are used by Agency and other risk assessors to identify appropriate input parameters for various exposure scenarios in assessing children's risks
- Leading a collaborative effort to develop and provide the consensus Guidance on Age Groups that is generally applicable to all risk assessments involving children's exposures
- Collaborating with federal and non-federal risk assessors to identify data gaps and prioritize research needs for periodically updating these important handbooks and guidance documents

Poster LTG3-16
Application of PBTK/TD Models in Assessing Neurodevelopmental Toxicity in Susceptible Populations

Presenter: Femi Adeshina (NCEA)
Contributors: Bob Sonawane (NCEA); Elaine Faustman, Nancy Judd, Tom Lewandowski, Julia Gohlke (University of Washington)

Science Questions:

This research addresses the following science questions:

- How can physiologically-based toxicokinetic/ toxicodynamic (PBTK/TD) models be used to assess the impact of neurodevelopmental toxicity during different life stages?
- What framework can be developed for incorporating toxicokinetic (TK) and toxicodynamic (TD) processes into the risk assessments of children?

The Research:

This study focused on how PBTK/TD models are particularly useful when assessing the impact of neurodevelopmental toxicants in sensitive populations, such as children. Specifically, modeling approaches were developed that can quantitatively address critical issues in neurodevelopmental processes based on windows of susceptibility, inter- and intra-species variability, mode of action, and extrapolation of toxicity data. Understanding the kinetics and dynamics of neurodevelopmental impacts in one species can help identify the potential dose range(s), time(s), and target tissue(s) in humans. The quantitative consideration of kinetic and dynamic processes provides an understanding of the response as an integrated process, and allows for the evaluation of dose-dependent differences in mechanisms of toxicity. In addition, PBTK/TD models facilitate the identification of critical rate-limiting steps that may control subsequent dynamic processes, and which may also be susceptible to chemical perturbation.

In this research, case studies of the developmental toxicity of ethanol and methyl mercury have demonstrated the utility of linking the PBTK/TD models to allow the assessment of dose, temporal, and tissue-specific effects. For ethanol, a dynamic model was developed that could predict the relative contribution of the chemical-induced changes in apoptosis versus proliferation. The research results suggest that early exposures to this chemical, and the subsequent impacts on proliferation, may account for significant proportions of observed reductions in cell number during neurodevelopment. In the methyl mercury model, windows of susceptibility, mode or mechanism of action, *in vitro* and *in vivo* issues, and exposure conditions were considered. The findings indicated that the effects on cell proliferation did not affect cell cycle kinetics up to concentrations of 3 ppm (rats embryonic tissues), in contrast to previous studies in mice. Equally important, the research suggests important species differences in toxicodynamic sensitivity.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing improved TK/TD methods for evaluating potential risks to children, a critically important sensitive subpopulation
- Developing a new framework, based on biologically-based dose response models, for assessing children's health
- Identifying future research needs to improve future risk assessments and reduce children's risks to environmental toxicants.

Poster LTG3-17
Application of Life Stage Specific Data in the Risk Assessment for Children: Case Study Presentation Using Pesticides

Presenter: Susan Makris (NCEA)
Contributors: Kacee Deener (NCER); Elaine Cohen-Hubal (NERL); Ginger Moser, Stephanie Padilla, and Tammy Stoker (NHEERL); Vicki Dellarco (OPP); and Elizabeth Doyle (OW)

Science Questions:

This research addresses the following science questions:

- How should life-stage specific data (i.e., prenatal, postnatal, and peri-pubertal exposures and toxicological effects) be addressed in the risk assessments for specific pesticides?
- What additional information may be necessary to fully characterize risk to children from specific pesticide exposures?

The Research:

The Office of Research and Development (ORD) has been instrumental in developing a number of tools (including risk assessment guidelines, testing guidelines, guidance documents, and workshops) that have had a critically positive impact on pesticide risk assessment in EPA's Program Offices. These efforts have generally been conducted as collaborative inter-office working group projects under ORD leadership.

In addition to the generic development of guidance for risk assessment, ORD has contributed to the risk assessments of specific individual pesticides or classes of pesticides through test methods development, the generation of data, and consultation with the Program Offices, providing scientific information and expertise informing the risk assessment process. Example cases where ORD input was essential to the interpretation of life-stage specific susceptibility and was critical to the assessment of risk to children's health are chlorpyrifos and atrazine, two widely-used pesticides with documented potential for exposure to children. Extensive collaboration and consultation between ORD and the Program Offices occurred during the process of developing the risk assessments. Research conducted or supported by ORD contributed to the characterization of life-stage specific susceptibility issues for each of these two chemicals. In the case of chlorpyrifos, ORD scientists conducted laboratory studies to characterize the age-related sensitivity to cholinesterase inhibition and developed tools to assess children's exposures to chlorpyrifos. For atrazine, seminal health effects research was conducted by ORD scientists to identify the critical non-cancer mode of action for risk assessment, i.e., disruption to the hypothalamic-pituitary-gonadal axis during development. Overall, for these two pesticides, ORD studies provided confirmation of susceptibility to the young, support for decisions regarding the adverse consequences of the observed effects, a basis for extrapolation from animal data to potential human response, methodologies to assess exposure to children, and

information critical in identifying the point of departure for risk assessments conducted by the Office of Pesticide Programs and the Office of Water.

Future research directions include:

- Multiple on-going efforts to develop and/or refine guidance for children's health risk assessment.
- Further ORD research on the basis of susceptibility for specific chemicals or chemical classes, which will be important in cumulative risk assessments.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing guidelines and guidance for risk assessment and advancing the state of the knowledge in specific scientific disciplines as they relate to susceptibility
- Implementing science designed to improve future risk assessments
- Providing leadership in the risk assessment community and in strengthening links between ORD research efforts and the risk assessment process. This has resulted in higher quality, defensible decision-making by the Program Offices and in greater consistency in risk assessment practices across the Agency
- Providing science that was used in Agency risk management decisions to protect susceptible populations for two widely used pesticides, chlorpyrifos and atrazine. Residential uses of chlorpyrifos were cancelled in mitigation efforts that became effective in 2001. Earlier CDC biomonitoring studies suggest that levels of urinary metabolites that are indicative of chlorpyrifos exposure are lower in the 1999-2000 period compared to the 1988-1994 period. Additionally, in an ORD STAR grant supported study of an urban minority cohort of newborn babies and their mothers, levels of chlorpyrifos in personal air and blood samples were substantially decreased from 1998-2002, and correlations between chlorpyrifos exposure levels and decreased birth weight/length observed in 1998 were no longer apparent in 2002. For atrazine, risk communication efforts were critical in refocusing public perception of potential risks, away from long-term cancer concerns (the focus of past risk assessments) and towards non-cancer risks to susceptible populations.

Poster LTG3-18
A Children's Health Risk Assessment Framework Using A Life-Stage Approach

Presenter: Stan Barone (NCEA)
Contributors: Carole A. Kimmel, Jacqueline Moya, Sherry Selevan, Bob Sonawane, and Susan Euling (NCEA); Elaine Cohen Hubal (NERL); Susan Makris (OPPTS); and Tracey Thomas, Chad Thompson (AAAS), and Rebecca Brown, (ASPH)

Science Questions:

This research addresses the following science questions:

- What is the basis for differential risk?
- What are the outcomes that need to be considered in a life-stage focused risk assessment framework?
- What is the impact of exposure to environmental pollutants throughout development on human health outcomes?
- How do we incorporate data on susceptible populations into the risk assessment process?

The Research:

The *Framework for Children's Health Risk Assessment* report, now in draft form, can serve as a resource on children's health risk assessment and will address the need to provide a comprehensive and consistent framework for considering children's health risk assessment at EPA. This framework lays out the process, points to existing published sources for more detailed information on life-stage specific considerations, and includes web links to specific guidelines and guidance. The document emphasizes the need to take into account the potential exposures to environmental agents during preconception and all stages of development and focuses on the relevant adverse health outcomes that may occur as a result of such exposures. This framework is not a guideline, but rather describes the overall structure and the components considered important for children's health risk assessment. The document expands upon the ILSI (2001) framework that described an approach that included problem formulation, analysis, and risk characterization, and also builds on Agency experience assessing susceptible populations. The problem formulation step focuses on the life-stage-specific nature of the analysis to include scoping and screening level questions for hazard characterization, dose response and exposure assessment. The risk characterization step recognizes the need to consider life-stage specific risks and explicitly describes the uncertainties and variability in the database. It is important to note that within this framework, life stage specific data gaps are not meant to convey an increase in the uncertainty to be applied in a given risk assessment, but rather to consider life stage specific data in order to better characterize the risk to susceptible groups within the population.

This framework document and a companion case study were presented and received a very favorable review by the Risk Assessment Forum, a cross program office group of stakeholders

and representative regional risk assessors. The next steps in the implementation of this framework will be the development of additional case studies and subsequent external peer review of the framework document.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing leadership in risk assessment by developing and publishing a framework addressing the questions of why and how an improved children's health risk assessment will strengthen the overall risk assessment process across the Agency
- Supporting ORD research that will result in improved scientific understandings that will add value to this new approach, including: 1) a more complete evaluation of the potential for vulnerability at different life stages; 2) an evaluation of the potential for toxicity after exposure during all developmental life stages; 3) the integration of adverse health effects and exposure information across life stages; and 4) a focus on the underlying biological events and critical developmental periods for incorporating mode of action considerations.

Poster LTG3-19
Reducing Chemical Exposure to School Children through the Buy Clean Initiative

Presenter: Zhishi Guo (NRMRL)
Contributor: Bruce Henschel and Kenneth Krebs (NRMRL); Cathy Fehrenbacher and Christina Cinalli (OPPTS)

Science Questions:

This research addresses the following science questions:

- How can differential risk to school children be mitigated?
- What hazardous chemicals, including VOCs, are contained in commonly used school supplies and should be avoided?
- What tools can school managers use to select products with lower health risks?

The Research:

Chronic inhalation exposure to hazardous chemicals is one of the factors that may exacerbate respiratory diseases and other health problems in school children. EPA's Buy Clean Initiative is a partnership with key stakeholders to promote the purchasing of products and services for healthy indoor environments in schools. Currently, Buy Clean projects are being conducted in 13 schools and school districts around the country. Many of these pilot projects are identifying products such as surface cleaners and art supplies and performing research that will reduce exposure to hazardous chemicals of concern. Studies to understand the characteristics of emissions from various products are underway to support the Buy Clean Initiative. The short-term goal of this project is to provide practical advice and tools to school managers for reducing the health risk to children. The long-term goal is to develop a broadly applicable set of tools and models that can be routinely used to evaluate alternatives for commercial products used in schools.

Water-based cleaners and erasable markers were selected for evaluation in consultation with the Office of Prevention, Pesticides and Toxic Substances (OPPTS). These products are widely used in schools. According to OPPTS' Source Ranking Database, they are among top-ranked health risk products used in schools. The initial evaluation of hard-surface cleaners is now complete. It involved an analysis of material safety data sheets (MSDSs) and the development of screening-level models for chemical emissions from cleaner applications. Eighty-six out of 267 cleaner products contained hazardous air pollutants (HAPs). In addition, among the 28 chemicals with threshold limit values, 22 have irritation effects and 9 can affect the central nervous system. To assist school managers' purchasing decisions, a screening-level model was developed to estimate the time-averaged concentration in classrooms. This model is easy to use and has been tested against the emissions data generated in environmental chambers. The model output can be compared with health-based critical values such as reference concentrations (RfCs) for chronic inhalation in EPA's Integrated Risk Information System (IRIS).

The evaluation of erasable markers is currently underway. Although most erasable markers sold in the US have safety seals, preliminary results of formulation analyses revealed that some products (including markers and cleaning liquids) contained HAPs such as ethylbenzene, toluene, and 2-butoxy ethanol. Experiments are being conducted to determine the solvent exposures both to school children under simulated real use conditions by using breathing manikins as well as the exposure to nearby occupants in the area where these markers are in use.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing easy-to-use models that can be employed by school and other risk managers to characterize exposures and select replacement materials for potentially harmful consumer products used in schools
- Providing improved scientific understandings and data for identifying high risk school products that support OPPTS, the Office of Radiation and Indoor Air, and the Regional Office efforts to implement the Agency's Buy Clean Initiative
- Providing practical advice to school managers to help them identify risk management techniques for reducing potential health risks to children. The major research results will be presented at the Agency's next Schools Workgroup meeting
- Working with school managers and risk managers to identify ways to integrate the new model into the Agency's Tools for Schools package, evaluate the results, and implement programs that reduce school children's risk.

Poster LTG3-20
A Framework for Research on the Susceptibility of Older Adults

Presenter: Andrew M. Geller (NHEERL)
Contributors: Hal Zenick (NHEERL); Barbara Glenn (NCER); Kent Thomas (NERL); and Karen Hammerstrom (NCEA); Kathy Sykes (OCHP)

Science Question:

- What key EPA research is needed to evaluate the potential susceptibility and vulnerability of older adults and to characterize and mitigate their health risks from exposures to environmental toxicants?
- What research is needed for EPA to understand the potential impacts of an aging society on natural resource utilization, land-use planning, and environmental quality?

The Research:

The rapid growth in the number of older Americans has many implications for public health, including the need to better understand the risks posed by environmental exposures to older adults. Biological capacity declines with normal aging, and may be exacerbated in individuals with pre-existing health conditions. This decline can result in compromised pharmacokinetic (PK) and pharmacodynamic (PD) responses to environmental exposures encountered in daily activities. In recognition of these issues and in response to its legislative mandate to protect susceptible sub-populations, the EPA has recently developed a research framework on the environment and older adults. This framework was constructed with input from an inventory of EPA research, an EPA-sponsored NAS Workshop on the Differential Susceptibility and Exposure of Older Persons to Environmental Hazards, public listening sessions, and discussions within the Office of Research and Development (ORD) and with EPA's federal partners. It will be used to develop and guide ORD research on aging and risks of exposure to environmental toxicants and to identify areas of collaboration outside of EPA.

To address health issues, EPA has proposed to apply an environmental public health paradigm to better understand the relationships between external pollution sources → human exposures → internal dose → early biological effect → and adverse health effects for this sub-population. In addition to considering the health effects of exposure on healthy older adults, EPA will use information about aging-related changes in exposure, PK, and PD factors to identify particularly susceptible or vulnerable sub-groups within this diverse population. Research is needed in areas of: 1) behavior/activity patterns and exposure to pollutants for older adults; 2) changes in absorption, distribution, metabolism, and excretion; 3) alterations in reserve capacity that alter the body's ability to compensate for the effects of environmental exposures; and 4) strategies for effective communication of risk and risk reduction methods to older individuals and communities.

In addition to potential health risks, aging adults have different resource needs than younger adults (e.g., housing, health care, transportation, and recreation). These needs will grow with the aging population, and they must be addressed in a manner that will promote the health of individuals and the health of the environment. EPA is developing a research plan to address this issue and to understand how older adults' changing needs may alter demands on community infrastructures and the nature of stress on the environment.

Impact and Outcomes:

ORD's research program on the exposures that the older adult population experiences and the subsequent PK and target organ responses will provide a better understanding of the environmental health risks associated with aging in healthy or compromised older adults by:

- Generating data on the exposures that the older adult population experience and the subsequent PK and target organ responses to estimate the corresponding risk.
- Using these data to generate models and guidance that will incorporate the differential susceptibility of this heterogeneous subpopulation into health promotion and intervention strategies to ameliorate risk from environmental exposures.
- Data on older adult needs and ecological stressors will help guide the development of the built environment that will improve quality of life for the aging population by reducing health risks and minimize ecological impacts.

Poster LTG3-21
Aging and Toxic Response

Presenter: Bob Sonawane (NCEA)
Contributors: Linda Birnbaum, Mike DeVito, Marina Evans, Andrew Geller, Joyce Royland, (NHEERL); Jerry Blancato, Miles Okino, Kent Thomas (NERL); and Myra Karstadt (OPPT)

Science Questions:

This research addresses the following science questions:

- What are the biological, behavioral, and geographical factors that make older adults more susceptible and/or vulnerable to the effects from environmental exposures?
- Are specific subgroups of older adults more vulnerable; if so, why?
- To what degree are susceptibility and/or vulnerability due to differential activity patterns and exposures to toxic environmental agents and to age-related differences in toxicokinetics and toxicodynamics?

The Research:

The Office of Research and Development (ORD) is conducting research to address the key issues regarding the susceptibility and vulnerability of aging adults, including:

Exposure Research: Older adults may experience increased risk from environmental stressors due to differential exposure or activity patterns. Data from studies of exposure to particulate matter (PM), for example, show that older adults spend more time indoors than younger adults, and that older adults in different residential situations may experience different exposures. Research on exposure and activity across the lifespan includes the PM panel studies, the National Human Activity Pattern Survey, the National Human Exposure Assessment Study, and the Consolidated Human Activity Database. The adequacy of these data for use in source-to-dose risk assessment models relevant to older adults will be assessed for important chemical and biological stressors. This assessment and data from other exposure measurement and activity studies will be gathered in order to identify critical data gaps and research needs. The data will also be used to identify sub-groups within the older adult population based on differential exposures or susceptibilities. Future exposure and activity-monitoring research will be prioritized to fill the critical exposure data gaps for the concerned populations.

Dosimetry Research: Research is being implemented to determine the contribution of aging-related alterations in toxicokinetics to the susceptibility of older adults. ORD has produced a report that examines changes in the pharmacokinetic (PK) and pharmacodynamic (PD) handling of therapeutic drugs in older adults and is currently compiling PK parameters for older adults. ORD is extending this work on environmental toxicants to evaluate age-related alterations in toxicokinetics using a model-based sensitivity analysis of parameters for absorption, distribution, metabolism and excretion (ADME) to identify the factors that are most important for specific classes of chemicals. This analysis will define the magnitude of change necessary to alter the

exposure-dose-response relationship for prototype chemicals. This, in turn, will focus future experimental research on those chemical-dependent parameters that change with increased age or with diseases of aging and have the greatest effect on tissue dosimetry, such as changes in metabolic enzyme activity or transport processes. Another possible contributor to susceptibility in older adults is polypharmacy, since the same biological mechanisms that clear environmental toxicants may be affected by therapeutic medications or diet. Research on susceptibility due to polypharmacy will be based on our understanding of ADME mechanisms shared by pharmaceuticals and environmental chemicals.

Health Outcomes: Data derived from mechanistic research to understand the age-dependence of toxicodynamic processes (e.g., protective, repair, compensatory, and plasticity mechanisms) can be used to describe and predict how age affects susceptibility to environmental agents. Research by ORD and its grantees on the respiratory and cardiovascular effects of PM and the gastrointestinal effects of water-borne pathogens has illustrated the particular susceptibility of older adults to these contaminants. ORD has compiled a report on baseline changes in physiology across organ systems in older adults to help identify factors that may result in increased susceptibility due to altered toxicodynamic response. As with the PK approach, future work on age-related changes in toxicodynamics will identify the processes or mechanisms that contribute to susceptibility in aged adults and test these with model environmental agents presumed to operate through similar mechanisms. Current work in ORD includes analysis of gene expression in different brain areas to identify potential susceptibility factors for neurotoxicity.

Impact and Outcomes:

This evolving research program will provide a scientific rationale for decisions on how to appropriately incorporate the differential sensitivity of the older adult sub-population into health promotion and intervention strategies to ameliorate risk from environmental exposures by:

- Producing data and tools that provide an improved understanding regarding the risks older adult experience compared with the general population due to exposures to environmental contaminants, including: key factors influencing older adult exposures; biological processes that result in tissue dose; and resulting health outcomes
- Providing data to EPA's Program Offices on whether current estimates of variability in the human population for the purpose of risk assessment encompass the potential vulnerability of aging adults to environmental exposures.

To date:

- ORD data and guidance have been used by the Office of Children's Health Protection and the Office of Air and Radiation for fact sheets and health advisories related to the air quality index to stakeholders in the older adult community (see http://www.epa.gov/aging)
- ORD has raised the issue of environmental health of older adults through symposia to stakeholders in the aging community and health care providers
- ORD has provided expertise to Council on State and Territorial Epidemiologists for development of environmental health indicators relevant to older adults and to Institute of

Medicine for their consideration of future issues in health promotion and disease prevention.

Poster LTG3-22
A Framework for Research on the Impacts of an Aging Society on Ecology and Environmental Quality

Presenter: Patricia Bradley (NHEERL)
Contributors: Wayne Munns, Laura Jackson, Jennifer Orme-Zavaleta, and Andrew Geller (NHEERL); Bernice Smith and Diana Bauer (NCER); Brett van Akkeren (OPEI)

Science Question:

- What research is needed for EPA to understand the potential impacts of an aging society on natural resource utilization, land-use planning, and environmental quality?

The Research:

The United States is undergoing a demographic transformation towards older adults, spearheaded by the aging Baby Boomers, but projected to last beyond the Boomer generation. While we can reasonably estimate the growth of the aging population, we are less certain about how this rapid demographic change will affect natural resource utilization, land-use planning, and environmental quality.

In August 2004, the Office of Research and Development (ORD) held a workshop on topics that included: (1) the change in aging demographics over time; (2) key issues (i.e., socio-economic, geographic) affecting demographic projections; (3) the potential impacts of an aging population on natural resources and environmental quality; and (4) the research needed to ensure both the desired amenities for this aging population and the protection of natural resources.

ORD is developing a research strategy based on the input from the workshop. The proceedings document is the starting point for a framework that links diverse lifestyles, cultures, and health status in the aging population to ecological stressors. Research will be structured along a simplified ecological risk assessment paradigm. This comprises sources of environmental stress (projected demographic and life-style patterns of an aging population), resulting exposure regimes (temporal and spatial changes in land-use patterns and the environmental stressors resulting from these patterns), and potential ecological effects. The strategy will also address issues of spatial and temporal scale.

An underlying assumption for this strategy is the necessity to consider human and ecological health in an integrated manner. Research will therefore be interdisciplinary, including natural scientists, ecologists, and engineers, as well as sociologists, economists, gerontologists, demographers, behaviorists, planners, social marketers, and other disciplines that interact with aging populations. Collaborative relationships and partnerships among local, state and federal agencies, the private sector, non-governmental organizations, and stakeholders will be central to the success of the effort.

Another assumption is that impacts from the aging society will vary regionally. Research is needed to characterize this variability to capture the consumption, waste, transportation, medical

needs, and lifestyle patterns by cohort and geographic area and to overlay aging population demographic data on an eco-regional base layer. Research is also needed to identify built-community planning practices that can be applied to minimize environmental stressors and enhance health promotion and the quality of life for different segments of the aging population.

Limitations of this work include our understanding that the ecological effects of the aging population may not be completely separable from those associated with increases in the size of the general population. Given the rapid demographic change, altered patterns of resource use may present novel challenges with respect to our ability to forecast those effects. ORD will conduct research to identify "tipping points"—thresholds in stressor levels or ecological effects beyond which the ecological systems change state—and the possibility that release rates, magnitudes, or combinations of aging-related stressors may exceed these thresholds.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Conducting research on the effect of the growing aging population on the environment that will allow the Agency to provide sound technical information to inform local and community-based decisions and minimize the impact of the growing aging population on the environment
- Partnering with the EPA Regional Offices to facilitate collaborations with regionally-specific stakeholders to develop and initiate the implementation of appropriate policies and management actions
- Providing data, tools, and strategies that will enhance the ability of city, county, and regional planners to meet the needs of the growing older adult population while at the same time enhancing the quality of the environment for the current and future generations, and contributing towards “Lifelong Quality of Life”.

Poster LTG3-23
Asthma Research in ORD: an Overview

Presenter: Hillel Koren (NHEERL)
Contributors: Ian Gilmour and Lucas Neas (NHEERL); Marc Menetrez (NRML); Steve Vesper and Ron Williams (NERL); Kathlenn Deener and Nigel Fields (NCER); Susan Stone (OAR/OAQPS); Laura Kolb and John Girman (OAR/IED); David Peden (University of North Carolina, at Chapel Hill); Dorr Dearborn and Carolyn Kercsmar (Case Western Reserve University); Tiina Riponen (University of Cincinnati); Peter Ashley (Housing and Urban Development); Teija Meklin (National Public Health Institute of Finland); Joachim Heinrich (GSF/Germany)

Science Questions:

This research addresses the following science questions:

- What are the factors responsible for susceptibility and vulnerability to asthma, and who are the populations most affected?
- How do pollutant and allergens affect the incidence and severity of asthma?
- What are the underlying mechanisms?
- What are the best risk management strategies to reduce the burden of asthma?

The Research:

Asthma is a complex, multifactorial disease characterized by chronic airway inflammation, mucus secretion, airway remodeling, and reversible airway obstruction. The asthmatic population constitutes 6.4% of the US population. Both genetic and environmental factors influence the development and exacerbation of asthma. The President's Task Force on Environmental Health and Safety Risks to Children selected asthma as one of the four childhood diseases to target. EPA's Office of Research and Development (ORD) has developed a targeted asthma research program, outlined by a peer-reviewed 2002 Asthma Research Strategy (http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=54825). The decision-making criteria to set research priorities were: risk-based planning; scientific excellence; programmatic relevance; capabilities and capacities; and sequence of research. EPA's ultimate goals are to prevent new cases and reduce the exacerbation, severity, and overall burden of asthma caused by environmental factors. ORD has taken a transdisciplinary approach in supporting intramural and extramural research. ORD's research focuses on the role of common air pollutants and bioaerosols in the onset and exacerbation of asthma in susceptible populations, the underlying mechanisms involved, and the development of improved risk management methods. Population studies play a key role in driving the asthma research agenda. They assess real world exposures of various populations to different pollutants (or their mixtures) at different concentrations. Populations vary in susceptibility to the disease, age, and SES. Some of the epidemiology studies (see Neas et al. poster) such as the Inner-City Asthma Study, and the Children's Environmental Health Research Centers have ended, while others are ongoing and/or being planned (e.g., Detroit Children's Study, and the National Children's Study). Many of these

studies resulted in the development of improved prevention and mitigation techniques. A complementary part of the ORD program focuses on bioaerosols (e.g., molds, endotoxins) which is a particular a suitable niche for the EPA's research efforts. The goal is to improve the identification and quantification of bioaerosols, molds in particular, by developing innovative diagnostic tools (see Vesper et al. poster). An important part of this research includes building construction design and maintenance efforts intended to improve the health of asthmatics (see Menetrez et al. poster). Because of the ubiquity of bioaerosols, this research is interwoven with the epidemiology and mechanistic parts of the asthma program. Controlled (toxicological and clinical) studies are aimed at better understanding the underlying mechanisms responsible for the onset and exacerbation of asthma in sensitive subpopulations (see Gilmour et al. poster). As part of this program, ORD scientists address the issue of genetic polymorphism in asthmatic populations in response to pollutants (see Gilmour et al. poster). In the future, EPA's asthma research will seek to improve the understanding of who are the most vulnerable and impacted susceptible individuals, and to reduce uncertainties in risk assessment for pollutants that induce or exacerbate asthma. An emerging part in this program is the development of new and better strategies to prevent environmentally related asthma using a chemopreventative strategy. In aggregate, ORD's asthma research program has an impact on regulatory, educational, and outreach activities providing critical information to protect public health.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing critical data reducing key areas of scientific uncertainty and supporting regulatory programs including the Criteria Documents for ozone and PM (http://cfpub.epa.gov/ncea), and the Health Assessment for diesel emissions
- Providing the science that served as the health basis for the development of the ozone and PM NAAQS and risk communications
- Contributing significantly, via collaborations and the scientific literature, to a better understanding of the underlying biological mechanisms responsible for the causation and exacerbation of asthma
- Developing innovative tools to characterize exposures to bioaerosols
- Developing prevention and intervention techniques that have been accepted and implemented by local health departments, Housing and Urban Development (HUD), and other organizations
- Implementing asthma outreach activities including programs which support health messages for Air Quality Index (AQI) (http://www.airnow.gov/health-prof/), (http://www.airnow.gov/airnow/publications.html), as well as educational material (http://www.epa.gov/asthma/).

Poster LTG3-24
Impact of Combustion Related Pollutants (CRPs) on the Development of Asthma

Presenter: Ian Gilmour (NHEERL**)**
Contributors: Robert Devlin, Stephen Gavett, Lucas Neas and Bill McDonnell (NHEERL); Bill Linak (NRMRL); Ron Williams (NERL); David Peden (University of North Carolina)

Science Questions:

The research addresses the following science questions:

- Which CRPs, and at what relevant concentrations and composition, affect the incidence or severity of asthma?
- What are the biological mechanisms resulting for these effects?
- How can this information be extrapolated to the public scenario?

The Research:

Asthmatics, children in particular, appear to be more sensitive to air pollutants than healthy individuals and thus represent a susceptible sub-population that has added risk to CRP exposure. Epidemiology studies have shown convincingly that during episodes of air pollution, emergency room visits and medication use in asthmatics increase. Recent studies supported by EPA have also suggested that exposure to CRPs such as diesel exhaust and secondary atmospheric products like ozone can increase the actual incidence of asthma events in adults and in children. These effects have been confirmed in limited human exposure studies as well as in multiple experimental animal systems.

The approach for this research, which is driven by the ORD Asthma Research Strategy http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=54825 , tests the general hypothesis that environmental factors influence the induction and exacerbation of asthma, and that these factors can be controlled. This multidisciplinary program spans numerous scientific areas including exposure assessment, combustion engineering and chemistry, epidemiology, pulmonary medicine, laboratory animal science, mucosal immunology, airway physiology and molecular biology. The Office of Research and Development (ORD) investigators and their collaborators have been working to identify which types of air pollutants increase the incidence and/or severity of asthma, and pursue the biological mechanisms and pathways that are involved. Epidemiology and exposure assessment studies provide information on what type and concentrations of pollutants are in the air, what sources they come from, and whether they are associated with the incidence or severity of asthma in the population. Clinical experiments and panel studies (with young and adult subjects) provide more specific and detailed information on personal exposures and susceptibility factors which may drive the progression of disease during or after exposures. Animal studies screen a large number of exposure scenarios for hazard identification and quantitative risk assessment purposes, and are used to test different biological mechanisms of the effects. Recent approaches in population studies are examining the relationship between asthma

prevalence and the proximity to roadways or presence of vehicle exhaust tracers. People respond differently to the same environmental exposures due in large part to genetic heterogeneity.

Ongoing clinical investigations are tracing single nucleotide polymorphisms (SNPs) in healthy and asthmatic individuals to identify genetic factors that influence asthma susceptibility and pathogenesis in response to inhaled pollutants. Strategies to protect individuals from air pollution health effects with chemo-prophylaxis may also be investigated. Current and future exposure studies in normal and transgenic animals are manipulating the chemistry of combustion atmospheres to find which components most affect asthmatic responses, and are then applying computational toxicology models to predict these effects in ambient air sheds.

Impact and Outcomes:

The research reduces uncertainty in risk assessment by:

- Providing an improved understanding of the fundamental science contributing to the development, onset and exacerbation asthma, and contributing to improved understandings of key host and environmental risk factors
- Generating results that directly feed into criteria documents and standard setting for various air pollutants (e.g., http://cfpub.epa.gov/ncea)
- Providing improved science understandings and tools to the Office of Air and Radiation and the Office of Transportation and Air Quality that can be used for hazard identification and risk assessment purposes
- Providing data and science helping guide advisories from the Office of Children's Health Protection
- Providing scientific knowledge that has supported the development of new educational materials and programs which support health messages for the Air Quality Index (http://www.airnow.gov/health-prof/).

Poster LTG3-25
Implementation of EPA Bioaerosol Research Findings Can Ensure Regulations Based on Sound Science and Protect the Health of Asthmatics

Presenter: Stephen Vesper (NERL)
Contributors: Robert Devlin, Mary Jane Selgrade and Marsha Ward (NHEERL); Nigel Fields (NCER); Ronald Williams (NERL); Marc Menetrez (NRMRL); and David Peden (University of North Carolina); Dorr Dearborn and Carolyn Kercsmar (Case Western Reserve University); Laura Kolb and John Girman (OAR-IED); Richard Haugland (NERL); Tiina Riponen (University of Cincinnati); Peter Ashley (Housing and Urban Development); Teija Meklin (National Public Health Institute of Finland)

Science Questions:

This research addresses the following science questions:

- What is the effect of bioaerosols on respiratory health, with an emphasis on asthma, especially in sensitive sub-populations like children and the elderly?
- What is the basis of their sensitivity?
- How can we measure the actual exposure?
- How can EPA mitigate the risk and then measure the effectiveness of EPA regulations, guidance, and risk assessments.

The Research:

The Office of Research and Development's (ORD) bioaerosol research is driven by ORD's Asthma Research Strategy http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=54825. The bioaerosol research program is interdisciplinary (epidemiological, exposure, mitigation, toxicology, and clinical) and represents the collaborative efforts of multiple organizations across ORD and EPA. Numerous centers and other research organizations also work in concert with EPA. Bioaerosols are airborne particles originating from dust mite, cockroaches, bacteria and household mold which can all trigger allergic response leading to asthma attacks. The role that bioaerosols play in the onset and exacerbation of asthma is poorly understood and under-investigated by other public health agencies.

Our research program focuses on two major bioaerosol types: molds which are possibly involved in the onset of asthma, and endotoxins which have been demonstrated to enhance the asthmatic response in allergic individuals. The large number of possible indoor molds required us to develop a new technology to identify and quantify molds. This patented technology is based on the unique DNA sequences found in each mold. Now that we know which molds are indoors, human subjects and animal models are being used to measure mold-allergen specific IgG and IgE and to develop an understanding of the role of endotoxins (model bioaerosol) and innate immune functions in the development of asthma. Moreover, the program investigates the role of endotoxins in potentiating the pro-inflammatory response to ozone. ORD research is designed to

determine the value of reducing exposures to bioaerosols in controlling asthma induction and exacerbation.

In ongoing collaborative studies with HUD and NIEHS, a National survey of molds in homes is being performed as well as studies of ventilation and humidity as asthma triggers. These research results will provide the sound science needed to allow EPA to develop the best tools for protecting and educating the public, especially sensitive subpopulations.

Impact and Outcomes:

This research reduces uncertainty in risk assessment by:

- Performing research demonstrating that reducing bioaerosol exposures can improve the respiratory health of sensitive subpopulations
- Identifying a potential marker (CD14) constitutive in human airways and capable of predicting the magnitude of the inflammatory response of atopic individuals to endotoxins
- Developing protocols for bioaerosol control used by GSA to improve indoor air quality in Federal buildings, including UVC Air Treatment as a useful method in controlling bioaerosols
- Providing science understandings and data being used by the Office of Pesticide Programs and Toxic Substances for developing recommendations for registration of new anti-microbial agents under the Antimicrobial Registration and Efficacy Testing http://www.epa.gov/oppad001/
- Supporting the Indoor Environments Division/OAR in their development of a number of popular public documents on molds (> 200,000 hard copies distributed since 2002 and ~100,000 down-loads from the website per month http://www.epa.gov/iaq/molds/moldguide.html
- Developing, in conjunction with HUD, “specifications” for cost effective home remediation
- Developing a patented mold identification technology (#6,387,652) licensed by 15 companies in the US and EU http://www.epa.gov/nerlcwww/moldtech.htm; a patent pending biomarker of mold exposure; and identification of specific mold allergens.

Poster LTG3-26
Asthmatic Children as a Susceptible Population and Strategies for Intervention

Presenter: Lucas Neas (NHEERL)
Contributors: Ron Williams (NERL); Erik Svendsen (NHEERL); Kathleen Deener (NCER)

Science Questions:

This research addresses the following science questions:

- What role does the environment play in susceptibility and vulnerability to the development and exacerbation of asthma?
- What types of environmental and educational interventions help to protect susceptible subpopulations?

The Research:

The differing prevalence of asthma among groups with similar genetic composition suggests that environmental and socioeconomic factors play a key role in the development of asthma, especially allergic asthma in children. The Office of Research and Development's (ORD) Asthma Research Strategy (http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=54825) drives ORD's research and focuses on environmental factors associated with children's susceptibility to the development of asthma and on the susceptibility of asthmatic children to environmental triggers of symptoms and clinical events. Innovative and peer-accepted research efforts supported and/or conducted by EPA have included the air pollution component of the Inner-City Asthma Study; the El Paso Children's Health Study; the North Carolina Asthma, Childhood, and Environment Studies; the Boston Inner-City Intervention Study; and the Children's Environmental Health Research Centers. These observational studies have shown that children from the inner-city develop increased allergic sensitization to cockroaches and mice by two years of age. They also develop high rates of respiratory symptoms requiring medical care, with the need for care increasing with increases in ambient concentrations of particulate matter and other pollutants, and resulting in reduced pulmonary function in children with allergy and asthma. The EPA-funded Children's Environmental Health Research Centers have developed effective intervention projects, at both the individual and community levels, that utilize a variety of different approaches combining clinical care with innovative environmental and educational programs. The educational programs have included personalized in-home education, community health fairs, and educational videos. The environmental programs have demonstrated that interventions, such as integrated pest management, can effectively mitigate risk by substantial reductions in environmental triggers (e.g.,cockroaches) that result in fewer symptoms (e.g., cough) and in improved lung function.

Future studies are being planned that will build upon what we have learned to further explore susceptibility and asthma, including the Detroit Children's Health Study and the National Children's Study.

Impact and Outcomes:

This research reduces uncertainty in risk assessment by:

- Providing research results that are being used by a variety of community partners, including advocacy groups, local health departments, and local housing authorities, to both extend the scope of the intervention projects and to impact decisions made at the local and state levels
- Providing improved science understandings and data that are answering important regulatory and public health questions (http://cfpub.epa.gov/ncea)
- Exploring the role of environmental exposures in susceptibility to the development of allergies and asthma, and providing vital information to protect public health, to mitigate risk where possible, and to address scientific uncertainties related to current environmental regulations.

Poster LTG3-27
Risk Management for Indoor Mold Contamination to Reduce Exposures of Asthmatic Subpopulations

Presenter: Marc Menetrez (NRMRL)
Contributors: Timothy Dean (NRMRL); Karin Foarde (Research Triangle Institute)

Science Question:

- What risk management measures can be used to reduce the exposure of children and sensitive sub-populations to mold contamination?

The Research:

Media attention has focused on numerous examples of uncontrolled mold growth and houses that have been rendered uninhabitable. Mold has been associated with a range of health problems, including asthma. However, few methods about mold exposure, its influence on asthma, or methods for prevention have been tested scientifically. The Office of Research and Development (ORD) has, since 1995, conducted research into managing the risk of indoor mold contamination. This research outlined in the ORD Asthma Research Strategy, focuses on improving the scientific understandings regarding the association(s) between exposure to bioaerosols and the onset of asthma, the identification of molds and their toxins that influence asthmatic reactions, and developing risk management tools for reducing exposure. This project focuses on the risk management aspects of mold, taking a multi-pronged approach.

A series of earlier research activities have produced key results that inform the current research. Earlier experimental studies quantified the effects of RH and moisture content on the growth of specific molds in various types of new and used indoor materials. Chamber studies have characterized the emission rate of *Stachybotrys chartarum* spores from indoor surfaces, as a function of environmental conditions such as relative humidity (RH) and air velocity. Modeling the surface emission relationship has resulted in guidance to manage exposure through heating ventilation and air conditioning (HVAC) operation and filtration. ORD is conducting studies evaluating the effectiveness of alternative risk management methods, demonstrating that moisture and RH control, cleaning chemicals, disinfectants and antimicrobial coatings can be effective in controlling the growth of mold. This research resulted in improved methods for sampling indoor submicron sized bioaerosols including allergen assays and improved impactor substrates, as well as in improved methods for analysis of biocontaminants in a PM sample by adapting existing methods such as PCR. Identification of mold particles in the $PM_{2.5}$ range has demonstrated the need for new methods of measurement.

ORD's research demonstrates that indoor mold contamination can be prevented and mitigated and provides the fundamental science for understanding and controlling the environmental conditions required for mold growth.

Future efforts will be made in PM research, to analyze the extent that fine and ultra fine biological particles (fungal, bacterial, pollen, animal dander, etc.) make up the entire biological

load as well as to improving methods of sampling for these size fractions. Research is initiating to generate wall board that has greater ability to withstand moisture and prevent mold growth following periodic water events. Optimization of ultra violet (UV) irradiation to destroy mold in the most efficacious manner, as well as use UV to generate microbial profiles that could potentially be used in real time analysis of fungal contamination. The use of bacteriophage (microbial viruses) will be examined, to eliminate existing microbial contamination, at the same time examining the prophylactic use of bacteriophage to prevent contamination of building surfaces. Molecular techniques based on the polymerase chain reaction (PCR) including genetic sequencing, multiplex PCR, mycotoxin analysis, and microbial volatile organic compound analysis to generate data that allow for better product development and remediation support.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Implementing research that has resulted in the development of engineering solutions which reduce exposure to bioaerosols, and ultimately improve the health of sensitive children and adults
- Providing research findings and engineering solutions that have been used by the Office of Pesticide Programs and Toxic Substances (Antimicrobial Registration and Efficacy Program requiring antimicrobial efficacy data), General Services Administration (GSA Building Codes requiring UVC installation in HVAC systems), American Society for Testing and Materials (ASTM Standard D6329-98(2003) Standard Guide for Developing Methodology for Evaluating the Ability of Indoor Materials to Support Microbial Growth Using Static Environmental Chambers), ASHRAE (ASHRAE proposed requirement of UVC installation in HVAC system design specifications), and California State Government (proposed requirement of UVC installation in HVAC systems).

Poster LTG3-28
Targeted Populations Overview: Scientific Strategies to Address Complex Environmental Hazards and Unique Vulnerabilities in Targeted Populations

Presenter: Nigel Fields (NCER)
Contributors: Robert Spangler, Daphne Mophett, Dean Seneca (ATSDR); Felix Basabe and Jamie Danatuto (Swinomish Tribal Community); Alan Vette (NERL); Susan Perlin (NCEA); Chris Saint (NCER); Pamela Miller (Alaska Community Action on Toxics); and Gwen Collman and Fred Tyson (NIEHS)

Science Question:

- How can EPA implement research that targets particular populations for protection from adverse effects of environmental stressors while advancing broader more transferable scientific methods and better health outcomes?

The Research:

A core mission of EPA is the protection of populations most at risk from exposure to environmental threats. Research and risk management programs designed to protect known or presumed susceptible or highly exposed populations involves an understanding of the biological factors, ambient exposures, and cultural activities that contribute to differential exposure and risk. Research to address these issues must also consider the diverse inhabited ecological settings in the United States and the vast array of cultures and behaviors. With authorizations from legislation such as FQPA, FIFRA, and Presidential Executive Orders such as E.O.12898—Environmental Justice, EPA has emphasized the protection of the most sensitive persons. The Office of Research and Development (ORD), in implementing programs addressing exposure in specific population-based ways, encourages investigators to collaborate across labs, centers, federal and state agencies in applying multiple exposure and health research strategies to address the challenging scientific, social, or happenstance underpinnings of unique environmental concerns. An important step in this process involves understanding *how* some populations may be differentially exposed. Sophisticated use of geographic information systems (GIS), remote-sensing technologies, refined survey instruments, and biological markers of exposures are often employed to answer the question. Other times, characterizing differential exposure is secondary to understanding potential short and long-term *consequences* of highly toxic environments. When facing an acute, abrupt, virtually saturating experience such as the collapse of the World Trade Center buildings, or conversely the long-term quietly bioaccumulating by-products of industrial or military wastes, communities, understandably, desire to know, “what does it mean?” and “what can I do?” In search of real answers to these difficult questions, ORD has established strong partnerships with local, regional and national agencies and organizations to promote data gathering and sharing approaches which aim to connect the points between sources, exposures, toxic body burden, early markers of effect, and health outcomes. Finally, ORD supports practical, locally-driven intervention efforts when the line from exposure to effect is clearly drawn in targeted communities. The goals of intervention research are to determine the most effective ways to block exposure pathways, to promote better health outcomes, and to culturally adapt these methods to encourage their sustainability after the research is complete.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Sharply reducing assumptions in human exposure, behavior and effects by addressing population-specific concerns in collaboration with local, state, and federal experts. This approach is producing remarkable innovations in scientific ORD methods, models, and intervention strategies, which can be translated beyond EPA. For example, analytical chemistry methods honed by EPA and CDC to biologically detect pesticide residuals in children along the US/ Mexico Border have broadly contributed to the field of pediatric environmental health. Molecular epidemiological approaches coupled with novel computational exposure models are providing valuable personal and population-level data on exposure and effect for pregnant women and workers in lower Manhattan, New York. Early efforts by ORD scientist in using GIS as the primary objective tool to quantify disproportionate community burden in areas fraught with industrial facilities and concerns of environmental injustice have been widely sited, replicated and adapted
- Providing technical expertise and support to community or tribally-driven investigations through extramural research that apply these ORD-developed scientific tools, approaches and strategies and find local solutions to their most pressing environmental concerns.

Poster LTG3-29
World Trade Center Disaster: Application of Novel Exposure Methods and Risk Assessment

Presenter: Alan Vette (NERL)
Contributors: Stephen Gavett (NHEERL); Alan Huber, Joachim Pleil, and Steven Perry (NERL); Mark Maddaloni (Region 2); Gertrud Berkowitz (Mt. Sinai School of Medicine); and Matthew Lorber (NCEA)

Science Question:

- What were the public's exposures and risks to ambient air pollution associated with the World Trade Center disaster?

The Research:

The World Trade Center (WTC) disaster and recovery resulted in a unique series of air pollution exposure events unlike any other previously encountered. The initial collapse of the WTC towers produced a dust cloud engulfing lower Manhattan and exposing thousands of people. The underground fires burned combustible materials from the collapsed buildings (furniture, plastics, etc.) and lasted for several months, producing irritating and potentially toxic gases and particles. The numerous heavy-duty diesel trucks and generators used during debris removal considerably increased emissions of diesel related air pollutants in lower Manhattan.

Scientists in the Office of Research and Development (ORD) immediately responded and undertook a broad effort to characterize the exposures, risks and potential health effects resulting from the collapse of the WTC towers and underground fires. An air monitoring network was established to characterize exposures in lower Manhattan and to determine the impacts of the fires on ambient air quality. Data on PM (mass and composition) and air toxics (volatile and semi-volatile organic compounds) were used in a risk assessment framework to determine the public's risks to ambient air exposures and potential health effects. ORD worked closely with EPA's Regional Office in New York providing expertise in air monitoring approaches and methods, and assessing and communicating risk to the public. In addition, ORD collaborated with the Environmental Occupational and Health Sciences Institute (EOHSI) to develop numerical and physical models of air movement and pollutant transport to gain a comprehensive understanding of the spatial and temporal variation of air pollution in lower Manhattan. Laboratory based studies were performed to determine the possible health effects from exposure to settled and airborne dust derived from the collapse of the WTC. The intramural ORD research was complemented by ORD-funded STAR Grants where academicians performed prospective epidemiological research to determine pregnancy outcomes from *in-utero* exposures to WTC derived pollution and growth and developmental endpoints in the children at birth, 9 months, 2 and 3 years of age.

Findings from this research indicate the potential for health effects to those highly exposed individuals during the initial collapse and first few days following 9/11, and possibly for workers at Ground Zero. Results from laboratory studies showed that relevant doses caused lung inflammation, which subsided, and airway hyper-responsiveness, which persisted at least 1-3 days after exposure. Pregnancy outcomes for mothers exposed to WTC pollution indicate a two-fold increased risk of small-for-gestational-age infants compared to a control cohort. The risk assessment focused on select air pollutants expected to be elevated due to the collapse of the WTC Towers and the ensuing fires. Key findings of the risk assessment, applicable for only those air pollutants evaluated, were: (1) people exposed during the initial collapse and several hours afterward were at risk for acute respiratory symptoms; (2) potential health impacts in the days immediately following 9/11 cannot be evaluated with certainty due to the lack of sufficient air quality data; (3) nonetheless, health effects have been observed including respiratory impacts, such as new onset asthma and "World Trade Center Cough", which have been observed not only in firefighters and rescue workers, but also in residents and other individuals living and working on the perimeter of Ground Zero. In addition, the reproductive effect of intra-uterine growth restriction resulting in low birth weight babies was observed to have occurred in mothers who were pregnant and present in Lower Manhattan during the collapse of the WTC Towers. It has been speculated that initial high exposures to WTC contaminants are responsible for these effects; and (4) except for 9/11 and possibly the next few days, people in the surrounding community were unlikely to suffer short- or long-term adverse health effects due to elevated ambient air concentrations. These elevated concentrations were measured mostly near Ground Zero, and persisted 1 to 3 months following the collapse of the towers.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Demonstrating that ORD-developed tools and science can be rapidly deployed and used to address real world health risk scenarios
- Providing rapid response, technical support, and science for characterizing exposures and risks
- Providing relevant information for understanding the exposures, risks and potential health effects associated with the WTC disaster. The exposure scenarios encountered in the WTC disaster impacted a relatively small segment of the general population, but occurred in such a way that was pervasive (in the case of the fires) and distinct (in the case of the dust cloud created by the collapse)
- Supporting the development of a risk assessment based on the extensive monitoring data and epidemiological research for those highly exposed that will yield significant contributions to better defining the public's risk and possible health effects due to WTC derived pollution. The lack of monitoring data in the days immediately following 9/11 does not allow for a direct evaluation of possible health effects to those exposed, but the extensive data that was collected is being used in the risk assessment
- Demonstrating leadership in conducting collaborative research addressing this catastrophe and by communicating the science by chairing sessions at

international exposure conferences devoted to discussing WTC related research, holding a workshop to develop recommendations on integrating research into emergency response and convening an expert technical review panel to characterize any remaining risks, identifying public health needs, and recommending steps to further minimize risks associated with the WTC disaster.

Poster LTG3-30
Developing Multiple Exposure Methods and Interventions to Understand and Mitigate Risks of Fish Consumption in Recreational Fishing and Subsistence Populations

Presenter: Barbara Glenn (NCER)
Contributors: Nigel Fields (NCER), Jacqueline Moya (NCEA), Susan Schantz (University of Illinois), Felix Basabe and Jamie Danatuto (Swinomish Tribal Community), Dana Wetzel and John Reynolds (Mote Marine Biological Laboratory), Pamela Miller (Alaska Community Action on Toxics), Neil Kmiecik (Great Lakes Indian and Fish and Wildlife Commission), Suzanne McMaster and Hal Zenick (NHEERL), Frederick Tyson (NIEHS) and Bob Spangler, Daphne Mophett, and Dean Seneca (ATSDR)

Science Questions:

This research addresses the following science questions:

- Are subsistence and recreational fishing populations differentially exposed to bioaccumulative toxics in fish and shellfish?
- What culturally appropriate methods to assess exposure, potential health effects, and interventions can be employed at the local or national level to identify and mitigate risks?

The Research:

Subsistence lifestyles, generally speaking, incorporate the use of ecosystems resources regularly as a means of obtaining the necessities for wellness of an individual or a community. There is increasing awareness at EPA that lifestyles and cultural practices associated with subsistence may lead to increased health risks. Although traditional subsistence practices may be protective against some health outcomes associated with current modern American life (e.g. obesity, type II diabetes, etc.), the risks to toxic exposures are substantially increased due to multiple contact points with environmental media when subsistence practitioners conduct a suite of culturally relevant activities or rituals. Thus, there are risks associated with both the sequestering and use of eco-resources. This is particularly the case when considering fish consumption and dietary intake, as there are a variety of baiting, catching, cleaning, storing and preparing techniques for fishes. Multiple uses of fish, in particular whales, allow for additional exposure routes beyond the catch and consumption. To elucidate the ways in which subsistence and recreational fishing populations are exposed to toxics differentially from the greater population, EPA has recently supported local and national level efforts to develop more refined exposure methodologies while concomitantly exploring risk mitigation options, particularly relevant to US Native American populations. Realizing that guidance on interviewing, survey design and critical data analysis are not available, EPA has launched a project to develop a survey instrument expressly designed to assess intake of home-caught fish and shellfish in two phases. The first phase will pilot the

assessment or regional variability across the United States. The second phase will develop guidance for EPA Regions and States on factors to consider when conducting recreational or high-end exposed population surveys.

To address these concerns at the local level EPA has awarded over $3M since 2002 to six tribal organizations and partnering academicians specifically to collect data on the interplay between culture and exposure. Most of these researchers and tribal experts are also developing intervention strategies applicable to neighboring subsistence populations who share ecological resources and behaviors, which aim to reinforce tradition while reducing exposure and health risks.

Two of the EPA/NIEHS Children's Environmental Health Centers are enrolling subsistence populations in longitudinal birth cohorts, one of which focuses on the Hmong population of Green Bay, Wisconsin where bioaccumulation of PCBs and mercury in fish from the Fox River are of concern. This community-university partnership is conducting basic science, exposure and epidemiologic research to raise awareness and to promote wellness in the community.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing and applying multiple ORD and community-based tools to track and incorporate specific fish consumption data in recreational fishing and tribal populations

- Collaborating with local and national-level leaders to assess exposure and risk specifically for recreational and subsistence populations. This activity represents EPA's first efforts in systematically incorporating cultural practices of sequestration, consumption, and use of foodstuffs in conjunction with ORD research designed to reduce community risks

- Developing a network of scientists and tribal leaders who are able to refine ORD-developed methods and approaches to determine unique exposure pathways; conduct dietary and cultural surveys by employing trained, knowledgeable tribal members; and to conduct and translate analytical chemistry on food stuffs and environmental media to reduce uncertainty in risks. For example, the Swinomish Tribe of Washington State have completed the first of several cancer/ non-cancer risk assessments for PCB congeners and dioxins in Butter and Steamer clams using toxics data sampled and analyzed by the tribe. Future plans include continued sampling and risk assessments of other shellfish, completion of documentary video on subsistence practices and targeted risk reduction education and outreach activities for tribal groups around Puget Sound.

Poster LTG3-31
US-Mexico Border Research Program

Presenter: Suzanne McMaster (NHEERL)
Contributors: Gary Robertson and Brian Schumacher (NERL); Pauline Mendola, David Otto, and Elizabeth Hilborn (NHEERL)

Science Question:

- What subpopulations have differential risk to environmental stressors? Specifically:

    - Are children living along the US-Mexico Border experiencing pesticide-related health effects?
    - Are they exposed to more organophosphate pesticides than children living in other areas?
    - Can we identify characteristics of children at high risk for exposure (e.g., by age, gender, etc.)?
    - Do pesticide exposures occur during critical developmental windows?

The Research:

Defined by the La Paz Agreement of 1983 as the area lying 100 kilometers north and south of the border between the United States and Mexico, the US-Mexico Border Region has several characteristics that create a potential for exposure to multiple pesticides from multiple sources. The region contains a large proportion of land devoted to year-round agriculture, creating a risk of repeated, year-round pesticide exposure. Agricultural pesticides are commonly applied by aerial spraying which can contribute to exposure via multiple pathways, including air, water and food. Residential use of pesticides is also a potential source of significant exposure as the same conditions that make the region suitable for year-round agriculture contribute to the potential for year round household pest infestations. The population of the area is large, young and growing. Approximately 17.9 million people live in the border region and almost half (47%) are under 20 years of age. The population growth rate on both sides of the border is higher than the national rates.

This research program is designed to determine if a health threat exists and, if so, to identify the major risk factors to facilitate intervention planning. A three phase approach is employed to address program objectives. Phase I was designed to build capacity for subsequent studies by pilot testing methods and gathering baseline information on the potential for pesticide exposure. Phase II was designed to identify high risk populations of children and potential health effects associated with exposure. Phase III is designed to describe pesticide exposure risk factors and possibly conduct a full scale study of specific exposures and health outcomes. This approach is integrated, with each subsequent phase, building on the results of earlier efforts.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Facilitating the communication on children's environmental health issues at the Federal, State and local levels throughout the Border region
- Demonstrating the feasibility of planned study approaches and providing the Agency with an enhanced ability to study young children (Phases I and II)
- Developing the research capacity to conduct a health effects study in young children with communities and organizations along the US-Mexico Border
- Developing and validating various innovative methods and approaches for characterizing exposures and risks (GIS data base approaches, methods for collecting biological samples from young children and sensitive analytical methods)
- Demonstrating the feasibility of employing innovative approaches to identify children for study participation, although attempts to characterize a high risk profile for children on the basis of age, gender or a symptom checklist were not successful
- Providing data that unexpectedly did not support the hypothesis that pesticide levels in young children vary as a function of proximity of their home and/or school to agricultural fields. This finding has lead ORD researchers to the development of new research hypotheses and plans for future consideration
- Providing the results for ORD and other research groups (including the NCS) to use in the design, planning and execution of future studies that will lead to improved risk assessment approaches for this subpopulation.

Poster LTG3-32
Study of the Health Effects of Children's Exposure to Prevalent Neurotoxicants in an Urban Community

Presenter: Chris Saint (NCER)
Contributors: Bruce Lanphear, Ph.D., Cincinnati Center for Children's Environmental Health, Cincinnati Children's Hospital.

Science Question:

This research addresses the following science questions:

- Are developmental disorders, behavioral problems, growth retardation, and hearing loss in children associated with exposures to environmental toxicant?
- Are adverse changes in brain function and morphology associated with exposure to environmental toxicants and/or the neurobehavioral effects potentially associated with these exposures?
- How safe and efficacious are the various methods used to reduce exposures to prevalent environmental toxicants?

The Research:

There is an increasing awareness that children living in the inner city of some major US urban areas are potentially more exposed to numerous environmental agents, including lead, mercury, PCBs, and environmental tobacco smoke. Fetal and postnatal exposures to these agents have been linked with adverse neurobehavioral effects. Still, the ideal biomarker for measuring *in utero* exposure to specific toxicants has not been established and the adverse effects of many potential neurotoxicants have not been rigorously tested. To address these related perinatal issues, the Office of Research and Development (ORD) STAR Grant program, in partnership with the National Institute of Environmental Health Science is supporting research conducted by the Cincinnati Children's Environmental Health Center (CCEHC). The CCEHC, a university-community partnership, is examining children's exposure to prevalent neurotoxicants and the resulting health effects in an inner-city population of Cincinnati.

Fetal exposure is typically measured with self-reported surveys, maternal blood and urine, or cord blood. In contrast, meconium as a biomarker, is a non-invasive method to simultaneously test for cumulative exposures to numerous toxicants. But it is unclear whether conventional biomarkers or meconium levels are more predictive of the adverse effects linked with specific toxicants. CCEHC is evaluating the efficacy of using meconium based biomarkers for quantifying fetal exposure by determining if these markers are more predictive than the more traditional methods for assessing *in utero* exposure. CCEHC researchers are conducting a cohort study of 400 children, followed from before 16 weeks gestation to 36 months of age, to examine the effect of low-level exposures to prevalent neurotoxicants. Endpoints include behavioral problems, such as conduct disorder and features consistent with Attention Deficit Hyperactivity Disorder (ADHD), cognitive deficits, and hearing loss. They are also conducting a nested, randomized controlled trial to test the efficacy of lead hazard controls on the development of adverse neurobehavioral effects. These studies determine if fetal and postnatal exposures to neurotoxicants are associated with adverse neurobehavioral

effects, growth delay and hearing loss in early childhood and if children in a lead reduction group have lower blood lead levels and fewer health and behavioral problems than a control group. These epidemiological studies are integrated with a study using Magnetic Resonance (MR) imaging and spectroscopy to relate environmental lead exposure with alterations in brain structure, neurochemistry and function. This study will determine if childhood lead exposure disrupts neuronal circuitry, resulting in changes in brain structure and metabolism and if these changes are associated with delinquent behavior and anti-social outcomes.

These ongoing studies will provide better measures of exposure to numerous neurotoxicants that will be used to simultaneously evaluate the adverse effects of exposures to multiple prevalent toxicants in the human population during early childhood and validate the use of meconium as a measure of *in utero* exposures to multiple environmental neurotoxins. The CCEHC will continue to recruit subjects and collect data from the HOME cohort during 2005. They will also begin data analysis of the biomarker and outcome data during this time. These analyses should be completed during 2006. The Center will also provide health management and community groups in Cincinnati with information concerning the effectiveness of methods for reducing childhood lead exposure.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Conducting collaborative research designed to develop and validate innovative biomarker methods for assessing risks to environmental neurotoxicants
- Providing validated exposure and effects data that will provide a better understanding of the remote behavioral effects of early lead exposure. This will allow EPA, HUD, and other collaborators to develop primary prevention methods (both environmental and cognitive /educational) that will alter the developmental trajectories of large numbers of lead-exposed children
- Providing tools for families and communities to identify environmental neurotoxins and disseminate information by establishing the Healthy Home Resource Center at the Better Housing League
- Communicating the results to the scientific and public communities and stimulating community-wide prevention efforts and exposure assessment by participants in population-based studies.

Poster LTG3-33
Studies on the Role of Environmental Factors on the Etiology of Autism

Presenter: Chris Saint (NCER)
Contributors: Isaac Pessah, Ph.D., University of California, Davis; and George Lambert, M.D., University of Medicine and Dentistry of New Jersey.

Science Questions:

This research addresses the following science questions:

- What is the relationship between childhood exposure to environmental factors and the incidence and severity of autism?
- What methods can be developed and employed to determine how these exposures may influence normal social development?
- What are the cellular and molecular mechanisms of autism underlying abnormal development of brain regions which confer important determinants of social behavior?

The Research:

In cooperation with National Institute for Environmental Health Sciences (NIEHS), the Office of Research and Development (ORD) is supporting research centers that integrate community-based health and exposure studies with mechanistic research to examine the relationships between toxic environmental exposures and autism. These centers are conducting the first large scale epidemiologic studies of environmental factors and autism and are the first to integrate the mechanistic studies with the collection of clinical and exposure data. The overall aims of these centers are to understand the common patterns of dysfunction in autism and elucidate mechanisms by which known environmental toxins contribute to abnormal development of social behavior in children so that rationale strategies for intervention and prevention can be developed. This research will help Agency risk assessors identify sub-populations that could be at risk for autism, and the underlying environmental and biological basis for this increased vulnerability.

Although these studies are ongoing, they have provided new tools for investigating autism and related neurobehavioral disorders including a number of new mouse and primate models for studying the effects of environmental toxins on brain development. These ORD-sponsored researchers have also provided new insights into possible immunologic and neurologic mechanisms that may explain the role of environmental toxins in autism. Studies have shown that blood mononuclear cells isolated from autistic children have different responses to antigen stimulations than those from non autistic children and that cells from autistic children are more sensitive to the actions of polychlorinated biphenyls (PCBs) and organic mercurials. Other studies have provided new information on the importance of various molecular and cellular processes such as the impact of xenobiotics on neurogenesis, alteration of dendritic cell function, regulation of calcium transport across the microsome, alterations in the expression of adhesion and repulsion molecules, and the induction of neuroactive cytokines. The researchers have also identified genetic factors that may increase the susceptibility of autistic children to the effects of environmental chemicals. These findings are guiding the data collection

activities in their epidemiologic and exposure data collection efforts and will help to interpret relationships between these data.

Impacts and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing and evaluating new methods and approaches for characterizing and assessing the role exposures to environmental toxicants result in autism
- Producing real-world data that will be used by Agency risk assessors for identifying sub-populations that could be at risk for autism, for identifying the underlying environmental and biological basis for this increased vulnerability, and for an improved understanding of the role that environmental toxins play in autism that will be utilized by US EPA Program Offices to improve exposure, dose-response and risk assessments
- Providing leadership by fostering collaborative research and working closely with community groups to coordinate research efforts regarding autism and the environment and are educating parents and other groups on the progress of research activities
- Communicating the results of this research to the broader scientific community (International Symposium on Autism Research, May 2004).

Poster LTG3-34
Innovative Methods for Locating and Counting People at Potential Risk

Presenter: Susan Perlin (NCEA)
Contributors: David Wong (George Mason University), Ken Sexton (University of Texas), Budhendra Bhaduri (Oak Ridge National Laboratory), Cheryl Itkin (NCEA), Jeff Yurk (EPA Region 6)

Science Question:

- What approaches are needed for characterizing the spatial distribution and size of populations at risk, where risk includes potential exposure to pollutants; distance to noxious and/or toxic sites/facilities; and threats from natural and/or anthropogenic events (e.g., floods, hurricanes, terrorist activities).

The Research:
In the 1990s, our research focused on developing methods to support Environmental Justice (EJ) evaluations. EJ literature of the 1980s-90s generally assumed that by living closer to sources of air pollution, such as Toxic Release Inventory (TRI) facilities, some demographic groups, defined by race and/or socioeconomic status, necessarily experienced higher exposures to facility air emissions compared to other groups who lived farther away.

Using 1990 TRI and census block group (BG) data, we developed three case studies in the industrialized areas of: 1) Kanawha Valley, WV; 2) metropolitan Baltimore, MD; and 3) the Mississippi River from Baton Rouge to New Orleans, LA. We examined relationships among the location of TRIs and demographics (race, age, income) of populations living within three miles of these facilities. Consistent results were observed across study areas. Although a substantial percent of people, regardless of race or income, lived near TRIs, African Americans (and people below poverty) were more likely to live closer to the nearest TRI and within two miles of more facilities compared with Caucasians (and people above poverty). Because of a lack of resources, we could not determine the relationship, if any, between residential proximity to TRI facilities and exposure to air pollution.

Our work raised several important issues concerning current methods, and underlying assumptions, used for apportioning census residential data in order to estimate numbers and locations of people. To apportion census counts using conventional methods (e.g., area weighting, point-in-polygon) requires information on the location of people within each census unit (block, BG, tract). As this key piece of information is not part of the residential census data, or readily available elsewhere, the default is to assume people are evenly distributed across each unit. This critical assumption, though often incorrect, can lead to misclassification of populations relative to defined geographic areas of interest. Our work also raised questions about the reliance on current methods and databases that can only be used to characterize nighttime (e.g., residential) populations and not important daytime (e.g., workers, shoppers, students) populations. As a result, ORD

supported the development of LandScan USA (LSUSA), a high-resolution, gridded, night- and day-time population distribution database and model developed by Oak Ridge National Laboratory (ORNL). The LSUSA prototype was developed in a 29 county pilot study area in SE Texas and SW Louisiana. Using the prototype data/model for industrialized areas of Beaumont and Port Neches in Jefferson County, TX, we developed two case studies to examine the location and size of day- and night-time populations potentially at risk from: 1) exposure to noxious airborne chemicals; or 2) being caught in flood waters and needing access to designated evacuation routes. Both case studies demonstrate the potential value added by using LSUSA compared to current population counting methods. Time of day had a direct impact on size and spatial distribution of populations and thus directly affecting the number and location of people potentially exposed to airborne chemicals or flood waters; and/or needing access to evacuation routes. In contrast to LSUSA, conventional population counting methods applied to residential census data can not take into consideration important spatio-temporal shifts in populations. Key advantages of using LSUSA gridded day/night population distribution data over conventional population counting methods and census residential data are: 1) gridded data can easily be re-aggregated to fit into any needed areal shape (e.g., circular buffer, polygonal flood-plain); 2) gridded data are compatible across heterogeneous data sets (e.g., facility point source data, air pollution concentration data); 3) the area of a LS cell (90x90m) is constant and small relative to the area of a census block, BG or tract, allowing analyses at much finer scales; 4) gridded data produce nighttime populations estimates that are stable and not influenced by artificial boundaries and variable sizes of census blocks, BGs or tracts; 5) estimates of the size and location of daytime populations can be generated; and 6) information and maps developed from LSUSA provide more detailed pictures of where people may be located relative to real or potential exposures/threats and therefore are of greater value to risk assessors and managers, homeland security and emergency preparedness teams, and the like.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Producing research results directly applicable for supporting many EPA, federal, and community needs, including risk/exposure assessment, homeland security, emergency preparedness, and EJ
- Supporting ORNL's development of the prototype population database/tool, LSUSA. The Department of Homeland Security funded ORNL to use this prototype to develop baseline national night/day population distributions by 2005. ORD and ORNL are collaborating to examine the feasibility and "value added" of LSUSA in simulating population exposures to environmental pollutants. This work should improve the LSUSA population distribution model by using information from ORD's Consolidated Human Activity Database (CHAD). The purpose is to develop high-resolution population distribution databases for U.S. metropolitan areas that will provide refined hour-of-day and cohort-specific population distribution data amenable for human exposure modeling
- Developing and validating innovative GIS methods for examining spatial

relationships between locations of populations and point sources that were incorporated into EPA's Population Estimation and Characterization Tool (PECT)

- Providing fundamental tools and methods that have been enhanced and used by the EPA's Office of Civil Rights to investigate potential Title 6 cases.