LONG-TERM GOAL 2
Aggregate and Cumulative Risk Assessment

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Overview

The US Environmental Protection Agency (EPA) and other regulatory agencies use risk assessment to evaluate the risk posed to humans through chemical exposures to contaminants in food, drinking water, or environmental media. Risk assessment for toxic agents is often conducted to evaluate the potential risks from exposure to a single toxic agent through a single route of exposure. Although it is important to evaluate individual toxic agents, people frequently are exposed to many chemicals simultaneously or in sequence by different exposure routes. These exposures to multiple chemicals through various media could cause unexpected cumulative effects. The combined risk from such exposures may be greater or less than what would typically be predicted from data on individual chemicals from single routes of exposure. Assessing multiple route exposures for a single chemical (aggregate) and assessing the cumulative toxicological effects of multiple chemicals has been addressed (US EPA, 1986, 2000). However, new exposure data and methods, toxicological data and statistical analyses techniques, and quantitative risk assessment approaches and guidance are still needed to conduct scientifically defensible aggregate and cumulative risk assessments.

Aggregate exposures are defined by EPA's Science Policy Council as "The combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and sources." Aggregate risk is defined as the "risk resulting from aggregate exposure to a single chemical or agent."

Cumulative Risk Assessment (CRA) is broadly defined by the Agency (US EPA, 2003) as "the combined risks from aggregate exposures to multiple agents or stressors." In this sense, CRA can include both chemical and non-chemical stressors, multiple-route exposures, and population factors that differentially affect exposure or toxicity. CRA has become an important research area, reflecting the interest of EPA's Regional risk assessors, Program Offices, Office of Environmental Justice, and Office of Children's

Health Protection. In 2002, EPA's Office of Research and Development (ORD) jointly sponsored a workshop with EPA's Regions to discuss current case studies, methods and research needs regarding CRA. Regional scientists continue to be confronted with conducting community-based CRA's (e.g., assessing risks from multi-media, multi-stressor exposures to a population in a specified geographic area). Successful completion of such assessments requires development of new data, methods, and guidance.

The need for tools to better address aggregate and cumulative risk is relevant throughout the Agency. EPA's Program Offices generally conduct CRA's on a select group of co-occurring chemicals, and set broad national standards. Several laws have been enacted over the years, requiring the EPA to consider various aspects of cumulative risk in its activities. Examples of programmatic interests include:

- The Office of Water needs to conduct chemical mixtures research to support the Safe Drinking Water Act Amendments of 1996, which require the EPA to evaluate mixtures of contaminants in drinking water.
- The Office of Air Quality Planning and Standards has used a CRA approach in conducting the National Air Toxics Assessment of 33 air pollutants (a subset of 32 air toxics from the Clean Air Act's list of 188 air toxics plus diesel particulate matter).
- The Office of Solid Waste and Emergency Response assesses contaminant mixtures at Superfund Sites under the Comprehensive Environmental Response, Compensation, and Liability Act.
- Under the Food Quality Protection Act (FQPA) of 1996, EPA's Office of Pesticide Programs is required to consider the potential human health risks of multiple route exposures to multiple pesticide residues and substances that have a common mechanism of toxicity.

While many research organizations are doing research in the area of mixtures, few are driven by a regulatory mandate and framework. Further, EPA/ORD conducts its research on aggregate and cumulative risk using realistic exposure conditions and environmentally-relevant concentrations. ORD uniquely has expertise to design and conduct exposure studies, models, and analyses to better ascertain the risk resulting from aggregate and cumulative exposures.

As discussed the Overview Section prepared for this Program Review, research on aggregate and cumulative risk has been identified as a high priority by numerous groups inside and outside the Agency. ORD has emphasized research on those issues that would have the greatest likelihood to improve the scientific basis for Agency regulatory decisions. Work that would complement problem-driven research questions is also given a high priority. ORD research aims to identify which environmental problems pose the greatest risk and which amelioration strategies have the greatest and most cost-effective impacts.

EPA's Long Term Goal for research on Aggregate and Cumulative Risk is that risk assessors and risk managers use ORD's methods and models to characterize aggregate and cumulative risk, which in turn reduces risks resulting from human exposure to multiple environmental stressors. The key research questions identified by ORD to meet this goal are:

- What are people's real world aggregate exposures?
- What contributes to aggregate exposures?
- How do we estimate cumulative risk from aggregate exposures?
- How do we mitigate aggregate/cumulative risk?

ORD is responding to these research questions by conducting research to (1) identify and implement cost-effective ways to measure human exposure via all relevant pathways; (2) develop methods and models to characterize aggregate and cumulative exposures and risks in human populations of concern; and (3) understand effects of mixtures of environmental stressors with similar and dissimilar modes or mechanisms of action to better assess risk under actual exposure conditions. Research outputs in the aggregate/cumulative area include measures indicative of human exposure across variety of environments, durations and conditions; models characterizing relationship among sources of environmental contaminants to assess aggregate and cumulative exposures and risks in human populations of concern; and models to predict the cumulative risk of chemical mixtures.

Selected Examples of Research on Aggregate and Cumulative Risk

The research program on aggregate and cumulative risk may be divided into two broad areas. First there is the development of tools to better address the complex issues related to aggregate and cumulative risk. Second, once these tools are developed they are applied to specific cases that both test the tools and aid the Agency in achieving its programmatic mandates using the best possible science.

Methods, Measures and Models to Advance the Science of Aggregate and Cumulative Risk Assessment

Analytical methods are being developed and/or enhanced to better assess the bioavailability of contaminants in environmental media. These include chemical extraction methods delineating contaminant availability, and bioassays, which measure the bioaccumulation of toxic elements from environmental media. ORD is using these methods in collaboration with the Department of Housing and Urban Development in the American Healthy Homes Survey (AHHS) to provide data from a national cross-section of residential soils collected near chromated copper arsenate (CCA) treated wood. ORD scientists are also evaluating the effectiveness of coatings in reducing dislodgeable arsenic from CCA-treated wood.

ORD has also developed analytical methods for perfluorinated compounds (PFCs) including perflurooctane sulfonate and perflourooctanoic acid in environmental and biological matrices. Prior to this work, methods were not available or lacked the requisite reproducibility. The methods will support research in a number of high priority programs including: AHHS, which will provide the first population-based assessment of PFCs; the Children's Total Exposure to Pesticides and Persistent Pollutants (CTEPP) program, where the first assessment of the volatile telomer alcohols has been completed; and animal research studies conducted to support priority research identified by the Office of Prevention, Pesticides, and Toxic Substances (OPPTS). This work provides a means to evaluate exposures to the PFCs, helps to establish risks associated with these exposures, and ultimately may support an assessment of the effectiveness of any mitigation strategies that may be put in place to control exposures deemed hazardous.

Alternative methods were and are needed to accurately determine the impact of pesticides on human health, especially for infants and young children. Faster and more

cost-effective field screening and monitoring methods can help achieve this requirement by increasing the amount of information available concerning the location and concentration of target analytes that might impact human health and the environment. Cost-effective immunochemical methods are being developed by ORD to measure contaminants in both indoor and outdoor environments, as well as to determine urinary biomarkers of exposure. This research provides direct support to the CTEPP project and the Agricultural Health Study.

ORD's portfolio of cumulative risk research projects focusing on developing methods to assess the toxicology of chemical mixtures, including four trihalomethanes (THMs), a mixture of 5 organophosphorus (OP) pesticides (chlorpyrifos, diazinon, dimethoate, acephate, and malathion), and the interactive effects of 18 PHAHs on thyroid function. These experimental efforts are largely completed and future efforts will focus on the development of techniques to evaluate interactions in the lower end of the dose-response curves. Future efforts will also focus on understanding the health impact of the unidentified fraction of highly complex, incompletely characterized, environmental mixtures.

Case Studies and Risk Assessment Applications of Aggregate and Cumulative Risk

ORD's Human Health Research Program supports diverse efforts aimed at reducing uncertainty in risk assessments. Notably, numerous in-house, collaborative, and grant-based measurement studies, both field- and laboratory-based, strive to exhaustively measure total exposure aggregated across all relevant pathways, particularly among susceptible populations, with due consideration of the cumulative deleterious effects of compounds with a common mechanism of toxicity.

Field studies are essential for establishing the importance of specific exposure pathways and for evaluating the influence of personal attributes and behaviors on exposure. Large field studies addressing aggregate exposure have a rich tradition in ORD. In the 1990s the Interagency National Human Exposure Assessment Survey (NHEXAS) evaluated multimedia exposures to multiple classes of pollutants and demonstrated the importance of dietary intake, exposure-related activities, and even demographic characteristics. The Minnesota Children's Pesticide Exposure Study (MNCPES) marked the beginning of a deliberate focus on susceptible populations, and

the Children's Total Exposure to Persistent Pesticides (CTEPP) study helped refine the methodologies used to characterize aggregate exposure and potential dose. More recent studies such as the Feasibility Study of the Macroactivity Approach for Assessing Dermal Exposure and the Dietary Intake of Young Children (DIYC) allow a rigorous evaluation of the algorithms currently used to estimate aggregate exposure (particularly the critical pathways of dermal absorption and indirect ingestion). Data from these field studies are being used to refine inputs of ORD and other human exposure models, as well as to evaluate model predictions.

Planned and recently initiated field studies employ increasingly sophisticated methodologies for estimating aggregate exposure and are explicitly guided by the concept of cumulative risk. The Detroit Exposure and Aerosol Research Study (DEARS) has begun to measure the combined exposure to particulate matter and air toxics and the influence of personal and residential factors. An upcoming STAR Grant Program directly addresses one of the principal deficiencies in assessing cumulative risk by quantifying inter- and intra-individual variability in behavioral factors.

Laboratory studies are used to evaluate assumptions related to the individual pathways that lead to aggregate exposure, such as the spatial and temporal distributions of the applied insecticides, the conditions that affect the resuspension and translocation of particulate matter, and the parameters that determine the transfer and subsequent uptake of residues. Moreover, laboratory studies provide a means of investigating cumulative risks, such as those related to the interactive effects of endocrine disruptors, or to the interaction of pyrethroids with calcium channels as a mechanism for neurotoxicity.

The Human Exposure Database System (HEDS) is an integrated database system that contains chemical measurements, questionnaire responses, documents, and other information related to EPA research studies of the exposure of people to environmental contaminants. A web-enabled data repository for human exposure studies, the mission of HEDS is to provide data sets, documents, and metadata for human exposure studies that can be easily accessed and understood by a diverse set of users. HEDS operates in conjunction with the Environmental Information Management System (EIMS), ORD's metadata repository. HEDS provides only data and accompanying documentation from

research studies; it does not provide interpretations. It allows a user to download documents for review or data sets for analysis on their own computer system.

Included in HEDS are data from The EPA National Human Exposure Assessment Survey (NHEXAS) studies conducted in the 1990s. These include three population-based survey and sampling programs conducted in three diverse areas of the U.S. The NHEXAS questionnaires elicited data on several exposure factors from people living in Arizona, Maryland and EPA's Region 5. Data are available by race, ethnicity, age, gender, education and income. NCEA is directing an effort to analyze data from NHEXAS on selected exposure factors to assist in future updates of EPA's Exposure Factors Handbook.

The Exposure Factors Program is a comprehensive program with the primary goal of compiling, analyzing, and summarizing exposure factors data to be used in future updates of the Exposure Factors Handbook (US EPA, 1996)and the Child-Specific Exposure Factors Handbook (US EPA, 2002). The EPA Exposure Factors Handbook and the Child-Specific Exposure Factors Handbook are tools available to exposure assessors, which summarize statistical data on exposure factors necessary to conduct human health exposure assessments. Data are presented for the general population and for various population cohorts. The use of the Handbook has resulted in more consistency among exposure assessments conducted by the Agency and outside. An Agency-wide advisory group has been established to assist ORD in identifying data gaps and set priorities for exposure factors research.

The Consolidated Human Activity Database (CHAD) is a database of almost 23,000 person-days of 24 hr human activity information on an activity-by-activity basis. Demographic information for each subject providing data are included in questionnaire format. The data were obtained from pre-existing human activity studies that were collected at city, state, and national levels over a twenty-year period. CHAD can be accessed on-line at www.epa.gov/chadnet1/ and is intended to provide input data in a consistent format for exposure/intake dose modeling and/or statistical analysis. CHAD data are used in a variety of Agency and external exposure models.

ORD researchers have developed a variety of computer models to simulate how pollutants enter and move through the environment, and how they contact, enter, and

move through exposed humans. For pesticides, several models have been developed and are being used for exposure and risk assessments. These models span the "source-to-effects" continuum of processes whereby chemicals are introduced into the environment, move through multiple environmental media, are contacted and absorbed into humans, and have effects on biological systems that can in turn lead to health effects. Use of such models will enable risk assessors to answer questions about the sources, pathways, and factors that contribute to aggregate and cumulative exposures and risk.

Working with colleagues in academia, ORD researchers have developed a model to simulate the indoor fate and transport of low-volatility pesticides. This model uses the chemical principle of fugacity to estimate the reversible movement of pesticides between indoor air and household surfaces such as carpets and vinyl, and incorporates ventilation rates to show the gradual exhausting of the chemicals to the outdoors. The indoor fugacity model is being linked to ORD's Stochastic Human Exposure and Dose Simulation (SHEDS) model for pesticides. This model is one of several indoor fate and transport models that ORD has developed.

SHEDS inputs include air and surface concentrations from the indoor fugacity model, human activity data extracted from ORD's Consolidated Human Activity Database (CHAD), and other exposure factors data as compiled in the EPA Exposure Factors Handbooks and collected through ORD measurement studies. SHEDS utilizes probabilistic modeling to estimate distributions of multiple-pathway (aggregate) exposure and absorbed dose for user-selected segments of the population. The outputs from SHEDS represent the inherent variabilities of exposure and dose that result from varying environmental conditions and human behavior, as well as the uncertainty surrounding those estimates.

ORD scientists have also developed the Exposure-Related Dose-Estimating Model (ERDEM), a physiologically-based pharmacokinetic (PBPK) model to simulate the human organism and its ability to absorb, store, metabolize, and eliminate chemicals. ERDEM has been used to simulate the reaction of multiple (cumulative) pesticides and their metabolites with cholinesterase enzymes in the nervous system, and will be interfaced with SHEDS for enhanced dose estimates. Model development to improve

organ representations and model applications to chemicals of regulatory interest to EPA are continuing.

In order to explore the use of computational toxicology methodologies, the specific example of exposure to mixtures of acetylcholinesterase (ACHE) inhibitors is being studied. Exposure to these pesticides is frequently as mixtures of chemicals that have the same (or similar) mechanisms of action. In this research, dose-response data for individual chemicals and information about the mechanism of action are being used to derive models for activity. These models may then be used to study the potential interactions between chemicals in this class, and therefore the cumulative risk of exposure to mixtures of ACHE inhibitors.

ORD researchers have also developed a PBPK/PD model for N-methyl carbamate. Three processes that may lead to interactions between chemicals have been identified. They are metabolism, distribution and interaction with the molecular target for activity, ACHE. In another effort, a series of theoretical PBPK/PD models (similar to the N-methyl carbamate model) is being developed to yield dose-response curves for idealized chemicals. The features that determine the shape of these curves may then be identified. The effect of exposure to multiple chemicals on these salient features is being explored in order to observe if and how interactions between chemicals may lead to deviations from dose additivity. In order to address issues of model structure and parameter uncertainty, molecular modeling methods are being used to study the interaction between ACHE and pesticide inhibitors. This research takes advantage of specific structural information about the enzyme to explore a mechanism for non-additivity. Experimental information available from the literature suggests that there are two binding sites per enzyme molecule. Each binding site serves a different purpose. One site is the catalytic site responsible for de-esterification. The other, less well-established, site is a peripheral site that is not directly responsible for catalysis but binding to this site affects the specificity and capacity of the enzyme to perform catalysis. The latter site is also called the allosteric site because there are indications that binding there changes the three-dimensional shape of the enzyme. The existence of these two interacting sites on the protein (with different specificities) has profound consequences for the assessment of the risk of a mixture of ACHE inhibitors. Additional state-of-the-

art molecular modeling studies are underway to determine the feasibility of determining metabolic parameters for another class of pesticides and explore whether these methods will be helpful for estimating metabolic parameters more generally.

In addition to these ORD-developed models, other models have been developed by academic researchers working under grants from ORD's National Center for Environmental Research (NCER). Future developments in ORD's modeling will include development of enhanced Computational Toxicology models, and the use of bionomic data such as that from genomic and metabonomic analyses which will yield even more detailed insights into susceptibility and the effects on organisms that result from environmental exposure and dose. To integrate recent advances from both ORD and extramural scientists and to provide guidance to those parts of the Agency that must consider mixtures data, ORD intends to sponsor a number of expert workshops to evaluate the state-of-the-science with regard to the limits of additivity.

Summary

The research in this area outlines how ORD has implemented programs to develop and apply improved tools (methods, measures, models, and databases) for conducting aggregate and cumulative risk assessments. This research reduces uncertainty in risk assessment by generating data, methods, techniques, and models, and evaluating these under real-world scenarios, that demonstrate the usefulness of ORD's research tools for aggregate exposures and cumulative risk. The research also produces fundamental science results that will be used to refine Agency guidance for conducting aggregate and cumulative risk assessments and provides opportunities for stakeholders to collaboratively develop new tools and guidance, and to conduct state-of-the-art cumulative risk assessments. ORD research also provides data for developing risk reduction and risk management strategies. ORD outputs contribute to the development of new hypotheses and identification and prioritization of future research at ORD.

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Poster LTG2-01
Methods, Measures, and Models to Advance the Science of Aggregate and Cumulative Risk Assessment: An Overview

Presenter: Marina Evans (NHEERL)

Contributors: James Starr, Peter Egeghy, and Ed Furtaw (NERL); Glenn Rice and Jackie Moya (NCEA); and James Rabinowitz and Jane Ellen Simmons (NHEERL)

Science Question:

The research in this topic area outlines how the Office of Research and Development (ORD) has implemented programs to develop and apply improved tools (methods, measures, models, and databases) for conducting aggregate and cumulative risk assessments. The tools help ORD and the scientific community address the following key research questions:

- What are people's real world aggregate exposures?
- What contributes to aggregate exposures?
- How do we estimate cumulative risk from aggregate exposures?
- How do we mitigate aggregate/cumulative risk?

The Research:

The Food Quality Protection Act (FQPA, 2006) and the Safe Drinking Water Act (SDWA, 2006) mandate that the US EPA shift from its traditional single chemical, single media assessments and consider approaches that include aggregate exposure and cumulative risk (multiple chemicals). Aggregate exposure is defined as exposures to a single chemical by all routes and pathways. FQPA defines cumulative risks as exposures to multiple chemicals with a common mode of action. The scientific community defines cumulative risk more broadly, exposures to chemical and non-chemical stressors. ORD is responding to these research needs by conducting research aimed at developing tools and applications that combine data gathering and computational approaches to fulfill these new needs.

New methods are being developed to generate high quality exposure data in ORD-sponsored field and laboratory studies. Starr et al. outlines the development of new analytical methods to measure the bioavailability of selected chemicals in different media. Examples of this methods research include measurements of chromated copper arsenate, perfluorinated compounds, and pesticide markers of exposure. Egeghy et al. summarizes key ORD measurement studies designed to characterize real world aggregate exposures to vulnerable populations, identify the various pathways and key factors influencing the exposures, and assess the co-occurrence of chemicals (i.e., mixtures). Example studies include the National Human Exposure Assessment Survey (NHEXAS), the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic

Pollutants (CTEPP) study, and the planned Children's Environmental Exposure Research Study (CHEERS). Moya et al. outlines how ORD concentrates on gathering data for relevant databases including the Human Exposure Database System (HEDS) and the Exposure Factors Program, and then updates and summarizes the resulting exposure factors that will be used in future risk assessments.

ORD employs a variety of computational techniques to generate relevant exposure data to extend the field and laboratory exposure databases needed for risk assessment. ORD research focuses on developing state-of-the-science mathematical models that integrate exposure models with dose-related models to assess both aggregate exposure and cumulative risk. Furtaw et al. takes the pesticide exposure outputs from ORD's Stochastic Human Exposure Dose Simulation (SHEDS) model and integrates these data with PBPK modeling using ORD's Exposure-Related Dose-Estimating Model (ERDEM). Rabinowitz et al. applies an innovative computational method to explore the interaction of exposures to a mixture of pesticides having a similar mechanism of action leading to acetylcholinesterase inhibition. Simmons et al. outlines ORD's research that has produced approaches for efficient experimental designs and statistical analyses for investigating interactions among chemicals. These approaches have been applied to mixtures of: four trihalomethanes; five organophosphate pesticides; and eighteen polyhalogenated aromatic hydrocarbons. Rice et al. provides insights for improved risk assessments by addressing risks posed by multiple environmental stressors and exposure routes by improving methods for using data on environmental transport, exposure and toxicokinetics, and mechanisms of toxic action. Research is conducted on estimating human doses of environmental mixtures, developing quantitative cumulative risk assessment methods, assessing both environmental and toxicological interactions, and addressing uncertainty in aggregate and cumulative exposures.

Impact and Outcomes:

This research outlined in this topic area reduces uncertainty in future human health risk assessments by:

- Providing improved science tools that can be used by ORD, EPA's Program Offices and Regional Offices, and the scientific community to generate high quality exposure data supporting future risk assessments
- Understanding the scientific basis of and key factors influencing aggregate exposures and cumulative risks
- Understanding and characterizing the biological basis for interactions resulting from exposures to chemical mixtures
- Developing and prioritizing hypotheses and areas of greatest uncertainty for future research
- Developing and implementing future risk intervention and prevention strategies that ultimately reduce human risk associated with exposures to single and multiple agents.

Poster LTG2-02
New Analytical Methods to Assess Aggregate Exposure and Cumulative Risk

Presenter: James Starr (NERL)
Contributors: Karen Bradham, Andy Lindstrom, Elin Ulrich, Mark Strynar, Sharon Harper, and Jeanette Van Emon (NERL); Mark Mason (NRMRL)

Science Question:

- What new and/or improved laboratory and field methods are needed to reduce current method uncertainties, fill critical exposure data gaps, and produce high quality real world exposure data for the development and evaluation of new exposure and dose models that can provide a better understanding of human aggregate exposures and cumulative risks.

The Research:

The Office of Research and Development (ORD) conducts research to produce new and/or improved methods to generate real world exposure data supporting Agency high priority science needs for performing risk assessments and risk management decisions. The methods provide a scientific foundation to characterize and reduce human risks resulting from exposures to single and/or multiple environmental stressors and to further the fundamental understanding of key factors influencing aggregate exposures and cumulative risks.

Current research is being performed to develop and/or enhance methods for assessing the bioavailability of selected contaminants in environmental media. These include chemical extraction methods delineating contaminant availability, and bioassays, which measure the bioaccumulation of toxic elements from environmental media. ORD is using the new methods for assessing potential exposures to Chromated Copper Arsenate (CCA) in various programs: 1) in collaboration with the Office of Pesticides Programs (OPP) and the Consumer Safety Product Commission (CPSC) to characterize and assess potential children's exposures (see Zartarian et al.) in support of OPP's current risk assessment; 2) in collaboration with the U.S. Department of Housing and Urban Development in the nationally representative American Healthy Homes Survey (AHHS) to provide estimates reflecting potential CCA exposures nationwide; and 3) in collaboration with OPP and CPSC, to evaluate the effectiveness of coatings in reducing dislodgeable arsenic from CCA-treated wood.

Analytical methods for Perfluorinated Compounds (PFCs) including perflurooctane sulfonate, perflourooctanoic acid, and the telomer alcohol in environmental and biological matrices have also been developed to support the Office of Prevention, Pesticides and Toxics (OPPT) enforceable consent agreement exposure data needs. Prior to ORD's research effort, methods were either not available or lacked the requisite reproducibility to be considered validated for use in characterizing environmental exposures. The validated methods are being employed to support various high priority

research programs including: 1)AHHS, producing the first population-based assessment of perfluorinated compounds; 2) selected Children's Total Exposure to Pesticides and Persistent Organic Pollutants (CTEPP) samples, providing the first assessment of exposures to the volatile telomer alcohols (completed); 3) the Children's Environmental Exposure Research Study (CHEERS), providing exposure data for very young children; and, 4) ORD-sponsored animal studies designed to better understand the effects resulting from exposures to PFCs.

Alternative methods are needed to accurately determine the impact of pesticides and other environmental agents on human health, especially for infants and young children. Faster, more cost-effective, and less-burdensome field screening and monitoring methods can increase the amount of information available concerning the location and concentration of target analytes that might impact human health and the environment. Cost-effective immunochemical methods are being developed by ORD to measure contaminants in both indoor and outdoor environments, as well as to determine urinary biomarkers of exposure. Sample extraction, cleanup, Gas Chromatograph/Mass Spectrometry (GC/MS), and Liquid Chromatography/Tandem Mass Spectrometry methods have been developed along with field sampling methods and devices for assessing pesticides exposures in relevant environmental media. These methods have been used to support CTEPP and the National Cancer Institute Sponsored Agricultural Health Study, and they are being made available for the planned CHEERS and National Children's Study.

Impact and outcomes:

ORD's methods research reduces uncertainty in future Agency risk assessments by:

- Providing validated laboratory and field sampling methods to ORD and the scientific community with increased sensitivity, selectivity, and subsequently reduced uncertainty
- Providing an evaluated toolbox of methods to produce high quality, real-world exposure data for characterizing and assessing aggregate exposures and cumulative risks
- Employing these methods in future exposure studies to fill critical exposure and exposure factor data gaps and subsequently replace default assumptions
- Improving our understanding regarding the linkages between exposures and associated health risks
- Supporting the development and evaluation of mitigation strategies for reducing and/or controlling future exposures to hazardous chemicals.

Poster LTG2-03
Measurement Studies to Reduce Uncertainty in Aggregate and Cumulative Risk Assessments: Identifying Critical Pathways and Factors

Presenter: Peter P. Egeghy (NERL)
Contributors: Linda Sheldon, Marsha Morgan, Lisa Melnyk, Gary Robertson, and Elaine Cohen Hubal (NERL); Tim Shafer (NHEERL); Kacee Deener and Chris Saint (NCER); Mark Mason (NRMRL), Alex Lu (University of Washington)

Science Questions:

This research program addresses the following questions:

- What are the real-world aggregate exposure levels among susceptible and vulnerable populations?
- How do these exposures differ from those of the general population?
- What are the critical pathways producing significant contributions to aggregate exposure?
- What are the most influential factors along each pathway?
- Is there evidence of common or complementary mechanisms among different compounds that would suggest cumulative risk?

The Research:

The validity of any risk assessment and the ultimate success of any ensuing risk reduction action(s), rests on the adequacy of the data used in the assessment. Cumulative risk assessment presents a significant challenge in the face of inadequate exposure data, incomplete understanding of relevant exposure pathways, and ignorance of influential exposure factors. The Office of Research and Development (ORD) conducts research to address these challenges through numerous in-house, collaborative, and STAR grant funded field and laboratory measurement studies. In these studies, ORD and its collaborators exhaustively measure aggregate exposures for selected susceptible populations with due consideration of the cumulative deleterious effects of compounds with a common mechanism of toxicity. These studies are designed to generate high quality, real-world data for understanding the importance of specific exposure pathways, for evaluating the influence of personal attributes and behaviors on exposure, and for supporting the development and evaluation of exposure and dose models.

Large field studies addressing aggregate exposure have a rich tradition in ORD. In the 1990s the interagency National Human Exposure Assessment Survey (NHEXAS) evaluated multimedia exposures to multiple classes of pollutants and demonstrated the importance of dietary intake, exposure-related activities, and even demographic characteristics as key factors influencing exposure. The Minnesota Children's Pesticide Exposure Study (MNCPES) marked the beginning of a deliberate focus on targeted susceptible (children) populations, and the Children's Total Exposure to Persistent

Pesticides and Other Persistent Organic Pollutants (CTEPP) study helped refine the methodologies used to characterize aggregate exposure and potential dose. The Feasibility Study of the Macroactivity Approach for Assessing Dermal Exposure and the Dietary Intake of Young Children (DIYC) has produced data to support a rigorous evaluation of the algorithms currently used to estimate aggregate exposure, particularly for the critical pathways of dermal absorption and indirect ingestion. ORD-funded STAR research has been used to improve the understanding of the sources and pathways of pesticide exposure among children and the factors that influence these pathways. Data from these field studies are being used to refine inputs of ORD and other human exposure and dose models, as well as to evaluate model predictions (see Furtaw et al. poster).

Planned and recently initiated field studies employ increasingly sophisticated methodologies for estimating aggregate exposure and cumulative risks. The Detroit Exposure and Aerosol Research Study (DEARS) is measuring exposures to particulate matter and selected air toxics along with collecting data representing personal activities and residential factors. An upcoming ORD STAR grant initiative directly addresses one of the principal deficiencies in assessing cumulative risk by quantifying inter- and intra-individual variability in behavioral factors.

Laboratory studies are rigorously evaluating the assumptions used in estimating and aggregating pathway-specific exposures. These include spatial and temporal variability in environmental concentrations, conditions affecting resuspension and translocation of contaminants, and parameters determining the transfer and subsequent uptake of residues. Moreover, laboratory studies are investigating mechanisms of toxicity. For example, pyrethroid disruption of neuronal networks is currently being examined to better understand how attacks on multiple sub-cellular targets ultimately produce neurotoxicity. Such information will improve the scientific basis for grouping compounds into classes based on mode-of-action for the purpose of cumulative risk assessments.

Future measurement studies will address persistent needs, including a more sophisticated appreciation of dermal transfer and of the relative contributions from the various exposure routes. The algorithms currently used to combine pathway-specific environmental data with exposure factors to estimate aggregate exposure and subsequent dose require further refinement. Moreover, a better understanding of mechanisms underlying deleterious effects is needed to properly assess cumulative risk from exposure to multiple compounds.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing comprehensive measurements of real-world, multi-pathway exposures to a wide variety of chemicals and mixtures, thereby reducing the reliance on default assumptions in the risk assessment process
- Identifying and measuring the key factors (transfer mechanisms, personal activities, and physical agents) influencing human exposures

- Providing updated algorithms for characterizing aggregate exposure among susceptible populations incorporating all relevant routes, pathways, and activities
- Generating experimental results providing the scientific justification for assessing cumulative risk on the basis of mode-of-action
- Providing high quality data for the development and evaluation of exposure and dose models
- Providing a risk database of exposure data that supports sophisticated human health risk assessments and substantially strengthens the foundation of the Agency's risk reduction decisions.

Poster LTG2-04
Computer Models to Estimate Real-World Aggregate and Cumulative Exposures and Doses

Presenter: Ed Furtaw (NERL)
Contributors: Valerie Zartarian, Fred Power, and Tom McCurdy (NERL); Chris Saint (NCER); Zhishi Guo (NRMRL**)**

Science Questions:

This research program addresses the following science questions:

- Can computer models be developed to estimate the human exposure and dose of various pollutants to humans exposed via multiple routes and pathways (e.g., inhalation, dietary, dermal contact)?
- Can models developed with data for one chemical be used to estimate human exposure and dose for other pollutants?
- What models are available to perform these assessments?

The Research:

Researchers with the Office of Research and Development (ORD) have developed a variety of computer models to simulate how pollutants enter and move through the environment, and how they contact, enter, and move through exposed humans. For pesticides, several models have been developed and are being used for exposure and risk assessments. These models span the "source-to-effects" continuum of processes where chemicals are introduced into the environment, move through multiple environmental media, are contacted and absorbed into humans, and have effects on biological systems that can in turn lead to health effects. Through the use of the evaluated ORD models, risk assessors will be able to answer questions about the sources, pathways, and factors that contribute to aggregate and cumulative exposures and risk.

ORD has developed several models to characterize the fate and transport of selected environmental contaminants indoors. Working with colleagues in academia, ORD researchers recently developed a model to simulate the indoor fate and transport of low-volatility pesticides. This model uses the chemical principle of fugacity to estimate the reversible movement of pesticides between indoor air and household surfaces such as carpets and vinyl, and incorporates ventilation rates to show the gradual exhausting of the chemicals to the outdoors. The indoor fugacity model is being linked to ORD's Stochastic Human Exposure and Dose Simulation (SHEDS) model for pesticides.

SHEDS inputs include air and surface concentrations from the indoor fugacity model, human activity data extracted from ORD's Consolidated Human Activity Database (CHAD), and other exposure factors data that have been collected through ORD measurement studies (see Egeghy et al. poster) and/or compiled in EPA's Exposure

Factors Handbooks (see Moya et al. poster). SHEDS utilizes probabilistic modeling to estimate distributions of multiple-pathway (aggregate) exposure and absorbed dose for user-selected segments of the population. The outputs from SHEDS represent the inherent variabilities of exposure and dose that result from varying environmental conditions and human behavior, as well as the uncertainty surrounding those estimates. The SHEDS model has been applied to modeling children's exposures to chlorpyrifos using information obtained from EPA's Office of Pesticide Programs (OPP) and available literature. Following the development of the SHEDS pesticides model for chlorpyrifos, ORD/NERL hosted a scientific Aggregate Residential Exposure Model Comparison Workshop in October 2001, at the request of OPP. The main objective of this workshop was to compare and evaluate several human exposure models (SHEDS, Calendex, Lifeline, and CARES) that were being developed for assessments under the Food Quality Protection Act of 1996 (FQPA).

ORD scientists have also developed the Exposure-Related Dose-Estimating Model (ERDEM), a physiologically-based pharmacokinetic (PBPK) model to simulate the human organism and its ability to absorb, distribute, metabolize, and eliminate chemicals. ERDEM has been used to simulate the reaction of individual and multiple (cumulative) pesticides and their metabolites with cholinesterase enzymes in the nervous system, and will be interfaced with SHEDS for enhanced dose estimates. ERDEM algorithm and modeling module development to improve organ representations, and model applications to chemicals of regulatory interest to EPA are continuing to be developed. Models being developed by academic researchers through the STAR grant program will also be examined and considered for integration with the evaluated ORD source-to-dose models in the future.

Future developments in ORD's modeling will include development of enhanced Computational Toxicology models, and the use of bionomic data such as that from genomic, proteomic, and metabonomic analyses which will yield even more detailed insights into the key mechanisms and factors influencing susceptibility and the effects on organisms that result from environmental exposures and resulting dose.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing exposure and dose model outputs extending the limited data being generated through laboratory and field studies
- Providing improved understanding regarding the transport and fate of chemicals both in various environmental media and within humans, and the relative importance of various factors in contributing to exposure, dose, and risk
- Identifying data gaps, generating research hypotheses, and prioritizing research
- Providing risk assessors and managers with tools for helping to understand the effects of the pollutants on health risks, the need for regulatory controls on the use of chemicals, and the likely effectiveness of various possible regulatory actions
- ORD's exposure and dose models have been used by the Office of Pesticide

Programs (e.g., exposure of children to chromated copper arsenate-treated wood playsets; children's aggregate exposure to chlorpyrifos; malathion exposures from head-lice treatment) and by EPA's National Center for Environmental Assessment to conduct exposure and dose assessments (several volatile organic compounds) that contribute important scientific information to Agency risk assessments that in turn inform risk-management decisions.

Poster LTG2-05
Databases for Use in Conducting Aggregate and Cumulative Assessments

Presenter: Jacqueline Moya (NCEA)

Contributors: Carry Croghan and Tom McCurdy (NERL); Amina Wilkins (NCEA)

Science Questions:

This research addresses the following science questions:

- What is the best available scientific information for assessing aggregate and cumulative exposures in support of Agency's regulations and decision- making?
- How can ORD develop, organize, integrate, synthesize, and communicate important exposure information with databases to support scientifically sound integrated solutions to complex environmental problems?

The Research:

Risk assessments are important components of EPA's decision making process. One of the Office of Research and Development 's (ORD) missions is to strengthen the scientific foundation of EPA's risk assessments and risk management decisions. In recent years, risk assessment has evolved from evaluating a single stressor in one environmental medium to evaluating aggregate exposures and cumulative risks. Therefore, it is critical that the best up-to-date data be available to the exposure and risk assessor to realistically refine aggregate and cumulative assessments. ORD has several research efforts designed to provide human exposure data necessary for assessing exposures to multiple contaminants in the environment.

The Human Exposure Database System (HEDS) is a web-enabled, integrated database system (www.epa.gov/heds/) that contains chemical measurements, questionnaire responses, documents, and other information related to ORD-sponsored human exposure measurement research studies (see Egeghy et al. poster). HEDS provides the validated data sets, along with the accompanying documents and metadata from ORD sponsored human exposure studies that can be easily accessed and understood by a diverse set of users. HEDS does not provide data interpretations. It allows a user to download the data and documents for review or analysis. HEDS operates in conjunction with the Environmental Information Management System (EIMS), ORD's metadata repository.

The *Exposure Factors Program* is a comprehensive program with the primary goal of compiling, analyzing, and summarizing exposure factors data to be used in future updates of the *Exposure Factors Handbook* and the *Child-Specific Exposure Factors Handbook*. The EPA *Exposure Factors Handbook* and the *Child-Specific Exposure Factors Handbook* are tools available to exposure assessors, which summarize statistical data on exposure factors necessary to conduct human health exposure assessments. These factors

include: water consumption, soil ingestion, inhalation rates, surface area, soil adherence to skin, body weight, life expectancy, food consumption, breast milk consumption, activity patterns, consumer product use, and residential building characteristics. Data are presented for the general population and for various population cohorts. The use of the Handbook has resulted in more consistency among exposure assessments conducted by the Agency and outside. These two documents are available on-line (www.epa.gov/ncea/). An Agency-wide advisory group has been established to assist ORD in identifying data gaps and set priorities for exposure factor's research.

The Consolidated Human Activity Database (CHAD) is a database of almost 23,000 person-days of 24 hr human activity information on an activity-by-activity basis. Demographic information for each subject in the database is included in questionnaire format. The data were obtained from pre-existing human activity studies that were collected at city, state, and national levels over a twenty-year period. CHAD can be accessed on-line at www.epa.gov/chadnet1/ and is intended to provide input data in a consistent format for exposure/intake dose modeling and/or statistical analysis. CHAD data are used in a variety of Agency and external exposure models.

The EPA National Human Exposure Assessment Survey (NHEXAS) studies conducted in the 1990s include three population-based survey and sampling programs conducted in three diverse areas of the U.S. (see Egeghy et al. poster). The NHEXAS questionnaires elicited data on several exposure factors from people living in Arizona, Maryland and EPA's Region 5. Data are available by race, ethnicity, age, gender, education and income. ORD is directing an effort to analyze data from NHEXAS on selected exposure factors to assist in future updates of EPA's Exposure Factors Handbook. The NHEXAS exposure factors data are available on a soon to be published in a user-friendly CD format.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Providing the most up-to-date data on environmental exposure and improving their access to Agency users, states, stakeholders, and the public. The use of these data and the Handbook is critical for scientists involved in conducting exposure assessments and have resulted in more consistency among exposure assessments conducted by the Agency and outside
- Providing risk assessors with the best scientific information to improve Agency efforts in identifying, assessing, and mitigating risks to those populations who may be exposed to environmental chemicals from various sources
- Identifying data gaps, developing research hypotheses, and prioritizing research so that future research efforts can be targeted to fulfill those data needs

- Integrating data and providing universal access to it via the Web is consistent with EPA's Information Management goal of improving access to environmental data.

Poster LTG2-06
Application of Computational Toxicology to Understand and Assess the Cumulative Risks Posed by Chemicals in Mixtures

Presenter: James Rabinowitz (NHEERL)
Contributors: Woodrow Setzer (NHEERL); Miles Okino and Rogelio Tornero-Velez (NERL)

Science Question:

- How can computational models based on data for individual chemicals be used to enhance the assessment of cumulative risk (the total risk due to all chemicals in the mixture that act by the same mechanism) reflective of real-world chemical mixtures?

The Research:

A particular dilemma for a number of Agency regulatory programs is that environmental chemical exposures are often to multiple chemicals while most of the experimental data available (to evaluate the risks due to these exposures) are for individual chemicals. Research is being conducted to explore the use of computational toxicology methodologies for addressing this generic problem. Specifically, exposure to mixtures of acetylcholinesterase (ACHE) inhibitors is being studied. Environmental exposures frequently occur as mixtures of these pesticides that have the same (or similar) mechanisms of action. In support of FQPA, the Agency is required to determine the cumulative risk (the total risk due to all chemicals in the mixture) resulting from exposures to multiple chemicals that act by a common mode of action. However, the data currently available to make this assessment are almost exclusively for the individual chemicals comprising the mixture.

These chemicals are manufactured for their biological activity and many of the actions of individual chemicals in biological systems are well understood. In this research, dose-response data for individual chemicals and information about the mechanism of action are being used to derive models for activity. These models may then be used to study the potential interactions between chemicals in this class, and therefore better understand the cumulative risk resulting from exposure to mixtures of ACHE inhibitors.

Related approaches are being pursued. A PBPK/PD model for N-methyl carbamate has been developed. Three processes that may lead to interactions between chemicals have been identified. They are metabolism, distribution and interaction with the molecular target for

activity, ACHE. In another effort, a series of theoretical PBPK/PD models (similar to the N-methyl carbamate model) is being developed to yield dose-response curves for idealized chemicals. The features that determine the shape of these curves may then be identified. The effect of exposure to multiple chemicals on these salient features is being explored to observe if and how interactions between chemicals may lead to deviations from dose additivity. In order to address issues of model structure and parameter uncertainty, molecular modeling methods are being used to study the interaction between ACHE and pesticide inhibitors. This research takes advantage of specific structural information about the enzyme to explore a possible mechanism for non-additivity. Experimental information available from the literature suggests that there are two binding sites per enzyme molecule, with each binding site serving a different purpose. One site is the catalytic site responsible for de-esterification. The other, less well-established, site is a peripheral site that is not directly responsible for catalysis but binding to this site affects the specificity and capacity of the enzyme to perform catalysis. The latter site is also called the allosteric site because there are indications that binding there changes the three-dimensional shape of the enzyme. The existence of these two interacting sites on the protein (with different specificities) has profound consequences for the assessment of the risk of a mixture of ACHE inhibitors. Additional state-of-the-art molecular modeling studies are underway to determine the feasibility of determining metabolic parameters for another class of pesticides and explore whether these methods will be helpful for estimating metabolic parameters more generally.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Developing new methodologies and approaches for using single chemical data to develop and evaluate state-of-the-art models for assessing cumulative risks for chemicals with a common mode of action
- Providing an approach and improved understanding for the cumulative effects of mixtures of pesticides that act through the enzyme acetylcholine esterase, a class of chemicals of direct interest to the Agency
- Demonstrating the applicability of the general approach of applying computational models of the mode of action to enhance the assessment of the cumulative risks of chemical mixtures
- Providing insight into the data needed to assess cumulative risk
- Providing testable predictions for further experimental studies on the cumulative risk of pesticides.

Poster LTG2-07
Component-Based Methods for Investigation of Interactions

Presenter: Jane Ellen Simmons (NHEERL)
Contributors: Linda Teuschler, Rick Hertzberg and Glenn Rice (NCEA); Ginger Moser, Kevin Crofton, Mike DeVito, and Dave Herr (NHEERL); Chris Gennings (Virginia Commonwealth University)

Science Question:

- Can efficient experimental designs and associated analysis methodologies be developed and used to examine priority mixtures that a) use single chemical data to predict the health effect of mixtures containing many chemicals, b) include estimates of variability, and c) have sufficient power to detect non-additivity in the low-dose region?

The Research:

The majority of risk assessments for chemical mixtures use component-based methods. The default assumption of additivity underlying component-based methods relies on an inadequate data base due, in part, to the lack of efficient experimental designs and approaches to evaluate higher order mixtures.

The approach outlined in this research is consistent with recommendations of the SOT Mixtures Task Force. Studies target important environmental mixtures and include environmentally-relevant mixing ratios with data points at the lower end of the dose-response curve. Efficient experimental designs and predictive models were used and experiments planned by multi-disciplinary teams (toxicologists, risk assessors, statisticians). The statistical methods developed are consistent with Berenbaum's definition of additivity.

The first effort focused on developing the basic methodology. The four trihalomethanes (THMs) formed during chemical disinfection of water, and regulated as a mixture, were assessed in female CD-1 mice as binary combinations and 4-THM mixtures after 14 days of oral exposure. Both 1:1 ratios and mixing ratios representative of finished drinking water disinfected by either chlorination or ozonation were investigated. The statistical method provides estimates of variability and predicts the mixture response from the individual chemical dose-response data (the additivity model). For serum enzymes reflecting hepatotoxicity, deviation from additivity (antagonism) was observed at the higher doses, with additivity being observed in the lower regions of the dose-response curves. Non-additivity was more frequent at the 1:1 mixing ratio.

The second effort examined a mixture of 5 organophosphorus (OP) pesticides (chlorpyrifos, diazinon, dimethoate, acephate, and malathion). The mixing ratio was based on the US EPA Dietary Exposure Evaluation Model. Neurochemical and

behavioral endpoints were assessed in adult male Long-Evans rats following acute oral exposure. Data were analyzed by comparing the additivity model (the dose additive response predicted from single chemical data) to a model that included the mixture data (the mixture model). A statistical method not requiring single-chemical dose-response data was developed. Greater than additive effects (synergism) were observed for all endpoints except tail-pinch response, which was additive. Synergism occurred in the lower portion of the mixture dose-response curves, with additivity at higher doses. Testing a subgroup of the 5 OPs revealed that a portion of the synergism was due to one component (malathion), but this was not consistent across all endpoints.

The third project examined the interactive effects of 18 PHAHs on thyroid function. Young female Long-Evans rats were evaluated in a short-term oral exposure model designed to examine the effects of mixtures on thyroid homeostasis. The effects of the individual chemicals and a mixture, whose mixing ratio was based on environmental concentrations, on serum T4 were measured. A flexible statistical model was used that does not require all individual chemicals to have the same asymptote. The lower portion of the mixture dose-response curve was predicted well by the additivity model, indicating dose additivity at those dose levels. There was a statistically-significant, greater-than-additive response in the higher regions of the mixture dose response curve.

These experimental efforts are largely completed. Future research will focus on the development of improved techniques to power adequately mixtures experiments. This becomes increasingly important as researchers continue to focus on lower-dose regions. Research will also be implemented to better understand the health impact of the unidentified fraction of highly complex, incompletely characterized, environmental mixtures.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Fulfilling the regulatory requirement of the Safe Drinking Water Act Amendments of 1996 charging EPA to develop new approaches to the study of mixtures found in drinking water
- Developing methods and applications for addressing dose additivity for chemicals with a common mode of action in support of the Food Quality Protection Act of 1996
- Developing useful methods for detecting a several-fold shift in dose-response and for testing mode-of-action hypotheses for mixtures
- Providing useful tools supporting research on carbamate mixtures and pyrethroid mixtures (see Crofton et al. poster)
- Providing, in the absence of mixtures data and under an assumption of dose additivity, a valuable predictive modeling tool for use in risk assessment as the mixture response can be predicted from single chemical data

- Providing methodology for addressing additivity under the “mixtures-only” data scenario, i.e., when sufficient mixtures data are available, but single-chemical data are not available.

Poster LTG2-08
Case Studies and Risk Assessment Applications of Aggregate and Cumulative Risk: An Overview

Presenter: Rogelio Tornero-Velez (NERL)
Contributors: Jerry Blancato, Curtis Dary, Fred Power, and Valerie Zartarian (NERL); Richard Hertzberg and Linda Teuschler (NCEA); Michael DeVito, Woody Setzer, and Kevin Crofton (NHEERL); Jacky Rosati (NRMRL); and Haluk Özkaynak (ORD)

Science Question:

The research in this topic area demonstrates how the Office of Research and Development (ORD) is applying innovative methods and models to conduct aggregate and cumulative risk assessment. Several research questions are addressed in ORD case studies:

- What is the scope of the aggregate and cumulative assessments?
- How are the linkages of the source-to-outcome continuum strengthened?
- How may we refine and guide future assessments?

The Research:

The practice of risk assessment within the EPA is evolving from single pollutant assessments toward integrated assessments involving mixtures of pollutants which may be present in multiple media. The emphasis on "cumulative assessments" is motivated, in part, by new legislation that includes the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act (SDWA), which mandate the Agency to consider aggregate (multi-route) and cumulative exposure (multi-chemical) in its future risk assessments. Furthermore, the approaches elaborated in these case studies will serve as a foundation to address the broader issues of cumulative risk such as susceptible populations.

To address the fundamental research needs, ORD has implemented programs to develop the tools (methods, measures, and models) for conducting aggregate and cumulative risk assessments. The session "Methods, Measure, and Model to Advance the Science of Aggregate and Cumulative Risk Assessment" highlights some of these new approaches. These new approaches and tools have been further elaborated in several ORD-sponsored case studies. Lorber et al. outline a regulatory strategy for dioxin and dioxin-like compounds to quantify the pathways of human exposures, starting from sources of dioxin release, through the environment and into the food chain. Using a probabilistic exposure model, Özkaynak et al. describe how ORD scientists conducted a probabilistic aggregate exposure and dose assessment on the As (a carcinogen) and Cr components of CCA treated wood using the Stochastic Human Exposure and Dose Simulation model updated for wood preservatives (SHEDS-Wood). In dose modeling, Dary et al. describe ORD's Exposure Related Dose Estimating Model (ERDEM), a modeling platform developed to enable researchers and risk assessors to estimate dose of parent chemicals and metabolites in various organs and tissues in humans. ERDEM is fundamental to studies of aggregate exposure and cumulative risk because it allows for the examination of

multiple exposure routes (e.g. oral, dermal and respiratory) simultaneously. Furthermore, ERDEM will be used to develop PBPK/PD models to facilitate the cumulative risk assessment of the N-methyl carbamate class of insecticides. Blancato et al. describe a PBPK/PD model of carbaryl, developed as a prototype to address questions associated with the assessment. These studies serve to strengthen the linkages along the source-to-outcome continuum, a paradigm that ORD has adopted to conduct aggregate/cumulative assessments.

Several case studies employed pharmacokinetic models or statistical methods to test additive action among a "contaminant group" and assign and relative potency factors. Teuschler et al. apply PBPK modeling to test the assumption of additive action of drinking water disinfection by-products (DBPs). Exposures to complex mixtures of DBPs occur internationally via oral, dermal, and inhalation routes. A novel method, the Cumulative Relative Potency Factors (CRPF) was developed to consider aggregate and cumulative exposure to DBPs. Devito et al. examine the strengths and limitations of the Toxic Equivalency Factor (TEF) methodology for providing estimates of cumulative risks for dioxin and dioxin-like effects that are mediated by the Ah receptor. The TEF methodology is a relative potency (REP) scheme that assumes dose additivity and that a single REP factor for each chemical can be used to assess all toxic endpoints in a risk assessment. The authors observe that the TEF methodology may underestimate the potential effects of a mixture if significant concentrations of non-dioxin-like chemicals are present. Crofton et al. outline a study to investigate the risks from exposures to mixtures of carbamate or pyrethroid insecticides. The specific research aims are to: 1) Test the hypothesis of additivity; 2) Test the effects of mixtures based on environmentally relevant exposures; and, 3) Integrate the experimental neurotoxicology data and *in vitro* mechanistic data with the aid of PBPK models. Setzer et al. describe the novel statistical methods to determine the relative potencies of OP pesticides. Estimates of relative potencies were based on dose-response modeling of registration data relating brain AChE activity to dietary OP doses. Dose-response modeling used hierarchical statistical models to combine data from multiple studies to provide a robust estimate of the dose-response shape for each single chemical.

Finally, Hertzberg et al. examines the Agency discourse and dialogue on the subject of aggregate/cumulative risk. Workshops held by the Office of Science Policy, the Risk Assessment Forum, and ORD range from training sessions on assessment methods in published EPA guidance to discussions of case studies from Regional and Program Offices. Ultimately, the dialogue between researchers, decision makers and stakeholders allows for better guidance.

Impact and Outcomes:

The research outlined in this topic area reduces uncertainty in risk assessment by:

- Generating data, methods, techniques, and models evaluated under real-world scenarios that demonstrate the usefulness of ORD's research tools for aggregate

exposures and cumulative risk

- Producing results that will be used to refine Agency guidance for conducting aggregate and cumulative risk assessments
- Providing opportunities to collaborative develop new tools and conduct state-of-the-art cumulative risk assessments for pollutant mixtures
- Providing data for developing risk reduction and risk management strategies
- Develop new research hypotheses, identify and prioritize future ORD research
- Cumulative risk assessment requires an interdisciplinary approach to manage effectively. By including the input of stakeholders, investigators, and the front-line enforcers of regulations, ORD guidance has broad concurrence and application.

Poster LTG2-09
Cumulative Risk Assessment (CRA) of Drinking Water Disinfection By-Products

Presenter: Linda K. Teuschler (NCEA)
Contributors: Glenn Rice, John Lipscomb, Richard Hertzberg (NCEA); Fred Power, Jerry Blancato (NERL); Jane Ellen Simmons (NHEERL); Charles Wilkes (Wilkes Technologies, Inc.)

Science Questions:

The research addresses the following science questions:

- What are people's real world aggregate exposures to drinking water disinfection by-product (DBP) mixtures?
- How do we estimate cumulative risk from multiple-route exposures to DBP mixtures?

The Research:

The assessment of potential human health risk(s) from DBP mixtures in drinking water is needed to support the mandates of the Safe Drinking Water Act Amendments of 1996. Ubiquitous oral, dermal and inhalation exposures to these complex mixtures are of concern for human health because positive data exist from both epidemiologic and toxicologic studies of DBPs. Of particular concern are epidemiologic associations of DBPs with various birth defects and spontaneous abortions. Although these data suggest human health effects are possible, human exposures are complex, making the interpretation of these positive results difficult. Occurrence information shows that the mix of DBPs may vary considerably with geographic location, source water characteristics and water treatment process. Furthermore, for the more volatile DBPs, inhalation exposures may be greater than ingestion, while for highly lipophilic DBPs, dermal exposures may also be important. Information from toxicologic studies has focused primarily on single DBPs administered orally at doses far above finished drinking water concentrations. Information from positive epidemiologic studies suggests that exposures to different mixtures of DBPs in various geographic locations may pose quite different health risks. Thus, to develop a regulatory and risk reduction strategy, there is a need to develop and evaluate new tools that consider the health risks associated with DBP mixtures and the various exposures from contact with finished drinking water.

This research examines the feasibility of performing a CRA for DBP mixtures by combining external exposure modeling and physiologically-based pharmacokinetic (PBPK) modeling results with a new mixtures risk assessment method. Three significant contributions to the science resulted from this research. First, external exposure modeling is conducted and linked with PBPK modeling to produce internal dose measures from exposure to all three routes for use in risk assessment. This methodology is important because it develops the exposure methods that have been needed to provide

realistic human exposure data for use in assessing health risks for multiple route exposures. The CRA approach then combines these internal blood or tissue concentrations with oral dose-response data (providing no portal of entry effects are observed). Second, in response to concerns for reproductive and developmental effects, multi-route internal doses were estimated for an adult female and an adult male, each of reproductive age, and for a child (age 6). Exposure distributions were estimated for 13 major DBPs, including the four trihalomethanes and five haloacetic acids that are currently regulated by EPA. Modeling accounted for human activity patterns that affect contact time with drinking water (e.g., tap water consumed, time spent showering, building characteristics) and physicochemical properties of the DBPs (e.g., inhalation rates, skin permeability rates, blood:air partition coefficients, etc.). The third accomplishment is the development of a novel CRA method, the Cumulative Relative Potency Factors (CRPF) approach. This method integrates the principles of dose addition and response addition, additivity concepts now presented in Agency guidance, to produce multiple-route, chemical mixture risk estimates using total absorbed doses. The CRPF approach logically evaluates human health risks using total internal doses and oral toxicology dose-response data based on knowledge or assumptions regarding toxicological modes of action. This new method is a novel approach to evaluating multiple route exposures that can be considered for generalization for the evaluation of other environmental mixtures.

Impact and Outcomes:

The research program reduces uncertainty in risk assessment by:

- Addressing an important health issue for a significant portion of the human population
- Providing methods and data that enrich the available library of cumulative risk assessment methods beyond what is currently published in EPA guidance
- Integrating ORD tools and producing a novel CRPF approach for evaluating multiple route DBP exposures that can be generalized for the evaluation of other multi-pathway, multi-route exposures to environmental mixtures
- Providing risk assessors with a practical risk assessment method, useful for choosing among risk management options by evaluating whether changes in DBP exposures impact health risk(s) across various drinking water treatment systems, disinfectants, and source waters
- Providing risk assessment information and tools to key interested parties (American Water Works Association, the American Chemistry Council, and stakeholder groups) who also implement programs to protect human health
- Providing EPAs Office of Water (OW) with methods and data to aid in interpreting epidemiologic study results on DBP health risks for use in OW's risk assessments
- Providing data supporting the evaluation and assessment of alternative drinking water treatment technologies developed to meet new promulgated standards

Poster LTG2-10
Researching Source-to-Exposure Pathways for Dioxin-Like Compounds Under the Dioxin Exposure Initiative

Presenter: Matthew Lorber (NCEA)
Contributors: John Schaum and David Cleverly (NCEA); Brian Gullett and Paul Lemieux (NRMRL); Dwain Winters, Joseph Ferrario, and Christian Byrnes (OPPTS), George Fries (USDA; retired), Cindy Deyrup (USDA), Randall Lovell (FDA)

Science Question:

- Can we quantify the pathways of dioxin exposure, starting from sources of dioxin release, through the environment and into the food chain, in order to assist in the development of a regulatory strategy for this important class of compounds?

The Research:

In September of 1994, the EPA released the first public review draft of the Dioxin Reassessment. At that time, EPA announced that it would initiate a Dioxin Exposure Initiative (DEI) to fill critical data gaps regarding the sources of dioxin that contribute to human exposure. The fundamental goal of the initiative is to quantitatively link dioxin sources to general population exposure. This is being accomplished by pursuing two simultaneous lines of inquiry: one line starts with identification of sources of dioxin-like compounds and works forward along their pathways of transport and deposition, and the second starts with human body burdens and works backward through the process of bioaccumulation and uptake.

The DEI has been marked by substantial individual efforts that stand out on their own merit. The Dioxin Sources Inventory has been developed to be a repository of congener-specific dioxin and furan emissions data from all known sources in the US. This inventory focuses on releases to land, water and air from incinerators, paper mills, land application of sewage sludge, mobile sources, metal smelting, PVC production, and refuse burning in backyard barrels. Emissions estimates for the Sources Inventory are derived from emission reports as well as research within the DEI itself, which includes direct emission measurements from diesel engine tail pipes, incinerator stacks, and controlled laboratory bench-scale mockups of incinerators, and from more diffuse sources of releases, such as forest fires. The National Dioxin Air Monitoring Network is a network of 34 monitoring stations in rural and remote settings throughout the US. In this network, air concentrations of dioxins have been measured four times/year starting in 1998, with a final year's measurements planned for 2004. Efforts to more directly quantify human exposure through food consumption began with EPA's cooperative efforts with the USDA in the mid-1990s. Using the USDA's slaughterhouses as a statistical framework, national surveys of dioxins in beef, pork, and poultry were conducted. A finding of a small number of highly contaminated poultry samples was

traced back to the poultry feed, which was contaminated by a minor component, ball clay, added as a flowability agent. This finding was the beginning of a primary focus in the DEI, which was on the role of animal feeds in the contamination of the food supply. EPA cooperated with the FDA on a sampling of other minor feed components, and found that animal fats recycled in the feed represented a meaningful route of animal exposure. A carefully controlled mass balance study of dioxins in lactating cows provided the evidence that feed was the primary source of dioxins in milk, and this was followed by a national survey of dioxins in dairy feeds. The link between sources and animal exposures has been supplemented with model simulation work. Models of the air-to-plant pathway have demonstrated that deposition of atmospheric dioxins, and particularly dioxins in the gas phase, is the primary pathway that leads to terrestrial vegetation contamination, and hence terrestrial animal exposures. Simple pharmacokinetic (PK) modeling has shown how typical human exposures translate to background body burdens of dioxins. These PK models were also used to research infant exposures, a key sensitive subpopulation, and to speculate on past as well as future exposures.

Impacts and Outcomes

The research program has reduced uncertainty in risk assessment by:

- Providing data, tools and expertise that are being used worldwide. Dr. Heidelore Feidler, an internationally recognized dioxin sources expert, has developed a "Toolkit" for the United Nation's Environmental Program that is used to develop national sources inventories. This toolkit directly mimics EPA's Sources Inventory structure and approach
- Identifying ball clay as a feed contaminant (the first reported incident) has lead to similar worldwide findings of feed contaminated with dioxin-like compounds (PCBs in Belgium poultry/pork feed; contaminated citrus pulp in Brazil; contaminated European poultry feeds, etc.)
- Developing laboratory procedures for measuring dioxins at trace levels in environmental matrices, through the DEI, established EPA as worldwide leaders in dioxin chemistry
- Employing ORD's procedures to evaluate exposures in site-specific assessments as well as national regulations. Exposure and risk assessments involving incinerators, such as the East Liverpool, Ohio hazardous waste incinerator or the Columbus Municipal Solid Waste Incinerator, have all used ORD's modeling and exposure pathway procedures. Risk assessments associated with national regulations on land application of sewage sludge, pentachlorophenol, 2,4-D, and others, have similarly relied on ORD's exposure procedures
- Providing the Agency with a holistic scientific basis (source characterization, exposure pathways, effects) upon which to develop a regulatory strategy that will reduce exposures of Americans to this important class of compounds.

Poster LTG2-11
The Use of the Toxic Equivalency Factor (TEF) Methodology for Cumulative Risk for Dioxins

Presenters: Michael DeVito and Linda Birnbaum (NHEERL)
Contributor: Janet Diliberto (NHEERL)

Science Question:

- What are the uncertainties in the use of the TEF methodology for dioxin risk assessment?

The Research:

Humans are exposed to complex mixtures of dioxins. Dioxins are a family of chemicals whose toxicities are mediated by binding and activating the Ah receptor. 2,3,7,8-Tetrachlorodibenzo-p-dioxin is the most potent of these chemicals. A TEF methodology has been developed to provide risk assessors with a means to estimate the potential adverse health effects resulting from exposure to these chemical mixtures. The TEF methodology is a relative potency (REP) scheme that assumes dose additivity and that a single REP factor for each chemical can be used to assess all toxic endpoints in a risk assessment. In addition, the method assumes that the REP value for a dioxin is consistent across species.

A series of experiments were designed to test the assumptions of the TEF methodology. One uncertainty was the lack of information on the variance of a REP. Literature values of REPs for dioxins used methods that provided only a point estimate of the REP. Thus, initial studies included the development of new statistical methods to assess the relative potencies of dioxin-like chemicals that would also provide an estimate of the variance. Using this statistical approach we tested: 1) whether the REP can be described by a factor or a function; 2) if the REP values varied by endpoint; and 3) if a single REP value could be used to estimate the dioxin-equivalents of a mixture across endpoints and species. The data indicate that the relative potencies for a given chemical were equivalent across endpoints in mice. The REPs were best described as a factor for the PCDDs and PCDFs. For some of the dioxin-like PCBs, the REPs were best described as a function, however in the low dose region of the dose response curves, a factor would provide good predictions of their REPs.

The assumption of dose additivity in the TEF method was examined in a series of experiments. A mixture of 13 PCDDs, PCDFs and PCBs was prepared based on human exposure data. Dose response studies with this mixture were designed to examine biochemical, endocrine and toxicological effects in mice and rats. Using REP values for hepatic enzyme induction in mice, the assumption of additivity provided good predictions of the ability of the mixture to induce hepatic enzymes, alter hepatic retinoids and suppress the immune system in mice. The REP values from mice also provided good

predictions of the dose response relationship for hepatic enzyme induction in rats. These studies also demonstrated that the TEF methodology would significantly underestimate some toxic responses, such as hepatic porphyria and thyroid hormone disruption, if the mixture contained chemicals which impact these endpoints through mechanisms in addition to the Ah receptor. Other studies examined mixtures of PCBs and found that the TEF methodology worked well for hepatic enzyme induction but not for alterations in serum thyroid hormone concentrations.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Improving the scientific understanding regarding the additivity of effects resulting from exposures to real-world mixtures of dioxins and the associated fundamental biological mechanisms and pathways
- Demonstrating the use of the TEF methodology for providing good estimates of cumulative risks for dioxin and dioxin-like effects that are mediated solely by the Ah receptor resulting from exposures to mixtures of dioxins. This approach may be applicable for assessments to other mixtures
- Documenting for endpoints with multiple pathways (porphyria, decreases in serum thyroid hormones), that the TEF methodology may underestimate the potential effects of a mixture if significant concentrations of non-dioxin-like chemicals are present
- Demonstrating that the TEF methodology may provide reasonable predictions across species
- Identifying potential limitations in the TEF methodology where future research is needed
- Providing risk assessors with a new tool (with insights on potential limitations) for assessing cumulative risks for dioxins. Risk assessors in OSWER and other EPA program offices, the Regions, and state/local levels currently use this methodology.

Poster LTG2-12
Research Supporting the Relative Potency Factor Assessment of OP Pesticides

Presenter: R. Woodrow Setzer (NHEERL)
Contributers: Vicki Dellarco, Anna Lowit and David Miller (OPPTS/OPP); Virginia Moser and Stephanie Padilla (NHEERL); Nicolle Tulve (NERL); Richard Hertzberg and Glenn Rice (NCEA)

Science Question:

- How do we estimate cumulative risk from aggregate exposures to organophosphate pesticides?

The Research:

The Food Quality Protection Act of 1996 mandated that the Agency reevaluate tolerances for current use pesticides by 2006. For the first time, the Agency had to include considerations regarding the combined effects of exposure to pesticides having the same mode of action in these reassessments. A large number of organophosphate pesticides (OPs) are registered, all of which inhibit the enzyme acetylcholine esterase (AChE). Thus, this class of pesticides was selected for the first cumulative risk assessment (encompassing 33 OP pesticides) conducted by EPA's Office of Pesticide Programs under the FQPA mandates.

Several ORD activities supported this critical first cumulative risk assessment possible. The document "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures" (USEPA, 2001) provided the basis for using a relative potency factor approach to the cumulative risk assessment for chemicals that attack a common target, in this case AChE. The strategy of the risk assessment was to develop a stochastic model for exposure to OPs through diet, drinking water, and residential uses, and to combine the toxicities of different OP exposures by scaling those exposures by their estimated relative potencies, relative to the index chemical methamidophos. These estimated relative potencies would possibly need to be modified with an additional uncertainty factor, when information about consequences of juvenile exposures warranted it or was lacking. The resulting distribution of margins of exposure (MOE) of methamidophos-equivalent exposures relative to the animal dose of methamidophos that results in 10% inhibition of AChE in the brain served as the basis for the risk assessment. Studies of in-home exposures and hand-to-mouth and other microactivity data were also critical to developing the residential exposure model used in the risk assessment.

Estimates of relative potencies were based on dose-response modeling of registration data relating brain AChE activity to dietary OP doses. There is a rich registration data set for almost all these chemicals. Dose-response modeling used hierarchical statistical models to combine data from multiple studies to provide a robust estimate of the dose-response shape for each single chemical. The dose-response estimates were used to interpolate the

dose expected to result in 10% brain AChE inhibition (BMD_{10}). Relative potencies for each chemical were calculated as ratios of the BMD_{10} for the index chemical methamidophos. The precision of the individual relative potency factors was at worst about 1% of the range of the potency estimates, with most of the estimates being substantially more precise.

Research on developmental effects from OP pesticide exposures has demonstrated that young and adult rats differed in the degree of sensitivity to OP exposure for a variety of OPs. These data were directly responsible for the inclusion of an additional uncertainty factor being used to evaluate the distributions of MOEs for safety.

Impact and Outcomes:

This research program has reduced uncertainty in risk assessment by:

- Developing and demonstrating the usefulness of ORD data, methods, models, and the innovative RPF assessment approach for conducting cumulative risk assessments addressing the FQPA mandates. The revised OP Cumulative Risk Assessment (http://www.epa.gov/pesticides/cumulative/rra-op/) was published in June, 2002
- Providing better understandings of the exposure scenarios, key factors, and biological mechanisms that support the inclusion of an additional safety factor when considering safeguarding children or other susceptible populations in pesticide registrations
- Developing and evaluating dose-response methods that will serve as the recommended approach for similar FQPA-mandated pesticide evaluations
- Providing an evaluated RFP approach and framework that can be considered by Agency risk assessors for addressing cumulative risks to other classes of compounds and mixtures.

Poster LTG2-13
Applying an ORD Probabilistic Exposure Model Supporting a Health Risk Assessment for Children who Contact Chromated Copper Arsenate (CCA) on Treated Playsets and Decks

Presenter: Halûk Özkaynak (NERL)
Contributors: Valerie Zartarian (NERL), Mark Mason (NRMRL), and Winston Dang (AD/OPP)

Science Question:

This research addresses the following science questions:

- What are the real-world aggregate exposures to arsenic (As) and chromium (Cr) for children who frequently contact Chromated Copper Arsenate (CCA)-treated wood in playsets, home decks, and the CCA-contaminated soil around these structures?
- What key variables and factors contribute to these exposures?
- How can the exposures and risks from CCA-treated playsets and decks be mitigated?

The Research:

Concerns have been raised regarding the safety of young children who contact As (a carcinogen) and Cr residues while playing on and around CCA-treated wood playground structures and decks. Although CCA registrants voluntarily canceled treated wood for residential use effective December 31, 2003, the potential for exposure from existing treated wood structures and surrounding soil still poses child health hazard concerns. ORD implemented research designed to: 1) conduct an aggregate exposure assessment assisting the Office of Pesticides Programs (OPP) in determining the potential health risks to children from frequent contact with CCA-treated wood in playsets, home decks, and CCA-contaminated soil around these structures; and 2) determine the impact of various sealants on reducing available CCA residues in treated wood and surrounding soil.

In the first activity, ORD scientists conducted a probabilistic aggregate exposure and dose assessment on the As and Cr components of CCA using the Stochastic Human Exposure and Dose Simulation model (see Furtaw et al. poster) updated for wood preservatives (SHEDS-Wood). Model inputs included wood surface residue concentrations and wood-to-skin residue transfer efficiencies using CCA-treated deck and playground samples from various US locations collected and analyzed by the American Chemistry Council and the Consumer Product Safety Commission. Two bounding climate scenarios; three exposure time periods (short-term, intermediate-term, and lifetime); and four exposure pathways (dermal contact with, and ingestion of, As and

Cr in both soil and wood residues) were considered for a population of children simulated using EPA's Consolidated Human Activity Database. Variability, sensitivity, and uncertainty analyses were conducted, as well as special analyses considering different subpopulations (e.g., pica children) and exposure reduction scenarios (e.g., sealants, hand washing).

The predicted central values for lifetime annual average daily As dose values were on the order of 10^{-6} to 10^{-5} mg/kg/day, with the predicted 95^{th} percentiles on the order of 10^{-5} mg/kg/day. Residue ingestion via hand-to-mouth contact was the most significant exposure route for most scenarios. The key variables influencing model estimates were: wood surface residue-to-skin transfer efficiency; wood surface residue concentrations; fraction of hand surface area mouthed; hand washing events; soil concentrations near treated playsets; daily soil ingestion rate; and time spent on/around treated residential decks. The results of several special analyses did not significantly impact the baseline results, except for reducing wood residues through hypothetical wood sealant applications.

The draft exposure assessment was presented to OPP's Scientific Advisory Panel in December, 2003, and is currently being revised and finalized. OPP has used the SHEDS-Wood modeled exposure and dose results to conduct a separate risk analysis and write a draft report on children's risks to CCA.

ORD continues to conduct additional risk management research to evaluate the effectiveness of different wood sealants on reducing available As and Cr residues in treated wood and surrounding soil. The sealants research is being conducted under field conditions using 40 outdoor mini-decks at the EPA-RTP complex, with the validated data being provided to OPP for future assessments.

Impact and Outcomes*:*

The research program reduces uncertainty in risk assessment by:

- Demonstrating the usefulness of ORD modeling tools to conduct an exposure assessment for characterizing children's risks for real-world environmental exposure scenarios
- Providing high quality data and expertise supporting OPP's re-registration eligibility decision for CCA
- Identifying key areas where more research and data is needed to improve model sensitivity and uncertainty analyses (e.g., residue dermal transfer coefficients, time children spend contacting treated wood, frequency of outdoor hand-to-mouth contact, saliva removal efficiency for arsenic residues on skin)
- Developing research hypotheses for future activities designed to quantify model and scenario uncertainty, in addition to parameter uncertainty, that can be applied to future EPA aggregate and cumulative exposure and risk modeling efforts
- Providing data supporting the development of future risk reduction and risk management strategies for CCA- treated wood

- Providing useful information and advise to OPP for advising the public how to minimize exposures and potential health risks from CCA-treated wood exposures.

Poster LTG2-14
Linking Exposure Measurements with Human Activity Data to Assess Dose in Human Tissues, Organs and Excreta through the Application of the Exposure Related Dose Estimating Model (ERDEM)

Authors: Curtis Dary and Fred Power (NERL)
Science Questions:

- Can a physiologically based pharmacokinetic (PBPK) model be used to determine the interactions among, and individual contributions of, multiple chemicals from aggregate exposures on absorption, distribution, metabolism and excretion?
- Can the information from model-simulated aggregate exposures be used to estimate cumulative risk?

The Research:

The Exposure Related Dose Estimating Model (ERDEM) was developed to enable researchers and risk assessors to estimate dose of parent chemicals and metabolites in various organs and tissues in humans. ERDEM is fundamental to studies of aggregate exposure and cumulative risk because it allows for the examination of multiple exposure routes (e.g. oral, dermal and respiratory) simultaneously. The ERDEM pharmacokinetic modeling engine mathematically represents physiological, biological, and pharmacodynamic data in the form of differential equations. Physiological compartments include arterial blood, brain, carcass, derma, fat, intestine, kidney, liver, rapidly perfused tissue, slowly perfused tissue, spleen, static lung, stomach and venous blood. Metabolic parameters are estimated from human subject data. Allometric scaling is used to adjust for differences in organ and tissue volume among humans by age and sex.

The ERDEM has been successfully used to assess risk in presumed sensitive populations to selected environmental agents, consumer products, and pesticides. In these case studies, time-histories of exposures were tested based on regulatory assumptions as specified under Federal Guidelines. For example, exposure time-histories that involve dermal contact rates with pesticide contaminated surfaces were used to derive dermal transfer coefficients (cm^2/hr) for input into the dermal absorption module. Inputs involving dermal transfer of residues via the oral pathway (hand-to-mouth activity) were allowed to simultaneously account for a portion of the mass transferred. Ultimately, contributions to dose were compared among exposure pathways (i.e., oral, respiratory, and dermal contact and transfer) and routes (i.e., ingestion, dermal absorption, and inhalation).

The ERDEM framework has been and currently is being applied in support of several Agency risk assessments. It was used to extrapolate tissue dose in humans from MTBE exposures from animal studies examining different routes of exposure. ERDEM is being used to implement a PBPK model for trichloroethylene to estimate toxicologically relevant doses in the on-going risk assessment update. Earlier versions of PBPK models

were also implemented in ERDEM and tied to exposure models to give relevant estimates of dose that resulted from realistic aggregate exposures to trichlorethylene and trichloroacetic acid in humans. A PBPK model for malathion was also implemented in ERDEM to estimate cholinesterase inhibition in susceptible populations (children) after exposure from head lice treatments. ERDEM is also being used to formulate and apply PBPK models for carbaryl and for the assessment of cumulative dose resulting from exposure to several members of the N-methyl carbamate class of pesticides (see Blancato et al. poster). ORD exposure models (see Furtaw et al. poster) are being constructed that will again be tied to ERDEM to give dose estimates resulting from a distribution of exposures from a number of chemicals in this class.

Impact and Outcomes:

This research program has reduced uncertainty in risk assessment by:

- Providing innovative and flexible PBPK modeling tools for estimating the disposition of toxic substances and metabolites in human organs, tissue and excreta in relation to simulated exposure time-histories
- Developing and evaluating new PBPK modeling modules that increase the modeling sensitivity and reduce uncertainty in the modeled estimates
- Producing data demonstrating how PBPK input parameter values might change for humans based on age, sex, body fat content, and over-all physiological health
- Providing an adaptable ERDEM platform for simultaneously testing exposure along separate pathways and routes. Parent chemicals and specified metabolites for each chemical can be modeled to obtain cumulative risk calculations
- Applying the evaluated ERDEM platform to address ORD and Agency risk issues (MTBE, TCE, malathion, N-methyl carbamates, etc.). In each case, ERDEM produced estimates of dose, to be used to quantify potential adverse effect from exposures, that are relevant, based on the knowledge of known physiologic and biochemical process, and that logically characterize and quantify uncertainty

Poster LTG2-15
Towards a Cumulative Risk Assessment of the N-Methyl Carbamate Insecticides

Presenter: Jerry Blancato (NERL)
Contributors: Fredrick Power, Miles Okino, Rogelio Tornero-Velez and Curtis Dary (NERL)

Science Question:

- How should physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models be used to estimate or characterize cumulative risk from aggregate exposure to the N-methyl carbamate class of insecticides?

The Research:

A case study was developed to consider the use of PBPK/PD models in cumulative risk assessment of the N-methyl carbamate class of insecticides. A PBPK/PD model of carbaryl was developed, using the Office of Research and Development's (ORD) Exposure Related Dose Estimating Model (ERDEM) platform, as a prototype to address questions associated with the assessment. Aggregate exposure was assumed to occur from dermal contact with surface residues and the resultant transfer of portions of the available residue to the skin on the hands. Oral exposure by hand-to-mouth activity was evaluated using regulatory-based assumptions for a three year old child. Dermal absorption was also evaluated as an alternative exposure scenario.

PBPK/PD modeling data were gathered from a variety of sources to support the parameterization of the carbaryl model and form the basic structure of the multi-chemical model for this common mechanism of action group. Certain PD toxicological characteristics are unique to N-methyl carbamates. The mechanism of action involves the rapid and reversible carbamylation of acetylcholinesterase (AchE). PD and PK data are needed in concert to develop and evaluate the model because metabolism competes with distribution of toxic parent compounds to sites of action. Metabolic and PD kinetic parameters were fit to data in an iterative stepwise fashion and statistically tested for improvement. Quantitative Structure Activity Relationships (QSARs) were used to obtain blood/tissue partition coefficients. Dermal and gastro-intestinal (GI) tract absorption rates were obtained from *in vivo* studies and compared with intra-venous dosing studies. The laboratory animal (rat) based-model provided the framework for "humanization"of specific physiological and biochemical processes. Age-specific human physiological characteristics were implemented and kinetic parameters were scaled with body weight.

Model simulations were compared with biomonitoring study data of cumulative mass excreted in urine. Relevant dose metrics were evaluated across different routes of exposure. The carbaryl model proved to be a substantial first step towards the cumulative risk assessment. The simulations illustrated the utility of PBPK/PD models for

addressing species-to-species extrapolation, route-to-route extrapolation, and the importance of selected parameters and pathways.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Addressing OPPTS/OPP and the Science Advisory Panel recommendations for ORD to initiate research to develop, evaluate, and apply innovative modeling approaches to support cumulative risk assessments
- Demonstrating the usefulness of employing an ERDEM-based carbaryl modeling approach to address cumulative risks from exposures to N-methyl carbamates insecticides
- Providing evaluated PBPK/ PD models and approaches that can be considered for use in meeting other FQPA mandates, especially cumulative risk from exposure to multiple chemicals that have a common mechanism of toxicity
- Providing technical expertise and improved science understandings regarding risks to N-methyl carbamate insecticides in support of OPP's risk assessment. The risk assessment is scheduled for review and comment

Poster LTG2-16
Impacts of Selected Cumulative Pesticide Exposure/Risk Projects

Presenting Author: Kevin Crofton (NHEERL)
Contributing Authors: Michael DeVito, David Herr, Michael Hughes, Virginia Moser, Stephanie Padilla, and Woody Setzer (NHEERL); Rogelio Tornero (NERL); Karl Baetcke and Anna Lowitt (OPP); and Chris Gennings (Virginia Commonwealth University).

Science Question:

This research addresses the following science questions:

- What are the risks from exposures to mixtures of carbamate or pyrethroid insecticides?
- What are appropriate exposure conditions?
- What statistical models should be used to analyze the mixture data?

The Research:

The Food Quality Protection Act of 1996 requires consideration of cumulative exposures in determining the risk from exposures to pesticides with a common mode of action (MOA). The current default for determining the cumulative risk to pesticide mixtures assumes dose-additivity of chemicals with common MOA. Previous efforts to determine cumulative risk of pesticides with a common MOA have been hampered by a number of uncertainties. These obstacles include a lack of neurotoxicology mixture studies, the previous use of relatively high doses, and the unavailability of efficient statistical models for properly analyzing mixtures data. The current research has been developed based on past work in evaluating environmentally relevant mixtures of organophosphates (OP) and OP-carbamate mixtures.

Two ongoing efforts aim to decrease the uncertainties in the cumulative risk assessments for carbamate and pyrethroid pesticides. Specific research aims are to: 1) Test the hypothesis of additivity; 2) Test the effects of mixtures based on environmentally relevant exposures (relative doses based on known human exposures); and, 3) Integrate the experimental neurotoxicology data with PBPK models and *in vitro* mechanistic data. PBPK models have been suggested for use in cumulative risk assessment because of their ability to integrate pharmacokinetics with pharmacodynamic effects to simulate intermittent human exposure scenarios. The goal of this work is to develop models, and to collect and analyze data, that will be used to improve the cumulative risk assessments for carbamates and pyrethroids. Compounds of interest, and their mixture composition, were selected after consultation with the collaborating Office of Research and Development (ORD) and Office of Pesticide Programs (OPP) scientists, and are based on their importance in upcoming cumulative risk assessment decisions. The approach involves the use of appropriate statistical models and efficient experimental designs. Neurotoxicity endpoints selected for detecting departures from dose-additivity were cholinesterase (ChE) inhibition produced by carbamates, or neurobehavioral effects

(changes in motor function) following pyrethroids. PBPK models will be developed from data obtained from the literature as well as from *in vitro* metabolic studies, and tested with limited *in vivo* pharmacokinetic studies. For the carbamates, single chemical dose-response and time-course data for inhibition of ChE in blood and brain, as well as behavioral alterations, have been constructed. Additionally, differences in the levels of ChE inhibition quantified using two different methodologies have been demonstrated. Tissue levels of selected carbamates will be provided for PBPK modeling. For the pyrethroids, single chemical dose-response data for motor function for 11 compounds have been collected. These will be used to determine relative potencies (i.e., iso-effective doses). These relative potencies will be adjusted by tissue dose from the PBPK models, two of which have been completed. Mixtures of pyrethroids or carbamates will be designed based on food residue data, as well as limited information on household residue (non-food) exposures. Future work will include testing a series of relevant mixtures, and analyzing the corresponding neurotoxicology data for additivity.

Impact and Outcomes:

This research program reduces uncertainty in risk assessment by:

- Establishing a collaborative research framework where ORD, OPP, and academic scientists have planned and implemented research designed to generate and evaluate new tools addressing cumulative risk
- Developing innovative statistical approaches through collaborative research with academia to enhance future cumulative risk assessments
- Generating data and developing/evaluating models for use in determining the cumulative risk of carbamates and pyrethroids, supporting the FQPA mandates, and reducing the uncertainties in these risk assessments for these two economically important classes of pesticides
- Providing the Agency with state-of-the-science tools that can be considered for used to conduct future cumulative risk assessments.

Poster LTG2-17
Guidance and Workshops on Aggregate and Cumulative Assessments

Presenter: Richard Hertzberg (NCEA)
Contributors: Linda Teuschler, Glenn Rice, and Bill Wood (NCEA); David Klauder and Ed Bender (OSP); Chris Saint (NCER); Moiz Mumtaz, (ATSDR)

Science Question:

This research addresses the following science questions:

- How can theoretical and laboratory research be developed into feasible tools and approaches for conducting and communicating aggregate and cumulative risk assessment?
- How can assessment models and procedures be harmonized across aggregate and cumulative assessments?
- How can we quantify environmental and physiological interactions in aggregate exposures to a single chemical so that those interactions can be incorporated into risk assessment guidance?
- How important, qualitatively and quantitatively, are interactions in transport, environmental transformation, and toxicity of multiple chemicals, especially at environmental levels?
- Can tiered approaches be developed to assist risk assessors in addressing interactions only when needed?

The Research:

The complexity of aggregate and cumulative risk assessments is best approached by an interdisciplinary team that ranges from bench scientists, epidemiologists and mathematicians to frontline enforcers of regulations. The Office of Research and Development (ORD) has stimulated that activity by two main vehicles: agency risk assessment guidance and open workshops. Agency guidance from ORD is usually either focused guidance from individual laboratories or centers, or guidelines from the Risk Assessment Forum that form Agency science policy. Risk assessment guidance often addresses complex issues using methods based mainly on structured scientific judgment, including science policy decisions for default approaches and values. By including Program and Regional Offices in the authorship and review of the guidance, ORD guidance usually has broad concurrence and covers wide ranges of application.

Published guidance on approaches for cumulative risk assessment include the 1986 mixture risk guidelines, the 1989 toxicity equivalence factor approach for dioxins, the 1997 guidance on planning and scoping for cumulative risk, the 2000 supplementary guidance for mixture risk, and the 2003 framework for conducting cumulative risk assessment. Future publications include a report on approaches for conducting cumulative risk assessment at contaminated sites (2005) and cumulative risk assessment guidelines (2012).

Workshops held by the Office of Science Policy, the Risk Assessment Forum, the National Center for Environmental Assessment, and the National Center for Environmental Research range from presentations of research results to training sessions on assessment methods in published EPA guidance to discussions of case studies from Regional and Program Offices. Most of these are open to the public. The interaction between the scientists, risk managers, academics and stakeholders addresses technical and implementation issues, such as relevant mathematical models, quantitative uncertainties, jargon differences, software, measurements, and critical research gaps. Recent workshops include the application of dioxin toxicity equivalence factors to fish and wildlife (1998), mixture risk assessment training jointly with the Agency for Toxic Substances Disease Registry at the Society for Risk Analysis annual meetings (1999-2004), and the joint ORD-Regional workshop on cumulative risk assessment (2002) at which several Regional and Program Office case studies of cumulative risk assessments were described. Future guidance will increasingly incorporate quantitative and mechanistic information on physical and biological interactions, and more details on cumulative exposure assessment. The most complex project will be the Risk Assessment Forum's development of cumulative risk assessment guidelines (2012), and related issue papers and case studies.

Impact and Outcomes:

This research program has reduced uncertainty in risk assessment by:

- Developing and communicating practical methods and approaches for conducting aggregate and cumulative risk assessment, in the form of risk assessment guidance and training. Such activity not only improves the dialogue between researchers, decision makers and stakeholders, but it also leads to more accurate and complete risk estimation.
- Gaining acceptance by the broader risk assessment community on approaches for conducting risk assessments through public workshops jointly conducted with the Agency for Toxic Substances Disease Registry
- Developing ORD's supplementary mixture risk guidance (EPA 2000) and related training workshops, which ultimately led to ORD participation in the Office of Pesticide Programs' development of cumulative risk guidance, and inclusion of ORD's relative potency factor approach in that guidance. Previous criticism that EPA's mixture risk assessments ignored synergism and antagonism is now solved by ORD's interaction-based Hazard Index (EPA 2000). Aggregate and cumulative risk assessments, both fairly new to EPA, will push toward a paradigm shift in Agency risk management
- Shifting ORD research from traditional source based risk assessments to population based cumulative risk assessments (EPA 2003), thus addressing environmental justice concerns of combined impacts on susceptible communities from multiple exposures. Risk estimates made for whole communities or for complex sites have the potential for tremendous health and economic impacts;

thus research to improve risk assessment methods, harmonization through Agency-wide guidance, and training on application of such methods is critical.

No Poster Presented
New Methods to Enhance Aggregate and Cumulative Assessments

Presenter: Glenn Rice (NCEA)
Contributors: Rick Hertzberg and Linda Teuschler (NCEA), Jane Ellen Simmons(NHEERL), Chris Saint (NCER), and Valerie Zartarian (NERL)

Science Questions:

This research program addresses the following questions:

- What are people's real world aggregate exposures including understanding the environmental transport issues that lead to these exposures?
- What contributes to aggregate exposures, including toxicokinetic processes that alter tissue doses?
- How do we estimate cumulative risk from aggregate exposures, particularly when considering mechanisms of toxicity that occur at different times or might differ across exposure routes?
- What are practical measurement methods that can be used to determine the toxicity of mixtures?
- Can sufficient data be gathered efficiently and economically to develop toxicokinetic models for chemical mixtures that are applicable to real-world complex exposures, including multiple pathways and exposure time frames?

The Research:

Individuals are concerned about whether there are increased health risks associated with real-world exposures to multiple chemicals and non-chemical stressors in their environment. Relatively little is known about risks posed by multiple environmental stressors (i.e., aggregate/cumulative risks). The research needed to provide scientific methods for characterizing such risks can be divided into three areas: 1) environmental transport; 2) exposure and toxicokinetics; and 3) mechanisms of toxic action. We describe ongoing research in the first two areas and suggest that research on the third, (i.e., mechanistic information that can inform the choice of dose-response models) is needed to credibly address concerns about aggregate exposures and cumulative risks.

Research is being conducted to characterize the transport of multiple chemicals in the environment and the degradation of chemical mixtures. The movement of stressors through the environment over time is complex due to the variability of natural processes that act on these stressors in heterogeneous environments. These movements can be extremely difficult to accurately measure or to predict with mathematical simulation models. Relevant ORD research projects addressing these science issues include:

- The Cumulative Risk Approaches for Contaminated Sites (draft document) provides a screening approach to guide the early phases of cumulative risk

assessments for sites contaminated with multiple chemicals, integrating basic information on environmental monitoring data and simulations of chemical transport in the environment from both the contaminated site and other anthropogenic sources.

- Human exposure and dose models are being developed in collaboration with the Office of Pesticides Program that simulate the co-occurrences of pesticide (e.g., pyrethroid) applications in space and time.
- Environmental mixtures degradation studies of toxaphene and polyaromatic hydrocarbons are being developed to evaluate changes in mixture composition and toxicity.
- The impact of metal ion-chelating agent complexes on adsorption, partitioning, and mass transport is being measured.

The research being conducted on exposures to multiple stressors and kinetics attempts to link levels of stressors in the environment to doses. This research has focused on developing exposure factors, understanding the toxicokinetics of chemical mixtures, and the development of screening procedures. Relevant research projects include the following:

- Human exposure factors that quantify exposures to media potentially contaminated with multiple chemicals (e.g., food, drinking water) have been extensively researched.
- ORD's Exposure-Related Dose-Estimating Model (ERDEM), a physiologically based pharmacokinetic (PBPK) modeling system, has been developed to quantify physiologic dose received from multimedia, multipathway exposures to chemicals of concern. This model has been used to simulate the simultaneous absorption, distribution, metabolism, and elimination of multiple chemicals, such as mixtures of water disinfection by-products and volatile organic compounds. There will be a continued reliance on this important model.
- Screening approaches are being developed to predict the impacts of changes in the absorption, distribution, metabolism and elimination on the toxicity of chemical mixtures.
- The screening process proposed in the draft Cumulative Risk Approaches for Contaminated Sites document uses models that evaluate the potential for metabolic interactions and common targets for mixtures of chemicals in humans.

Impact and Outcomes:

This research reduces uncertainty in future risk assessment by:

- Providing initial data and methods enabling risk analysts to develop preliminary aggregate and cumulative assessments
- Providing basic dose data associated with the transport, exposure and toxicokinetics of environmental chemical mixtures
- Developing a framework for generating hypotheses and initiating research to develop dose-response data for combined exposures to chemical and non-chemical stressors (e.g., exposures to chemicals plus a non-chemical stressor such

as noise)

- Developing hypotheses and implement research to better understand the toxic mechanisms by which multiple stressors jointly cause damage
- Using the draft Cumulative Risk Approaches for Contaminated Sites to demonstrate the feasibility of future cumulative risk assessment approaches and serving as input to Agency cumulative risk guidance
- Supporting the development of improved mathematical models that decrease the uncertainty in human health risk assessments of aggregate exposure and cumulative risks
- Provide data and insights that eventually lead to decisions resulting in the design and implementation of appropriate interventions to reduce significant risks.