FY2005 Annual Performance Measure 33

"Compendium of NERL-sponsored children's exposure data and tools for assessing aggregate exposure to residential-use pesticides in support of the August 2006 reassessment."

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DISCLAIMER

The National Exposure Research Laboratory, Office of Research and Development, United States Environmental Protection Agency, prepared this compendium of research activities that have been performed and/or funded by NERL and it's collaborators. The individual technical reports summarized within this compendium have undergone Agency peer review. This report is intended as a reference document for use by EPA and other exposure assessors. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

The Food Quality Protection Act of 1996 (FQPA, Public Law 104-170) requires EPA to upgrade the risk assessment procedures for regulating pesticides, including the introduction of aggregate exposure and cumulative risk assessments. FQPA also specifies that special consideration must be given to infants and children when demonstrating that “no harm” will result from aggregate pesticide exposures. Thus, exposure and risk assessments must be conducted for infants and children. In 1997, scientists within the National Exposure Research Laboratory (NERL) developed a conceptual model for identifying the highest priority FQPA-related exposure research needed to fill the critical exposure data gaps and provide the science to reduce uncertainty in future pesticide risk assessments. In collaboration with Agency scientists and risk assessors, NERL implemented focused exposure methods, measures, and modeling research activities to address the highest priority exposure needs, with special emphasis on research issues addressing children’s pesticides exposures. This report provides a compendium of NERL-sponsored exposure research activities that have been implemented in support of the 2006 FQPA mandate. Key research findings, along with copies and/or links to the corresponding technical publications, are included as a reference for use by risk assessors in conducting future pesticide exposure assessments. Pesticide exposure research activities that are currently on-going are also included for completeness as these data will be used to support future FQPA mandates.

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1. INTRODUCTION

The Food Quality Protection Act of 1996 (FQPA, Public Law 104-170, available at http://www.epa.gov/oppfead1/fqpa/gpogate.pdf) requires EPA to upgrade the risk assessment procedures for regulating pesticides, including the introduction of aggregate exposure and cumulative risk assessments. FQPA defines aggregate exposure as human exposures to a single chemical via all routes and environmental pathways. Cumulative risks are defined as exposures to multiple chemicals with the same mechanism of toxicity, also referred to as the chemicals with a common mode of action (MOA). Under FQPA, EPA can establish or leave in effect a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if it is determined to be "safe." “Safe” is defined as “a reasonable certainty that no harm will result from aggregate exposures to the pesticide's chemical residue from all anticipated dietary sources as well as all exposures from other sources for which there are reliable information." FQPA also specifies that special consideration must be given to infants and children when demonstrating that “no harm” will result from aggregate pesticide exposures. Thus, future exposure and risk assessments must be include considerations for infants and children.

In 1997, the National Exposure Research Laboratory (NERL) of the Office of Research and Development (ORD) designed and initiated an integrated research program to address the highest priority FQPA-related exposure research needs. This research program was developed in collaboration with the scientists and managers of EPA’s Office of Pesticides Programs (OPP), within the Office of Prevention, Pesticides, and Toxics Substances (OPPTS), and the Office of Children’s Health Protection (OCHP). A conceptual model was first developed to identify and prioritize the exposure research needs, and then used to design NERL’s future research program. Fundamental sound science and specific problem driven research activities were implemented to develop and apply the exposure tools (methods, measures and models) to generate the critical data needed to better understand and quantify children’s aggregate exposures to pesticides and to estimate the dose resulting from these exposures. Specific NERL objectives included:

- To develop aggregate and cumulative exposure and dose models to assess and predict exposures from non-agricultural use of pesticides; these models will include both dietary and non-dietary exposure sources;
- To develop and use common and widely available platforms for exposure, exposure-to-dose, and source-to-dose models;
- To develop methods and approaches for understanding pesticide use by people in their environments, especially in and around the home;
- To identify and characterize major factors that contribute to the magnitude and variability in human aggregate and cumulative exposure to pesticides;
- To conduct surveys to determine distributions of aggregate and cumulative exposure for the general population and sub-populations of interest; this includes seeking to better understand food use and consumption patterns; and,
- To design and implement exposure studies and to analyze, interpret and report the exposure measurements data.

A wide variety of exposure research programs have been planned and implemented in collaboration with the OPP and OCHP scientists since the enactment of FQPA. This Report compiles a listing of NERL pesticides exposure research activities and published results that can be used by the Agency with other scientific and manufacturer data to respond to the 2006 FQPA mandate. Completed and currently ongoing pesticides research activities are included in this compendium. Brief synopses of the research activities and key findings, along with copies of and/or links to the individual technical products, are provided as ready reference and use by the Agency risk assessors. Each research activity was designed to fill one or more critical exposure data gap(s), identify factors influencing exposures, and/or to provide risk assessors with the skills, knowledge, abilities, and tools for reducing uncertainties in future pesticides exposure assessments. The results of completed studies and key findings have been previously reported to the OPP collaborators through a variety of media including publications, presentations, Annual Performance Measures, technical reports, seminars, etc. These research results have also been used in an iterative fashion by NERL and ORD to identify research gaps and to develop hypotheses that will be used to inform and implement future FQPA-related research programs.

NERL's research program has been designed to develop the fundamental sound science tools for filling critical data gaps and reducing uncertainties in pesticides exposure and risk assessments. Significant research and technical support has been devoted over the past 10 years to assisting OPP in addressing specific FQPA-related risk assessments. While this report was originally intended to provide the Agency risk assessors with a ready reference of validated exposure research results and tools that can be used in future pesticides risk assessment, it is important to note where the NERL exposure research has already been used to fill critical data gaps and reduce uncertainty in recent risk assessments. Table 1 summarizes where NERL exposure research and/or tools have been used by OPP to inform its exposure and risk assessment decisions.

OPP is the principal recipient of this Report. However, NERL's exposure research was designed to also address the children's exposure-related scientific priorities for OCHP. In general, the research results compiled in this Report are intended to inform all risk assessors within and outside EPA who are challenged with the responsibility for protecting children and performing aggregate/cumulative pesticide risk assessments.

This Report fulfills NERL's Fiscal Year 2005 Annual Performance Measure 33. It provides the completed pesticides exposure research products and results to OPP in Fiscal Year 2005 for use in addressing the 2006 mandates. Summaries of on-going exposure research, to include anticipated outputs that will be used by the Agency to reduce uncertainties in risk assessments and address future FQPA mandates are also provided. Products within this ready-reference compendium include: published peer-reviewed journal articles and EPA reports; measurement-method protocols for use in sampling and analyzing pesticides and pesticide residues in a variety of environmental and biological media; databases of measured results from field and laboratory studies related to children's exposure to pesticides; and models that can be used for assessing pesticide exposures and doses for children and the general population. Collectively, these products provide OPPTS and other exposure assessors with a set of knowledge tools that can be used to enhance the scientific basis for future pesticides exposure and risk assessments, especially for assessing children's aggregate pesticide exposures.

Table 1. Significant FQPA-Related Exposure Research Accomplishments

RESEARCH AREA	PRODUCT	DESCRIPTION	USE IN RISK ASSESSMENT
Models	Stochastic Human Exposure Dose Simulation (SHEDS) Model	2-stage Monte-Carlo concentration-to-exposure-to-dose model yielding improved estimates of variability and reducing uncertainty in exposure assessments	1) Chlorpyrifos risk assessment (SHEDS chlorpyrifos assessment was reviewed by OPP but not used directly in their risk assessment) 2) CCA-treated wood risk assessment 3) Pyrethroid cumulative risk assessment (ongoing)
	Exposure-Related Dose Estimating Model (ERDEM)	Physiologically-based pharmacokinetic (PBPK) model used to estimate internal tissue dose resulting from exposure	1) Diomethoate risk assessment 2) Malathion in head lice risk assessment 3) Carbaryl and other N-Methyl Carbamates cumulative risk assessment (ongoing) 4) Pyrethroid cumulative risk assessment (ongoing)
	Children's Dietary Intake Model (CDIM)	Calculates total dietary intake by a child of a chemical including excess exposure due to handling during consumption	1) Provides accurate estimates of total dietary exposure of children to chemical contaminants 2) Incorporates excess dietary exposures caused by chemical contaminant transfer from surfaces and/or hands to foods prior to consumption
Measures	Children's Exposure Studies	Various studies to include: 1) Minnesota Children's Pesticide Exposure Study 2) Children's Daycare Study 3) Children's Total Exposure to Pesticides and Other Persistent Pollutants (CTEPP) 4) NAFTA Border Studies 5) National Children's Study 6) Dietary Intake of Young Children 7) Children's Dietary Lead Study	1) Filling critical exposure data gaps for young children (3-6) 2) Estimating children's exposures from various indoor environments 3) Identifying key factors influencing children's exposures 4) Estimating aggregate exposures 5) Providing validated protocols for collecting high quality children's exposure data 6) Designing future prospective children's studies (on-going) 7) Providing data to support the Risk Assessment Forum Children's Age Bins

	Population Exposure and Occurrence Studies	Various studies including: 1) Agricultural Health Study 2) National Human Exposure Assessment Survey Studies 3) HUD/EPA Environmental Health Survey of Child Care Centers 4) HUD/EPA American Healthy Homes Survey	1) Providing data relating farm children exposures to the general population 2) Providing estimates of general population exposures 3) Providing pesticide occurrence data in daycares across the US 4) Providing pesticide occurrence data in US residences (ongoing) 5) Providing input data for exposure and dose models
	In-house Research to Understand Factors Influencing Exposures	1) Food transfer studies 2) Test house 3) Fluorescent Study 4) Pet study	1) Filling critical data gaps 2) Estimating children's exposures from indoor environments 3) Identifying key factors influencing children's exposures 4) Provides input data for exposure and dose models
Databases	Consolidated Human Activity Database (CHAD)	A database compiling the results of a wide variety of human personal activity data from studies reported in the literature into a consistent and readily assessable framework	Providing human activity data by age and gender for understanding exposure and dose
	Human Exposure Database System (HEDS)	A readily available database of the validated exposure data from the NERL-sponsored studies	Validated exposure data from NERL-sponsored exposure studies

2. OVERVIEW OF THE FOOD QUALITY PROTECTION ACT (FQPA)

The Food Quality Protection Act of 1996 (FQPA, Public Law 104-170; available at http://www.epa.gov/oppfead1/fqpa/gpogate.pdf), mandated that the EPA consider aggregate exposure of humans to pesticides and pesticide residues. Aggregate exposure refers to the multiple environmental media and pathways by which humans are exposed to pesticides. In setting tolerances or upper limits of pesticides for food, the EPA must determine "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." (FQPA Section 405).

The FQPA specifically requires the EPA to consider the protection of infants and children in setting tolerances for foods. For infants and children, assessments must consider their food consumption patterns, their "special susceptibility" including neurological differences relative to adults and *in utero* exposures, the cumulative effects of multiple chemicals that have a "common mechanism of toxicity", and "exposure from other non-occupational sources".

Thus the FQPA places a scientific burden on EPA's exposure and risk assessors to consider all pathways and routes of pesticide exposure. In addition, special interest must be given for safeguarding children and infants. Furthermore, the FQPA requires EPA to use reliable information in assessing such exposures.

3. OVERVIEW OF NATIONAL EXPOSURE RESEARCH LABORATORY RESEARCH

EPA's scientific responsibility to consider children's aggregate pesticide exposures using reliable information motivates EPA's Office of Research and Development (ORD) to generate new and refined information tools and provide technical support to OPP. Through ORD's Human Health Research Program (HHRP), ORD strives "...to provide fundamental understanding of the physical and biological processes that underlie environmental systems and human populations at risk. It is expected that the products of this program will provide an integrated information base for scientifically defensible risk assessment and risk management decisions…" (excerpt from the Final Report of the HHRP Review by the ORD Board of Scientific Counselors, July 27, 2005).

ORD's National Exposure Research Laboratory (NERL) developed and implemented a responsive pesticides exposure research program, framed within the ORD HHRP, to help address the FQPA mandates. NERL established an FY 2005 Annual Performance Measure (APM 33) to provide OPP/OPPTS with the validated data and tools for assessing aggregate exposures of children to residential-use pesticides that could be used to meet the 2006 FQPA mandate. NERL has addressed this commitment by pursuing, in an iterative fashion, a multiple-disciplinary research program that has included the following major elements:

- development and publication of a knowledge framework for understanding and studying children's aggregate pesticide exposures;
- development of a protocol that defines the data needs for quantifying aggregate exposures by multiple routes and pathways

- development of analytical and exposure measurement methods for use in sampling and analyzing pesticides and pesticide residues in a variety of environmental and biological media;
- development of methods for collecting and interpreting data on children's activities and other exposure factors
- implementation of field and laboratory studies related to children's exposure to pesticides;
- development and dissemination of databases of measured results from these studies;
- development and application of computational models for assessment of pesticide exposure and dose; and
- publication of peer-reviewed journal articles and EPA reports.

This Report provides a compendium of the NERL research activities that have been implemented since 1997. It includes brief synopses of the research activities and the key research findings, and provides copies of the technical reports and/or appropriate linkages to the science products to facilitate user access to these documents. Within each document, the reader can learn the specifics regarding the research objectives, results, and guidance for how the research tools and sound science findings can be used to inform future risk assessments.

4. CHILDREN'S EXPOSURE RESEARCH FRAMEWORK

NERL was already conducting research on children's exposures to pesticides and other environmental contaminants prior to 2006 and FQPA. However, after the passage of the FQPA, NERL increased its commitment to conducting focused pesticides exposure research in collaboration with OPP/OPPTS and OCHP scientists and managers to help address the FQPA mandates. A systematic approach was taken to planning and implementing the research that was ultimately needed to provide exposure and risk assessors with the knowledge tools for developing improved exposure and risk assessments for children. Several internal and external workshops were conducted to gain a better understanding of the state of the science and frame the research needs. One important workshop focused on dermal and non-dietary ingestion exposure research, areas where the Agency had identified major research gaps. Information was gathered on the state-of-the-art in measuring and assessing children's exposures to pesticides via dermal contact with contaminated surfaces and objects as well as by non-dietary ingestion. Special attention was given to methods and approaches for characterizing concentrations of pesticides in the exposure media (on surface/object) and on quantifying the transfer of contaminants to the skin surface or mouth. The workshop report summarizes the workshop discussions and identifies research priorities based on a review of the literature, scientists discussions, and expert input.

Concurrently, NERL initiated activities to systematically define and plan the future research program. Two seminal papers outlined the children's pesticides exposure and assessment tools research needs. The first of these papers, "Children's Exposure Assessment: A Review of Factors Influencing Children's Exposure, and the Data Available to Characterize and Assess That Exposure" (Cohen Hubal et al. 2000a) was published in *Environmental Health Perspectives*. This paper lays out a conceptual framework for assessing children's aggregate exposure

(Figure 1). Several equations and/or algorithms are presented that represent exposure via each of several routes: inhalation; dermal contact and transfer for two different approaches (a macroactivity approach, and a microactivity approach); nondietary ingestion due to mouthing of hands and objects; and dietary ingestion. For each of these algorithms, the input factors are defined and discussed. Data needed to implement the algorithms are described, and the availability and quality of the needed data discussed. This approach resulted in the identification of several general areas of research needed to fill critical exposure data gaps and reduce uncertainty, including:

- identification of appropriate age/developmental benchmarks for categorizing children in exposure assessment;
- development and improvement of methods for monitoring children's exposures and activities;
- collection of activity pattern data for children (especially young children) required to assess exposure by all routes; and
- collection of data on concentrations of environmental contaminants, biomarkers, and transfer coefficients that can be used as inputs to aggregate exposure models.

This publication was followed by a second, related journal article “The challenge of assessing children’s exposure to pesticides” (Cohen Hubal et al. 2000b). This second paper specifically described the research strategy NERL would employ in addressing the identified data gaps specific to children’s aggregate exposure to pesticides. Four priority exposure research areas were identified:

- pesticide use patterns in microenvironments where children spend time;
- temporal and spatial distribution of pesticides following application in residential settings;
- dermal and nondietary ingestion exposure assessment methods and exposure factors; and
- dietary exposure assessment methods and exposure factors for infants and young children.

Another important paper further developed the modeling framework for conducting children’s exposure assessments (Zartarian et al., 2000). In this paper, Zartarian et al. presented the first generation of the Stochastic Human Exposure and Dose Simulation (SHEDS) modeling framework for assessing pesticide exposure. The SHEDS model combines activity data from NERL’s Consolidated Human Activity Database (CHAD) with probability distributions of environmental concentrations and exposure factors. This initial SHEDS publication described the 1-stage Monte Carlo modeling framework and presented an assessment for children’s residential exposures to chlorpyrifos, an organophosphorus (OP) insecticide, from lawn, garden, and indoor crack and crevice application methods. The paper focused on the difficult-to-model pathways of dermal contact and transfer (using the micro-activity approach described by Cohen Hubal et al. (2000a,b), and non-dietary ingestion that result from hand-to-mouth and object-to-mouth activity of children, addressing the third highest-priority research areas identified by Cohen Hubal et al. (2000b). This initial SHEDS paper identified non-dietary ingestion as an important exposure pathway for children in residences. When evaluated against real-world data,
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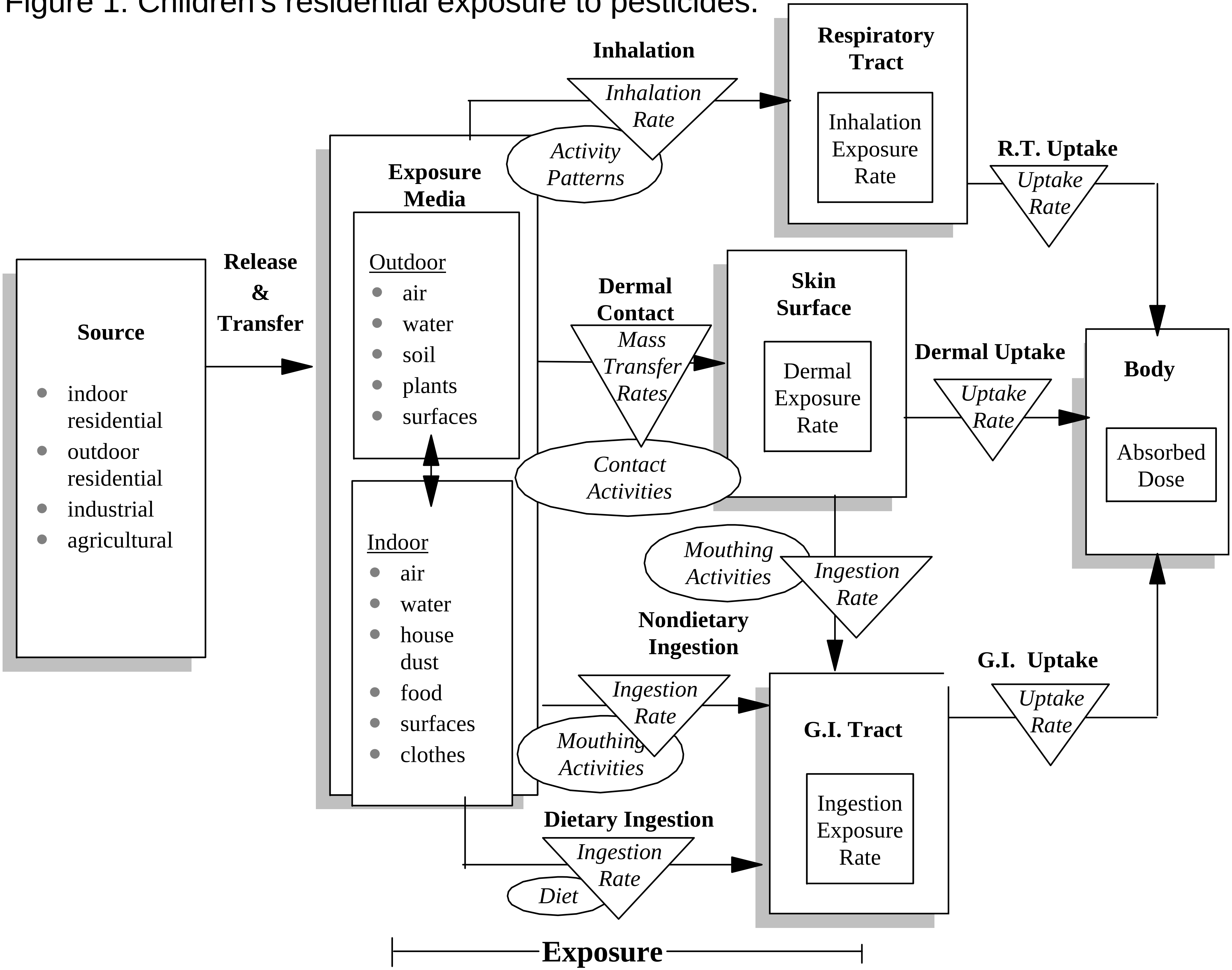
Figure 1: Children's residential exposure to pesticides.



the SHEDS-Pesticides model simulated urinary excretion rates of the chlorpyrifos metabolite 3,5,6-trichloro-2-pyridinol that were comparable to other peer reviewed published measurements. This evaluation of the model against real-world data supported the scientific robustness of the model.

The SHEDS-Pesticides model was then enhanced to a 2-stage Monte Carlo aggregate model, including the inhalation and dietary ingestion routes as well as the dermal route (using the macro-activity approach described by Cohen Hubal et al. (2000a,b) and the non-dietary ingestion route. This second generation model was an embodiment, in a computational software program, of some of the aggregate exposure concepts identified in the framework papers.

These three papers provided NERL with a sound science foundation for defining and developing a consistent conceptual framework for assessing children's aggregate exposures to residential pesticides. They were use to systematically identify and prioritize research activities and programs designed to improve the tools for performing these assessments.

Over the last five to seven years, NERL has conducted extensive research in the area of children's residential pesticide exposures with the research designed to fill the identified critical data gaps and provide scientific understandings that reduce uncertainty in risk assessment. The research has been framed in four major categories: (1) the development of **methods (sampling and analytical) and protocols** for characterizing pesticide residue levels in various environmental and biological media and in microenvironments where children live and play; (2) the conduct of laboratory and field **measurement studies** to obtain new data describing children's aggregate residential pesticide exposure and the key factors influencing these exposures; (3) the development and application of exposure and dose **models** for the simulation of these exposures and the resulting doses; and, 4) development of internet accessible **databases** to store, maintain, retrieve, and disseminate validated data. The remainder of this Report provides the reader with brief summaries of NERL's research activities within each of these four major categories.

References

Cohen Hubal, E. A., K. W. Thomas, J. J. Quackenboss, E. J. Furtaw Jr., and L. S. Sheldon. Dermal and Non-Dietary Exposure Workshop. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-99/039 (NTIS PB99-150922), 1999.

Cohen Hubal E.A., Sheldon L.S., Burke J.M., McCurdy T.R., Berry M.R., Rigas M.L., Zartarian V.G., and Freeman N.C.G. "Children's exposure assessment: A review of factors influencing children's exposure, and the data available to characterize and assess that exposure," *Environ. Health Perspect.* 108:475-486, (2000a)

Cohen Hubal E.A., Sheldon L.S., Zufall, M.J., Burke J.M., and Thomas K.W., "The challenge of assessing children's exposure to pesticides," *J. Expo. Anal. Environ. Epidemiol*.10:638-649, (2000b)

Zartarian, V., Ozkaynak, A.H., Burke, J.M., Zufall, M.J., Rigas, M.L., and Furtaw, Jr., E.J., "A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and non-dietary ingestion." *Environmental Health Perspectives* 108 (6):505-514 (2000). EPA/600/J-01/112.

5. EXPOSURE METHODS AND PROTOCOL RESEARCH

One of NERL's core capabilities is the expertise for developing sophisticated methods and protocols for characterizing chemical contaminant concentrations in environmental and biological media, characterizing potential human exposures to the chemicals, and identifying the key factors influencing these exposures. During NERL's FQPA research needs assessment, major shortfalls were identified regarding the availability of sophisticated methods and protocols that would produce consistent, high quality data for characterizing very young children's exposures to pesticides. Significant research was planned in three areas:

- Protocol development
- Environmental and biological sampling and analysis methods
- Survey methods for characterizing
    1. Pesticide and other household product use
    2. Children's activity patterns, including diet diary, activity diary, accelerometer, and videography

The following sections highlight the research accomplishments within each of these areas.

5.1 Protocol Development

5.1.1 Draft Protocol for Measuring Children's Non-Occupational Exposures to Pesticides by All Relevant Routes

Prior to FQPA, standard protocols for conducting exposure field studies that provide data for measurement-based exposure assessments did not exist. In addition, protocols for developing exposure factor data to be used for modeling assessment were not available. Although children's exposure research was on-going both within and outside EPA, the protocols that were being employed in the various studies were developed to meet individual study objectives. More importantly, researchers used a wide variety of methods that produced data of different quality and quantity, and in many instances didn't collect all the necessary data required for reliable exposure assessments. As a result of these differences in design and implementation, the data from the various studies could not be readily compared and/or interpreted.

After the implementation of FQPA, NERL's children's aggregate exposure research program was designed to address these shortfalls. Research was implemented to better understand children's multimedia, multipathway exposures and to determine what environmental, biological, exposure factor, and other physical and meta data needed to be collected to characterize and estimate children's exposure to pesticides by each route and pathway. The goal of this program was to develop and publish a protocol that could be used by all researchers examining children's exposures to pesticides that could be used to generate comparable data across these studies for assessing children's aggregate risk. As a result of this effort, a draft protocol was developed for measuring children's exposures to pesticides by all relevant pathways (EPA, 2001). This draft protocol addressed approaches and methods for measurements for children's exposures that can be used as part of future field monitoring studies. It describes the algorithms for each route of exposure, specifies the data required to conduct the aggregate exposure assessment, and describes the methodology for collecting the data. The protocol did not include the specific sampling and analysis method or Standard Operating Procedures as there are numerous comparable methods readily available within the scientific community. NERL implemented methods research to address the key methods supporting selected NERL exposure studies. These are described in the next section. The protocol provides the approach for estimating exposure by each route. References are also provided to assist the reader in obtaining detailed information on the utility of measurement methods, procurement of materials and supplies, and the implementation of the methods and materials in the field.

Reference:
Berry, M.R.,Cohen Hubal, E.A., Fortmann, R.C., Melnyk, L.J., Sheldon, L.S., Stout, D.M., Tulve, N.S., and Whitaker, D.A., "Draft Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways," EPA 600/R-03/026, September 2001.

5.1.2 Measurement and Analysis of Exposures to Environmental Pollutants and Biological Agents during the National Children's Study (NCS)

In 1997 the President's Task force on Environmental Health Risks and Safety Risks to Children was charge with developing strategies to reduce or eliminate adverse effects on children caused by environmental exposures. In addition, the Task Force proposed the conduct of a longitudinal children's cohort study. The Children's Act of 2000 authorized the National Institute of Child Health and Human Development (NCIHD) to conduct a national longitudinal study. The National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, and ORD/EPA were challenged to collaborate with NICHD in designing and planning the National Children's Study (NCS), http://nationalchildrensstudy.gov/. The NCS is a longitudinal study that will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. The goal of the study is to improve the health and well-being of children. The study defines the term "environment" broadly and will take a number of issues into account, including:

- Natural and man-made environment factors
- Biological and chemical factors, including pesticides
- Physical surroundings
- Social factors
- Behavioral influences and outcomes
- Genetics
- Cultural and family influences and differences
- Geographic locations

Researchers will analyze how these elements interact with each other and what helpful and/or harmful effects they might have on children's health. By studying children through their different phases of growth and development, researchers will be better able to understand the role of these factors on health and disease. The study will also allow scientists to find the differences that exist between groups of people, in terms of their health, health care access, disease occurrence, and other issues, so that these differences or disparities can be addressed.

Since 2000, NERL and other EPA scientists have served on various workgroups and panels to help plan and design the NCS. NERL and ORD scientists have also conducted specific research activities in support of NCS hypotheses and research needs. Several methods and protocol research activities have been completed by NERL scientists, and are discussed in the following sections. One major NCS activity where NERL scientists contributed significantly has been in the development of the white paper, "Measurement and Analysis of Exposures to Environmental Pollutants and Biological Agents during the National Children's Study", located at http://nationalchildrensstudy.gov/research/methods_studies/final-white-paper-113004.cfm. This document establishes the framework for the development of the future NCS study design, study protocols, and the final implementation plan. While only limited pilot study data are currently available, we anticipate that the future NCS study results will be used by all risk assessors in assessing children's exposures and health, with key data being used to meet post-2006 FQPA mandates.

References:

Needham L.L., Ozkaynak H., Whyatt R.M., Barr D.B., Wang R.Y., Naeher L., Akland G., Bahadori T., Bradman A., Fortmann R., Liu L.J., Morandi M., O'Rourke M.K., Thomas K., Quackenboss J., Ryan P.B., and Zartarian V., "Exposure assessment in the National Children's Study: Introduction." *Environ Health Perspect.* 113(8):1076-82. (2005)

Ozkaynak H., Whyatt R.M., Needham L.L., Akland G., and Quackenboss J., "Exposure assessment implications for the design and implementation of the National Children's Study," *Environ Health Perspect.* 113(8):1108-15. (2005)

5.2 Environmental and Biological Sampling and Analysis Methods

NERL's sampling and analysis methods research program has focused on providing the scientific community with a toolbox of sophisticated methods that will produce the data quality and quantity needed to support EPA aggregate risk assessments. Aggregate exposure sampling and analysis methods are needed to provide risk assessors with accurate information on chemical concentrations, relevant pathways and routes of human exposure. Key issues of analytical and sampling uncertainty, including precision, accuracy, stability and recovery have been addressed. NERL's high quality methods program, integrated with the exposure measurements program, ensures consistently high quality exposure measurement data are collected for use in children's aggregate risk assessments. Sampling and analytical methods for current-use and emerging residential pesticides and their residues in various environmental media including air, food and water, and surfaces (including dust) have been developed and validated. Innovative methods have also been developed to address key uncertainties in assessing children's pesticides exposures. Enhanced dietary methods have been developed to improve pesticide analyte and/or metabolite extraction, detection and quantification in complex dietary samples. Sampling and analysis methods for collecting urine in young children's diapers have been developed to allow researchers to generate data filling critical gaps and better understanding the linkages between environmental concentration, exposure and dose. NERL has also conducted research to develop biomarkers methods for collecting and analyzing human biological samples (urine, blood, etc.) for the presence of the appropriate biomarker, i.e., the pesticide or its metabolite(s) as evidence that exposure and dose have occurred.

In 2004, NERL provided OPP with a first "Compilation of Developed Methods Used to Measure Children's Exposures to Pesticides and Other Environmental Contaminants" (Medina-Vera et al., 2004). This report provided OPP and other Agency risk assessors with a readily accessible inventory of validated Standard Operating Procedures for use in exposure laboratory and/or field studies. It also provided SOPs for the analysis of numerous current-use residential pesticides and other persistent pollutants that NERL historically has measured in the environment using these sampling media. Since this publication, additional pesticide and pesticide-related sampling and analysis methods have been developed and validated by NERL. These validated methods are being reported herein for use in by scientists in future exposure research programs.

5.2.1 Methods Published in Peer Reviewed Journal Articles

Numerous analytical and sample measurement methods have been developed, evaluated, and published in the peer reviewed scientific literature. These new methods produce the high quality needed in exposure field studies to characterize children's pesticides multimedia exposures.

- "Evaluation of Analytical Methods for Determining Pesticides in Baby Food". Chuang, J. C., M. A. Pollard, M. Misita, and J. M. Van Emon. ANALYTICA CHIMICA ACTA 399(1-2):135-142, (1999)
- "Organophosphorus Hydrolase-Based Assay for Organophosphate Pesticides," Rogers, K. R., Y. Wang, A. Mulchandani, P. Mulchandani, and W. Chen. BIOTECHNOLOGY PROGRESS 15(3):517-521, (1999)
- "Collecting urine samples from young children using cotton gauze for pesticide studies", Hu, Y.A., Barr, D.B., Akland, G., Melnyk, L.J., Needham, L., Pellizzari, E.D., Raymer, J.H., and Roberds, J.M.," *Journal of Exposure Analysis and Environmental Epidemiology*, 10: 703-709, (2000)
- "Dietary exposure of children in lead-laden environments", Melnyk, L.J., Berry, M.R., Sheldon, L.S., Freeman, N.C.G., Pellizzari, E.D., and Kinman, R.N., *Journal of Exposure Analysis and Environmental Epidemiology*, 10: 723-731, (2000)
- "Contribution of children's activities to lead contamination of food", Freeman, N.C.G., Sheldon, L.S., Jimenez, M., Melnyk, L.J., Pellizzari, E.D., and Berry, M.R., *Journal of Exposure Analysis and Environmental Epidemiology*, 2001, 11: 407-413, (2001)
- "Determination of pesticides in composite dietary samples by gas chromatography/mass spectrometry in the selected ion monitoring mode by using a temperature-programmable large volume injector with pre-separation column", Rosenblum, L., Hieber, T. and Morgan, J.N., *JAOAC International*, 84:891-900 (2001)
- "Evaluation of Analytical Methods for Determining Pesticides in Baby Foods and Adult Duplicate-diet Samples," Chuang, J.C., K. Hart, J.S., Chang, L.E. Boman, J.M. VanEmon, and A.W. Reed *Analytical Chimica Acta*, 444 (2001) 87-95
- "Human Blood and Environmental Media Screening Method for Pesticides and Polychlorinated Biphenyl Compounds Using Liquid Extraction and Gas

Chromatography-Mass Spectrometry Analysis". Liu, S. and J. D. Pleil. *J. Chromatraphy: B Biomedical Sciences and Applications* 769(1):155-167, (2002)

- "Comparison of five extraction methods for determination of incurred and added pesticides in dietary composites", Rosenblum, L., Garris, S. T. and Morgan, J.N., *JAOAC International*, 85:1167-1176, (2002)
- "Transfer efficiencies of pesticides from household flooring surfaces to foods", Rohrer, C.A., Hieber, T., Melnyk, L.J., and Berry, M.R., *Journal of Exposure Analysis and Environmental Epidemiology*, 13: 454 – 464, (2003)
- "Determination of metals in composite diet samples by inductively coupled plasma-mass spectrometry", Melnyk, L.J., Morgan, J.N., Fernando, R., Akinbo, O., and Pellizzari, E.D. "Determination of Metals in Composite Diet Samples by ICP-MS," *Journal of AOAC International*, 86 (2): 439 - 447, (2003)
- "Comparison of Immunoassay and Gas Chromatography/Mass Spectrometry Methods for Measuring 3,5,6-Trichloro-2-pyridinol in Multiple Sample Media". Chuang, J. C., J. M. Van Emon, A. W. Reed, and N. Junod. ANALYTICA CHIMICA ACTA 517(1-2):177-185, (2004).
- "Development and Evaluation of an Enzyme-Linked Immunosorbent (ELISA) Method for the Measurement of 2,4- Dichlorophenoxyacetic Acid in Human Urine." Chuang, J.C., Van Emon, J.M., Durnford, J., Thomas, K.; Talanta 67 (2005) 658-666.

5.2.2 Methods Published in EPA Peer Reviewed Technical Reports

Four key methods have been produced and published as EPA documents, with two of these designed to direct support the planning and design of the National Children's Study.

- "Comparison of Methods for the Determination of Alkyl Phosphates in Urine". James, R. R., S. N. Hern, G. L. Robertson, AND B. A. Schumacher. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-03/075 (NTIS PB2004-103372).
- "Evaluating Commercially Available Dermal Wipes, Cotton Suits, and Alternative Urinary Collection Materials for Pesticide Sampling from Infants", EPA/600/R-04/087 May 2004.
- "Identification of Time-Integrated Sampling and Measurement Techniques to Support Human Exposure Studies," EPA 600/R-04-043, May 2004
- "Demonstration of Low Cost, Low Burden, Exposure Monitoring Strategies for Use in Longitudinal Cohort Studies," EPA/600/R-04/109, September 2004.

5.2.3 NERL Approved Laboratory Analysis and Field Measurement Standard Operating Procedures

Numerous NERL developed and approved procedures are available for use by Agency risk assessors. Each procedure describes in detail the steps required for generating high quantity data through the collection and analysis of environmental and biological samples. Each electronically available procedure has been reviewed for quality assurance and updated, as needed, on a yearly basis with the updated electronic versions available through http://www.epa.gov/heds/ .

- Collection of Soil Samples for Persistent Organic Pollutants, NERL Standard Operating Procedure EMAB 016.1E, Revision September 2004
- Collection of Floor Dust Samples for Persistent Organic Pollutants, NERL Standard Operating Procedure EMAB-015.1E, Revision September 2004

- Collection of Dislodgeable Residues-PUF Roller Samples for Persistent Organic Pollutants, NERL Standard Operating Procedure EMAB-014.1E, Revision September 2004
- Collection of Food Preparation Surface Wipe Samples for Persistent Organic Pollutants, NERL Standard Operating Procedure EMAB-013.1E, Revision September 2004
- Collection of Hard-Floor Surface Wipe Samples for Persistent Organic Pollutants, NERL Standard Operating Procedure EMAB-012.1E, Revision September 2004
- Collection of Dermal Hand Wipe Samples for Persistent Organic Pollutants Procedures, NERL Standard Operating Procedure EMAB-011.1E, Revision September 2004
- Collection of Urine Sample Procedures, NERL Standard Operating Procedure EMAB-010.1E, Revision September 2004
- Collection of Food Samples, NERL Standard Operating Procedure EMAB-009.1E, Revision September 2004
- Collection of Fixed Site Indoor and Outdoor Air Samples for Persistent Organic Pollutants, NERL Standard Operating Procedure EMAB-008.1E, Revision September 2004
- "Enantiomer specific analysis of the pyrethroid insecticide *cis*-permethrin in sample extracts by chiral Gas Chromatography and Mass Spectrometry", NERL Standard Operating Procedure MDAB-020.1, May 2005
- "Experimental protocol for the determination of chlorpyrifos, permethrin, cyfulthrin and diazinon in sample extracts by liquid chromatograpy tandem mass spectrometry (LC/MS/MS)" NERL Standard Operating Procedure MDAB-049.0, August, 2005
- Extraction of PUF for Pesticide Analysis by ASE, NERL Standard Operating Procedure MDAB-047.0, August 2005

5.2.4 Book Chapter

- Van Emon, J.M. and Chuang, J.C., *"Immunoassay Methods for Measuring Atrazine and 3,5,6- Trichloro-2-Pyridinol in Foods,"* in Pesticide Analysis: Methods and Protocols, Volume I. Analysis for Human Exposure. Editor, Jose Luis Martinez Bidal, Department of Analytical Chemistry, University of Almeria. 04071 Almeria Spain. (In press)

5.3 Survey Methods

As previously noted in the Protocol Development section, aggregate risk assessments require knowledge regarding the environmental concentrations of the chemicals of interest that humans may be exposed, the microenvironments where these exposures occur, when they occur, how they occur, how often they occur, and other key factors that may influence multimedia human exposures. This is particularly true when researchers are designing observational studies and assessing children's exposures to pesticides and other important pollutants. Following the implementation of FQPA, NERL identified the need to develop and refine survey methods for consistently collecting key factor data that help researchers translate and interpret environmental and biological sample results into children's aggregate exposures and understand where and how these aggregate exposures occur. One focus area was the development of survey tools/inventories that could be used to characterize pesticide and other household product use in residences. Research was also conducted to generate and validate tools for capturing children's activities and understanding how these activity patterns influence children's pesticide exposures by lifestage. Standard survey instruments were designed and validated for generating reproducible data on children's activities and patterns, including diet. Techniques were evaluated for characterizing the intensity of children's activities (accelerometer) and relate these to their micro- or macroactivities. Videographic techniques were developed for assessing activities to environmental concentrations. A suite of survey methods have been validated and used in NERL's recent children's exposure studies, including:

- Home Pesticide Inventory and Use Screening Questionnaire. Used to capture information on the frequency of pesticide use over various periods, methods of application, locations of application, who applied the pesticides, etc.
- Time Activity Diary and Questionnaire. Both recall and real-time activity diaries and questionnaires are available. Recall questionnaires are administered after a monitoring event to identify where the child has spent his or her time during the period. At the end of each day, parents and/or caretakers take a few minutes to record the time their child spent in each of several specific locations, to include: the home, school, in transit, or other locations. Real-time diaries capture macroactivity data during specific monitoring periods, e.g., during a videotaping session. These tools focus on activity level (eating, sleeping, quiet play, active play), locations, and other key factors that may influence exposure, e.g., clothing and washing events.
- Food Diary. A standard food diary has been developed to assess children's dietary intake and potential exposures to pesticides. The current data form is designed to collect the duplicate diet sample information during the 24-hour post-application data collection period. The form is completed by the adult caregiver of the child and submitted at the end of the 24-hour data collection period.
- Accelerometer. A frequently used technique for assessing physical activity in the exercise physiology field is accelerometry, and its use seems to be increasing due to improvements in equipment design and construction. When a person moves, the body is accelerated in rough proportion to change in muscular force, and thus, to energy expenditure. Accelerometers utilize a one-, two-, or three-dimensional (3-D) piezoelectric transducer in a cantilever mounting that generates a pulse which is counted and stored in memory for a user-defined time period (e.g., from a second to one day). These pulses are converted to "counts," and internal algorithms transform these counts into energy expenditure estimates in terms of kilocalories per minute (or multiples thereof). The algorithms also produce activity-specific METS (metabolic equivalents of work) estimates, which are ratios of the work expended to the subject's basal metabolic rate.
- Videotaping. Videotaping techniques are commonly used to capture the activities and related exposures for young children. Early research focused on developing microactivity videography techniques. Recent research has been designed to capture and interpret macroactivity level.

Copies of current NERL survey instruments, along with instructions for use, are available electronically at http://:www.epa.gov/heds/ or by contacting Dr. Linda Sheldon, 919-541-2454 (Sheldon.linda@epa.gov).

6. EXPOSURE MEASUREMENT RESEARCH

NERL researchers and their exposure researcher collaborators have conducted extensive exposure measurement research over the past 10 plus years designed to fill critical data gaps and reduce uncertainties in the following broad scientific areas:

- the occurrence and co-occurrence of pesticides and relating these to residential pesticide use
- residential pesticide concentrations and the temporal and spatial distribution of these pesticides in environments where you children spend their time
- key factors influencing the dermal transfer and indirect ingestion of pesticides, and the efficiency of these transfers
- children's direct ingestion of pesticides
- relationships between and among environmental concentrations of pesticides in various media, children's activities, and the results of biomarkers of exposures as measured in urine and/or blood.

NERL's exposure measurements research activities, addressing one or more of these broad areas, are summarized below in four categories: 1) laboratory and pilot scale studies to identify and evaluate factors influencing children's exposures; 2) pilot scale studies to test and evaluate exposure protocols; 3) exposure and occurrence field measurement studies; and 4) data analysis activities to inform future research. The validated NERL-sponsored study data have been incorporated into the readily accessible Human Exposure Database System (HEDS) http://www.epa.gov/heds/, discussed in the Modeling Research Section later.

6.1 Laboratory and pilot scale studies to identify and evaluate factors influencing children's exposures

6.1.1 Identification of Important Parameters for Characterizing Pesticide Residue Transfer Efficiencies

This laboratory study was designed to evaluate the various parameters that affect pesticide residue transfer from surface-to-skin, skin-to-objects, skin-to-mouth, and object-to-mouth (Cohen Hubal et al., 2004). The approach was to use fluorescent tracers as surrogates for pesticide residues (Ivancic et al., 2004). Transfers of riboflavin, the tracer in the initial tests, were compared to transfers of chlorpyrifos and bioallethrin. Following the application of the tracers to common surfaces (e.g., carpet, laminate), controlled transfer experiments were conducted to evaluate the importance of parameters such as surface type, surface loading, type of contact (press versus smudge), contact duration, contact pressure, and skin condition (dry, moist, or sticky). The study involved tests to evaluate repetitive contacts with contaminated surfaces, measurements of transfers off the skin, and simulated mouthing removal using saliva moistened polyurethane foam (PUF). Surface loading, skin condition, and surface type were determined to be significant parameters in the initial tests. In the second phase of this study, an additional tracer with different physiochemical properties was evaluated. Controlled transfer experiments were performed to refine the understanding of significant parameters and to develop a more comprehensive set of transfer efficiency data that can be used to predict dermal and indirect ingestion exposure from field measurements. Key outputs include: transfer efficiency data, information on type of microactivity data needed to estimate dermal exposure, and inputs for multipathway exposure models.

References:

Cohen Hubal, E.A., J.C. Suggs, M.G. Nishioka, W.A. Ivancic., "Characterizing residue transfer efficiencies using a fluorescent imaging technique." *Journal of Exposure Analysis and Environmental Epidemiology*. Vol 15, No.3, pp 261-270 (2005)

Cohen Hubal, E.A., P. Egeghy, M.G. Nishioka, W.A. Ivancic., "Applying a fluorescent imaging technique to characterize potential pesticide residue transfer efficiencies" (In preparation. Planned for 2006)

Ivancic W.A., Nishioka, M.G., Barnes, R.H., and Cohen Hubal E.A., "Development and evaluation of a quantitative video fluorescence imaging system and fluorescent tracer for measuring transfer of pesticide residues from surfaces to hands with repeated contacts." *Annals of Occupational Hygiene*. Vol. 48, No. 6, pp. 519-532 (2004)

Riley, W.J., T.E. McKone, and Cohen Hubal, E.A., "Estimating Contaminant Dose for Intermittent Dermal Contact: Model Development, Testing, and Application." *Risk Analysis*. Vol 24, No. 1:73-85 (2004)

6.1.2 Feasibility of Using the Macroactivity Approach to Assess Dermal Exposure

This study was designed to test the feasibility of employing a macroactivity approach to assess children's dermal exposures to pesticides in daycare centers. Two main approaches are currently used by the scientific community to assess children's dermal exposure, the macroactivity and microactivity approaches. In the macroactivity approach, exposure is estimated for each macroactivity that the child conducts within each microenvironment (e.g. quiet play in the living room, active play in the kitchen, etc.). Exposure is then estimated using empirically-derived transfer coefficients to aggregate the mass transfer associated with a series of contacts with a contaminated medium. In the microactivity approach, exposure is explicitly modeled as a series of discrete transfers resulting from each contact with a contaminated medium. With this more exacting approach, dermal exposure must be estimated for each individual contact made by the child during an observational period, generally 24 hours. In the pilot study, screening measurements were made in nine daycares where pesticides were applied as crack and crevice treatments by commercial applicators. At one daycare, children were asked to wear full-body cotton dosimeters for short time periods while involved in selected macroactivities (e.g., story time, playtime indoors). Surface sampling of pesticide residues and videotaping of activities were performed simultaneously. Results were used to calculate transfer coefficients and to evaluate this approach for estimating dermal exposure. Significant results from the study include: pesticide distributions in nine daycare centers; verified protocols for collecting both aggregate surface measurements and transfer coefficients; and children's dermal transfer coefficients developed for evaluation with the default assumptions used in OPP's Residential SOPs.

References:
Cohen Hubal, E.A., "Issues in dermal exposure of infants." *Journal of Children's Health.* Vol 2, No. 3-4, pp 253-266 (2004)

Cohen Hubal, E.A., P. Egeghy, K Leovic, G Akland., "Measuring potential dermal transfer of a pesticide to children in a daycare center. *Environmental Health Perspectives.* (2005) doi:10.1289/ehp.8283 available via *http://dx.doi.org/* [Online 20 September 2005]

6.1.3 Distribution of Pesticides and Polycyclic Aromatic Hydrocarbons in House Dust as a Function of Particle Size

House dust is a repository for environmental pollutants that may accumulate indoors from both internal and external sources over long periods of time. Dust and tracked-in soil accumulate most efficiently in carpets, and the pollutants associated with it may present an exposure risk to infants and toddlers, who spend significant portions of their time in contact with or in close proximity to the floor and engage in frequent mouthing activities. The availability of carpet dust for exposure by transfer to the skin or by suspension into the air depends on particle size. In this study, a large sample of residential house dust was obtained from a commercial cleaning service whose clients were homeowners residing in the Research Triangle area of North Carolina. The composite dust was separated into seven size fractions ranging from <4 um to 500 um in diameter, and each fraction analyzed for 28 pesticides and 10 polycyclic aromatic hydrocarbons (PAHs). Over 20% of the fractionated dust sample consisted of particles less than 25 um in diameter. Fourteen pesticides and all 10 of the target PAHs were detected in one or more of the seven size-fractionated samples. Sample concentrations reported range from 0.02 to 22 ug/g, with the synthetic pyrethroids cis- and trans-permethrin being the most abundant pesticide residue. The concentrations of nearly all of the target analytes were found to increase gradually with decreasing particle size for the larger particles, then dramatically for the two smallest particle sizes (<25 um and <4 um).

Reference:

Lewis, R. G., C. R. Fortune, R. D. Willis, D. E. Camann, and J. T. Utley. Distribution of Pesticides and Polycyclic Aromatic Hydrocarbons in House Dust as a Function of Particle Size *Environmental Health Perspectives* 107(9):721-726, (1999)

6.1.4 Influence of Residential Lawn Pesticide Applications on Indoor Levels and Exposures

The transport of lawn-applied 2,4-D into 13 actual homes was measured following both homeowner and commercial application of this herbicide to residential lawns. Collection of floor dust in five rooms of each house, corresponding to an entryway, living room, dining room, kitchen, and a child's bedroom, both prior to and after application, indicated that turf residues are transported indoors and that the gradient in 2,4-D dust loading (ug/m2) through the house follows the traffic pattern from the entryway. The removal of shoes at the door and the activity level of the children and pets were the most significant factors affecting residue levels indoors after application. Spray drift and fine particle intrusion accounted for relatively little of the residues on floors. Prior to application, the median 2,4-D bulk floor dust loading was 0.5 ug/m2; one week after application, the median 2,4-D floor dust level in the living room was 6 ug/m2, with a range of 1-228 ug/m2 on all carpeted floors in occupied homes, and 0.5-2 ug/m2 in unoccupied homes. The 2,4-D loadings on the carpet surface (dislodgeable residue/dust) were highly correlated with the 2,4-D bulk dust loadings. From these data we estimate that approximately 1% of the bulk dust is on the carpet surface, and it is this surface dust that may be readily available for dermal contact. Tabletop levels of 2,4-D were approximately 10% of carpet loadings, and were largely due to in-home dust resuspension. Non-dietary ingestion of carpet dust and inhalation for a 1-yr old child in these homes may produce exposures of 0.04-7 ug/day. These exposure estimates would be substantially higher, 4-70 ug/day, if the non-dietary ingestion was based on contact and transfer from hard surfaces such as contaminated table tops. In limited cases, these hypothetical exposures would approach the U.S. EPA IRIS RfD limits for 2,4-D of 10 ug/kg/day.

References:

Nishioka, M. G., H. M. Burkholder, and M. C. Brinkman., "Distribution of 2,4-Dichlorophenoxyacetic Acid in Floor Dust Throughout Homes Following Homeowner and Commercial Lawn Applications: Quantitative Effects of Children, Pets, and Shoes." *Environmental Science and Technology* 33(9):1359-1365, 1999.

Nishioka, M. G., H. M. Burkholder, M. C. Brinkman, and C. E. Hines., "Transport of Lawn-Applied 2,4-D from Turf to Home: Assessing the Relative Importance of Transport Mechanisms and Exposure Pathways." U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-99/040 (NTIS PB99-156358), 1999

6.1.5 The Distribution of Chlorpyrifos Following a Crack and Crevice Type Application in the U.S. EPA Indoor Air Quality Test House

This study was designed to examine the spatial and temporal distributions of the insecticide chlorpyrifos following a routine crack and crevice application by a professional pesticide applicator. The pilot study was conducted in the EPA Indoor Air Quality Test House located in Cary, NC (Tichenor et al., 1990). Measurements were collected over a 21-day study period immediately before and following the application. Samples collected included air concentrations using both polyurethane foam (PUF) and the OSHA Versatile Sampler (OVS) sampler, surface transferable residues using the PUF roller, surface concentrations (loadings) employing deposition coupons and the total extractable residues from carpet sections. Results of the study have been published (Stout and Mason, 2003). Findings demonstrate that the crack and crevice application resulted in the deposition of chlorpyrifos residues onto non-target surfaces. Surface deposition measured in the kitchen, where the application was performed, were non-uniform in distribution. Airborne chlorpyrifos rapidly distributed within the house through diffusive processes and an active air conditioning system. An exposure assessment employing chlorpyrifos concentrations following a crack and crevice application and a total release aerosol application (Mason et al., 2000) shows the latter application posing a higher potential risk. Key outputs include decay rates for study sampling periods, identification of translocation and exposure pathways, and data inputs to algorithms for SHEDS.

References:

Mason, M. A.; Sheldon, L. S.; Stout II, D. M., "The Distribution of Chlorpyrifos in Air, Carpeting, and Dust and its Reemission from Carpeting Following the Use of Total Release

Aerosols in an Air Quality Test House." In *Engineering Solutions to Indoor Air Quality Problems,* Proceedings of a Symposium, Raleigh, NC, 17-19 July, 2000. pp. 92-102.

Stout II, D. M.; Mason, M. A., "The Distribution of Chlorpyrifos Following a Crack and Crevice Type Application in the US EPA Indoor Air Quality Research House." *Atmospheric Environment 37*: 5539-5549. (2003)

Tichenor, B. A.; Sparks, L. E.; White, J. B.; Jackson, M.D. Evaluating Sources of Indoor Air Pollution. *J. Air Waste Manage Assoc, 40*: 487-492. (1990)

6.1.6 Study to Evaluate the Potential for Human Exposure to Pet-Borne Diazinon Residues following Residential Turf Applications

A series of pilot exposure measurement studies were conducted to investigate the potential for indoor/outdoor pet dogs to transport residues into homes following a routine residential turf application of a granular formulation of diazinon. Initially, a demonstration pilot study was conducted in one home to test the methodologies and feasibility for performing this assessment. The results of this demonstration study (Morgan et al., 2001) showed that diazinon was transferable from the treated turf by the pet indoors and/or to children up to 15 days after the application. The study results also suggested that the diazinon intruded into the dwelling through both the air and by track-in pathways. Analysis of fur clippings, and fur and paw wipes from the family's dog suggested that these served as an important medium for the uptake of turf transferable residues. The draft protocol was revised and subsequently tested at six homes in North Carolina. In each home, the homeowner made a single application of a granular diazinon formulation to turf following the application instructions. Samples were collected at pre-application and at 1, 2, 4, and 8 days post-application. Environmental samples were collected to determine the mass of diazinon applied to the lawn, the movement of residues into the structure, and the spatial and temporal distribution following the application. Residues were measured in samples from the fur, paws and blood of the family dog and from the hands and urine of a child in each home. The study also included videotaping of the child playing with the dog and collection of transferable residues by petting the dog with cotton gloves. The field measurements have been completed and the samples have been chemically analyzed. The data are currently undergoing a quality assurance review and further analysis will follow.

<u>Reference:</u>

Morgan, M. K., Stout, D. M., II; Wilson, N. K., "Feasibility study of the potential for human exposure to pet-borne diazinon residues following lawn applications." *Bull. Environ. Contamin. Toxicol.* 66, 295-300. (2001)

6.1.7 Children's Dietary Lead Study

The concept of potentially significant excess exposure (above levels associated with the inherent levels on the foods themselves as a result of production and preparation) that is caused by how young children consume foods in contaminated environments had been confirmed in a study of children living in lead-laden homes (Melnyk et al., 2000). This study was conducted to measure potential dietary lead intakes of children 2 to 3 years of age who live in homes contaminated with environmental lead. Study objectives were to estimate lead intakes for children consuming food in contaminated environments, recognizing unstructured eating patterns and to investigate if correlations exist between daily dietary exposure and measured blood lead levels. Dietary exposure was evaluated by collecting samples that were typical of the foods the young children ate in their homes. A 24h duplicate of all foods plus sentinel foods, i.e., individual items used to represent foods contaminated during handling, were collected from 48 children. Ten homes were revisited to obtain information on the variation in daily dietary intakes. Drinking water was evaluated both as part of the segregated beverage sample composite and by itself. Additional information collected included lead concentrations from hand wipes, floor wipes, and venous blood; and questionnaire responses from the caregiver on activities potentially related to exposure. Activities and hygiene practices of the children and contamination of foods in their environment influence total dietary intake. Estimated mean dietary intakes of lead (29.2 μg Pb/day) were >3 times the measured 24-hr. duplicate-diet levels (8.37 μg Pb/day), which were almost six times higher than current national estimates (1.40 μg Pb/day). Statistically significant correlations were observed between floor wipes and foods contacting contaminated surfaces; hand wipes and foods contacting contaminated hands and surfaces; and hand wipes and floor wipes. This study indicated that the dietary pathway of exposure to lead is impacted by eating activities of children living in lead contaminated environments and that analysis of foods themselves was not enough to determine excess dietary exposures that occurred. The methods used in the lead study represented an initial attempt at quantifying dietary exposure of children, which included excess exposures from their activities and unstructured eating habits associated with surface contaminants. The study clearly demonstrated the potential importance of this phenomena and laid the foundation for developing refined methods to more accurately characterize and quantify dietary intake of pesticides by young children as required by FQPA.

<u>Reference:</u>

Melnyk, L.J., Berry, M.R., Sheldon, L.S., Freeman, N.C.G., Pellizzari, E.D., and Kinman, R.N. "Dietary Exposure of Children in Lead-Laden Environments," *Journal of Exposure Analysis and Environmental Epidemiology*, 2000, 10: 723-731.

6.1.8 Transfer Efficiencies of Pesticides from Household Surfaces to Foods

A young child's total dietary exposure includes both contaminants associated with the production and preparation of foods and the physical transfer of the contaminant from a contaminated surface to a food item during the act of ingestion. This transfer can occur through either direct contact between a food item and a contaminated surface (surface-to-food) or through an intermediate surface such as hands (surface-to-hand-to-food). The extent of food contamination for young children during an eating event is determined by both the transfer efficiency of the chemical from surfaces and the child's activity patterns. The amount or ratio of contaminant transferred resulting from physical contact, called the mass transfer efficiency, plays an important role in governing the extent of transfer to food per contact event. The child's activity patterns are defined by the frequency, duration, and associated physical factors of food-to-surface, hand-to-surface, and hand-to-food interactions and determines the extent of the net transfer resulting from multiple contact events. The transfer of pesticides from household surfaces to foods was measured to determine the degree of excess dietary exposure that occurs when children's foods contact contaminated surfaces prior to being eaten (Rohrer et al, 2003). Three common household surfaces (ceramic tile, hardwood flooring, and carpet) were contaminated with an aqueous emulsion of commercially available pesticides (diazinon, heptachlor, malathion, chlorpyrifos, isofenphos, cis and trans-permethrin) frequently found in residential environments. A surface wipe method, as typically used in residential studies, was used to measure the pesticides available on surfaces as a basis for calculating transfer efficiency to the foods. Three foods (apples, bologna, and cheese) routinely handled by children before eating were placed on the contaminated surfaces and transfers of pesticides were measured after 10 minute contact. Other contact durations (1 and 60 min) and applying additional contact force (1500g) to the foods were evaluated for their impact on transferred pesticides. More pesticides transferred to foods from the hard surfaces, i.e., ceramic tile and hardwood flooring, than carpet. Mean transfer efficiencies for all pesticides to the three foods ranged from 24 to 40% from ceramic tile, and 15 to 29% from hardwood, as compared to mostly non-detectable transfers for carpet. Contact duration and applied force notably increased pesticide transfer. The mean transfer efficiency for all seven pesticides increased from around 1% at 1 minute to 55 - 83% when contact duration was increased to 60 min for the three foods contacting hardwood flooring. Mean transfer efficiency for 10-min contact increased from 15% to 70% when a 1500 g force was applied to bologna placed on hardwood flooring. Contamination of food occurs from contact with pesticide-laden surfaces, thus increasing the potential for excess dietary exposure of children.

<u>Reference:</u>

Rohrer, C.A., Hieber, T., Melnyk, L.J., and Berry, M.R. "Transfer Efficiencies of Pesticides to Household Flooring Surfaces," *Journal of Exposure Analysis and Environmental Epidemiology*, 2003, 13: 454 - 464.

6.1.9 Dietary Intake of Young Children

A small-scale field study was designed to test the efficacy of NERL's Children's Dietary Intake Model (CDIM). The study was designed using a pharmakokinetic model to relate the important design factors to diazinon metabolites measured in urine (Hu et al., 2004). The study was designed to demonstrate that pesticide contamination in a home can contribute to excess dietary exposures of children. Environmental concentrations were measured in a 3-home study designed to evaluate a single pathway model from dietary intake of diazinon (Melnyk et al., submitted). Environmental samples were collected following routine application of diazinon to determine levels potentially available for food contamination. (**Note:** Diazinon was approved and commonly used for indoor pesticide applications at the time of the study, but has since been banned for residential use.) Indoor air concentrations ranged from 0.2 to 4.9 μg/m^3 with Home 1 having consistently higher levels that remained constant up to 8 days after application. Surface wipe concentrations from kitchen counters, floors, and play-mats ranged from 4 to10 ng/cm^2, whereas, press samples were below detectible levels (BDL) for most of the samples taken in the same areas. Homes 2 and 3 had higher surface wipe (3 to 85 ng/cm^2) and measurable press sample concentrations (4 to 24 ng/cm^2) from kitchen floors and counters. Soft surfaces were press sampled with variable concentrations ranging from BDL to18 ng/cm^2. Diazinon on children's hands were $<$0.2 ng/cm^2. Air and surface diazinon levels indicate exposure potential exists. Household surfaces are often contacted by foods that are handled, dropped, and then eaten by children. When diazinon is transferred to food, the residential-use pesticide becomes a dietary exposure issue requiring consideration in risk assessments for children.

References:
Hu, Y.A., Akland, G.G., Pellizzari, E.D., Berry, M.R., and Melnyk, L.J. "Use of Pharmacokinetic Modeling to Design Studies for Pathway-Specific Exposure Model Evaluation," *Environmental Health Perspectives*, 2004, 112(17): 1697-1703.

Melnyk, L.J., Whitaker, D., Akland, G.G., Hu, Y., Pellizzari, E.D., and Berry, M.R. "Diazinon Residues after Applications in Homes with Children," *Environmental Health Perspectives*, submitted.

6.2 Pilot scale studies to test and evaluate exposure protocols

6.2.1 Children's Pesticide Post-Application Exposure Studies (EOHSI and RTP)

Two pilot field studies were performed to assess children's potential exposures to pesticides resulting from the routine indoor application of residential pesticides. In both post-application studies, aggregate exposure measurements were made following a crack and crevice application by professional applicators. Objectives of these studies included the development of dermal transfer coefficients for young children engaged in specific activities, the evaluation of the macroactivity approach, and the evaluation of the methods and approaches needed to collect environmental, biological, personal, and activity pattern data in an integrated manner. In a collaborative study with researchers at the Environmental and Occupational Health Sciences Institute (EOSHI), aggregate exposure measurements were made at nine residences following a professional chlorpyrifos crack and crevice application (Hore, 2003; Hore et al., 2005). Measurements included indoor air, air exchange rates, surface residue wipes, dust wipes, toy wipes, dermal wipes (hands, knees, feet), activity diary, videotaping, cotton dosimeters, and urine. Chlorpyrifos levels in the indoor air and surfaces ranged from 2.2 to 816 ng/m^3 and 0.07 to 25 ng/cm^2, respectively, reaching peak levels between days 0-2 (Hore, 2003; Hore et al., 2005). Results of the study showed that pesticide loadings on the cotton dosimeters were related to exposure duration, surface loading, activity level and type of surface, suggesting that the macroactivity approach may be useful for estimating children's dermal exposure. Dermal chlorpyrifos hand loadings also related to the activity level of the children (Freeman et al., 2005).

The second post-application exposure study, conducted in four homes in and around Research Triangle Park (RTP), North Carolina, complemented the first study with similar objectives and methods. This study, however, addressed potential exposures following a residential crack and crevice application of the synthetic pyrethroid pesticide, cyfluthrin. The results showed that the methods and approaches needed to systematically collect environmental, biological, personal, and activity pattern data can be implemented by caregiver's of young children.

These studies provided key data describing pesticide distributions in microenvironments where children spend their time. Important pathways of exposure were evaluated. Data describing the transfer of pesticides from the microenvironmental media to the children and those key factors influencing these transfers were also identified.

References:

Freeman, NCG, Hore, P, Black, K, Jimenez, M, Sheldon, L, Tulve, N, Lioy, PJ., "Contributions of children's activities to pesticide hand loadings following residential pesticide application." *Journal of Exposure Analysis and Environmental Epidemiology.* 15:81-88 (2005)

Hore, P. May, 2003. Pesticide accumulation patterns for child accessible surfaces and objects and urinary metabolite excretion by children for two weeks after a professional crack and crevice application. Ph.D. Dissertation. Rutgers and the School of Public Health at the University of Medicine and Dentistry of New Jersey

Hore, P, Robson, M, Freeman, N, Zhang, J, Wartenberg, D, Ozkaynak, H, Tulve, N, Sheldon, L, Needham, L, Barr, D, Lioy, PJ., "Chlorpyrifos accumulation patterns for child-accessible surfaces and objects and urinary metabolite excretion by children for 2 weeks after crack-and-crevice application." *Environmental Health Perspectives.* 113(2):211-219 (2005)

6.2.2 Characterizing Children's Pesticide Exposures in Jacksonville, Florida

NERL scientists collaborated with scientists from the Centers for Disease Control and Prevention (CDC) and the Duval County Health Department (DCHD) on a study to characterize young children's (4 to 6 years) exposures to pesticides in residential environments in Jacksonville, FL in 2001. The goal of the study was to collect information on children's exposures to pesticides in Jacksonville in order to enhance the DCHD community outreach efforts regarding pesticide-related intervention and health education.

The study was comprised of three components:

- Biological monitoring: the CDC recruited approximately 200 children (walk-ins for routine immunizations and health care) at County health clinics; caregivers completed a questionnaire and a urine sample was collected from each participating child.
- Environmental screening assessment: the DCHD performed environmental screenings at the homes of approximately 25% of the enrolled children; the screening included surface wipe measurements, a pesticide inventory, and an additional urine sample.
- Environmental measurements: at a subset of nine homes, the EPA collected environmental samples (air, surface wipe, transferable residues), duplicate diet samples, questionnaire information, pesticide inventories, and activity pattern data to evaluate the methods and approaches for aggregate exposure assessments that could be applied in large observational studies.

The design for the study was jointly developed by DCHD, CDC, and EPA. CDC assumed the primary responsibility for coordination of the study and DCHD was responsible for implementation. The DCHD was responsible for identifying and contacting participating families, administering the questionnaire and consent form, compiling the completed forms, maintaining the confidentiality of participating families, providing copies of the questionnaire data to CDC for entry and analysis, collecting and shipping urine samples, and collecting and shipping environmental samples. NERL assisted DCHD in developing protocols and methods for the screening assessment and provided training on sample collection. NERL researchers conducted the nine home pilot study to evaluate exposure assessment protocols and methods.

Urine samples were analyzed for both the metabolites of organophosphate pesticides and pyrethroid pesticides. Environmental samples were analyzed for 21 organophosphate pesticides, 15 pyrethroid pesticides, piperonyl butoxide (a synergist), and fipronil using a single multi-residue analytical method.

Analyses of the data have been completed and draft manuscripts have been prepared for publication in the peer-reviewed scientific literature. Following completion of internal peer review, CDC will submit a manuscript on the biological monitoring in the fall of 2005. The EPA principal investigators also plan to submit the manuscript on the pilot study methods evaluation in the fall of 2005. Citations for these technical reports are not available as of this report date.

6.2.3 Exposures and Health of Farm Worker Children in California

A collaborative research effort was conducted between the University of California at Berkeley, NERL, and EPA's National Center for Exploratory Research (NCER) in support of the National Children's Study (NCS). The Center of Children's Environmental Health Research in association with the Center for Health Assessment of Mothers and Children of Salinas Study (CHAMACOS) conducted an aggregate exposure assessment for a sub-population of infants and toddlers potentially exposed to pesticides. The study involved measuring pesticide exposures of twenty children of farm workers in Salinas, CA, during the summer and fall of 2002. Ten children ages 5 to 11 months and ten children ages 21 to 27 months were monitored. Measurements were conducted for the relevant exposure sources and exposure routes to obtain aggregate exposure assessments for the children in each age group. The following types of samples were collected and analyzed in an attempt to identify potential exposure routes.

- Indoor and outdoor air samples to estimate inhalation potential,
- House dust to estimate amounts available for dermal adsorption and indirect ingestion,
- Transferable residues (wipes) from floors and toys to estimate amounts available for dermal adsorption and indirect ingestion,
- Cotton union suits and socks to estimate dermal exposures,
- Duplicate diet foods, water if from untreated source, and breast milk (when possible) to estimate direct ingestion, and
- Urine for metabolite measurements to estimate the total exposure.

Additional information was collected using activity diaries, videotaping, and questionnaires. For several participants, exposure measurements of transferable residues were conducted concurrently with videotaping to quantify exposure associated with the recorded activities. The resulting data will be used to identify the most important pathways, evaluate factors and algorithms for estimating exposures, and develop simple approaches and protocols for assessing exposure as part of the National Children's Study. The goal of this research is to understand the importance of each route and pathway, in order to classify children's aggregate exposure to pesticides by a few simple measurements and/or exposure questions. Results will also be used to evaluate multimedia exposure models for children, another important tool for classifying aggregate exposures.

Results of this study indicated that pesticides were detected more frequently in house dust, surface wipes, and clothing (union suits and socks) compared to other media. Chlorpyrifos, diazinon , dacthal and *cis*- and *trans*-permethrin were detected in 90 -100% of these samples. Concentrations on socks and union suits were higher for the toddlers compared to crawling children. Several OP pesticides as well as 4-4'-DDE, atrazine, and dieldrin were detected in food samples and a novel, low-literacy activity timeline survey instrument based on pictures was successful for obtaining activity information for participants. A manuscript has been prepared and is in the final stages of review prior to submission for publication.

Reference:

Bradman, A. ; Whitaker,D.; Quirós, L.; Castorina, R.; Claus-Henn, B.; Nishioka, M.; Morgan, J.; Barr, D.; Harly, M.; Brisbin, J.; Kauffman, P.; Sheldon, L.; McKone, T.; and Eskenazi, B., "Quantitative Pesticide Exposure Assessment of Farmworker Children in the Salinas Valley, CA" Draft manuscript to be submitted for publication. Anticipated submission October 2005.

6.3 Conduct of exposure and occurrence field measurement studies

6.3.1 National Human Exposure Assessment Survey (NHEXAS)

NHEXAS was a series of three field studies implemented in the mid-to-late 1990s designed to evaluate methods and protocols for measuring the general population's (including children's) exposures to pesticides and other environmental contaminants exposure. The overall objectives of the NHEXAS pilot studies were to 1) test the methodologies and ensure they produced the data needed to assess exposures, and 2) to evaluate the feasibility for conducting a truly national survey. The NHEXAS studies considered multiple-pathway exposures to several different classes of high risk pollutants including volatile organic compounds, metals, and pesticides. Environmental, biological and survey questionnaire data were collected for the more than 500 individuals who participated in these three studies. Individual study designs were developed based on the general NHEXAS scientific hypotheses and implemented in the three locations across the US (EPA Region 5, Arizona, and Baltimore, MD). The NHEXAS Region 5 study included a sub-study (the Minnesota Children's Pesticide Exposure Study (MNCPES)) focused on assessing exposures to children. The study obtained pesticide exposure data (chlorpyrifos, diazinon, malathion, and atrazine) for about 100 children (ages 3-13), including measurements of personal exposure (air, hand rinse, duplicate diet), activity patterns (questionnaire, diary, and videotaping), environmental concentrations (indoor and outdoor air, surface residues, drinking water, soil), and metabolites in urine (Quackenboss et al., 2000; Adgate et al., 2001). The Arizona NHEXAS study also included multi-media measurements of pesticides in households with children (Robertson et al., 1999). Whereas the Region 5 and Arizona NHEXAS protocols were cross-sectional in nature, the Baltimore NHEXAS study was designed to investigate approaches for investigating longitudinal exposures with measurements repeated up to six times during a year long period. The results of the NHEXAS studies have been reported through a variety of NERL Annual Performance Measures (2001 APM 148, 2002 APM 31, 2003 APM 29) and a variety of peer reviewed publications. The validated NHEXAS data is electronically available at http://www.epa.gov/heds/.

In general, the NHEXAS studies provided data describing the occurrence, distributions, and determinants of total exposure to the general population for selected environmental contaminants; geographic trends in multimedia exposure; and total exposures in selected minority and disadvantaged subsets of the population. Specific findings include:

- Pesticides were more frequently detected in food samples during the spring and summer months (Baltimore)
- Dermal contact and pesticide usage activities reported for a single day or short term may not accurately reflect longer term activities and not be sufficient to estimate or classify long-term (chronic) exposures (Baltimore)
- Comparisons with measured dietary intakes, suggest the food consumption-chemical residue model can reasonably estimate population distribution of dietary chlorpyrifos intake, but has little ability to predict dietary exposure for individuals; the intake of chlorpyrifos from food was a minor contributor to its metabolite concentration measured in urine. (Baltimore)
- Gender, age group, and racial/ethnic group were related to the frequency of contact with soil, grass, and carpeting (Baltimore)
- For adults, exposure from inhalation of indoor air accounted for the majority of aggregate daily exposure to chlorpyrifos (Baltimore)
- Pesticide exposures were greater for those living in households with more carpeting, preparing or using pesticides in their homes or having higher household incomes (All studies)
- Food items ranked by their contribution to dietary chlorpyrifos exposure (Region V)
- The major metabolite of chlorpyrifos was present in 98% of the participating children's urine samples (MNCPES)
- Urban children urine levels were higher than non-urban levels, and nearly twice the measured values for adults in previous studies (MNCPES)
- For children, intakes for all of the four primary pesticides appeared to come principally from the ingestion rather than the inhalation route (MNCPES)
- Despite the importance of the ingestion route for total intake, the urinary metabolite of chlorpyrifos exhibited a stronger correlation with the air measurements than with the dietary measures. This may be due to the short half-life of chlorpyrifos in the body and the different time periods represented by the exposure measurements. (MNCPES)
- Personal air samples were highly correlated with indoor air samples for chlorpyrifos, malathion, and diazinon (MNCPES)
- Indoor air chlorpyrifos and diazinon exposure represents about 25% of the total exposure to these pesticides (Arizona)
- The highest 10% of pesticide exposures related to questions about pesticide usage, at home and at work (Arizona)

References

Arizona Study

Buck, R.J., Ozkaynak, A.H., Xue, J., Zartarian, V., and Hammerstrom, K., "Modeled estimates of chlorpyrifos exposure and dose for the Minnesota and Arizona NHEXAS populations." *Journal of Exposure Analysis and Environmental Epidemiology* 11 (3):253-268 (2001). EPA/600/J-02/228.

Gordon SM, Callahan PJ, Nishioka MG, Brinkman MC, O'Rourke MK, Lebowitz MD, Mosschandreas DM. Residential environmental measurements in the National Human Exposure Assessment Survey (NHEXAS) pilot study in Arizona: Preliminary results for pesticides and VOCs. *J Expo Anal Environ Epidemiol.* 1999; 9(5): 456-470.

Lebowitz MD, O'Rourke MK, Rogan S, Reses J, Van De Water PL, Blackwell A, Moschandreas DJ, Gordon S, Robertson G. Indoor and outdoor PM10 and associated metals and pesticides in Arizona. *Inhalation Toxicol.* 2000; 12 (Suppl 1): 139-144.

Moschandreas DJ, Karuchit S, Kim Y, Ari H, Lebowitz MD, O' Rourke MK, Gordon S, Robertson G. On predicting multi-route and multimedia residential exposure to chlorpyrifos and diazinon. *J Expo Anal Environ Epidemiol*. 2001; 11(1):56-65.

Moschandreas DJ, Kimm Y, Karuchit S, Ari H, Lebowitz MD, O'Rourke MK, Gordon S, Robertson G. In-residence, multiple route exposures to chlorpyrifos and diazinon estimated by indirect method models. *Atmospheric Environment* 2001; 35:2201-2213.

Moschandreas DJ, Karuchit S, Berry MR, O'Rourke MK, Lo D, Lebowitz MD, Robertson G. Exposure apportionment: Ranking food items by their contribution to dietary exposure. *J Expo Anal Environ Epidemiol.* 2002; 12(4): 233-243.

Robertson GL, Lebowitz MD, O'Rourke MK, Gordon S, and Moschandreas D.,"National Human Exposure Assessment Survey (NHEXAS) study in Arizona-introduction and preliminary results," *J Expo Anal Environ Epidemiol.* 9(5):427-434. (1999)

<u>Maryland Study</u>
MacIntosh DL, Spengler JD, Ozkaynak H, Tsai L, Ryan PB. Dietary exposures to selected metals and pesticides. *Environ Health Perspect.* 1996; 104(2):202-9.

MacIntosh DL, Needham LL, Hammerstrom KA, Ryan PB. A longitudinal investigation of selected pesticide metabolites in urine. *J Expo Anal Environ Epidemiol*. 1999; 9(5): 494-501.

MacIntosh DL, Hammerstrom KA, Ryan PB. Longitudinal exposure to selected pesticides in drinking water. *Human and Ecological Risk Assessment* 1999; 5(3):575-588.

MacIntosh DL, Kabiru CW, Ryan PB. Longitudinal investigation of dietary exposure to selected pesticides. *Environ Health Perspect* 2001; 109(2):145-50.

MacIntosh DL, Kabiru C, Echols SL, Ryan PB. Dietary exposure to chlorpyrifos and levels of 3,5,6-trichloro-2-pyridinol in urine. *J Expo Anal Environ Epidemiol*. 2001; 11(4):279-85.

Echols SL, Macintosh DL, Ryan PB. Temporal patterns of activities potentially related to pesticide exposure. *J Expo Anal Environ Epidemiol*. 2001; 11(5):389-97.

Pang Y, MacIntosh DL, Camann DE, Ryan PB. Analysis of Aggregate Exposure to Chlorpyrifos in the NHEXAS-Maryland investigation. *Environ Health Perspect*. 2002; 110(3):235–240.

Egeghy PP, Quackenboss JJ, Catlin S, Ryan PB. Determinants of temporal variability in NHEXAS-Maryland environmental concentrations, exposures, and biomarkers. *J Expo Anal Environ Epidemiol.* 2004; 15(5):388– 397.

Minnesota Children's Pesticide Exposure Study (Region V Study)

Reed KJ, Jimenez M, Freeman NCG, Lioy P J. Quantification of children's hand and mouthing activities through a videotaping methodology. *J Expo Anal Environ Epidemiol*. 1999; 9(5): 513-520.

Quackenboss JJ, Pellizzari ED, Shubat P, Whitmore RW, Adgate JL, Thomas KW, Freeman CG, Stroebel C, Lioy PJ, Clayton AC, Sexton K. Design strategy for assessing multi-pathway exposure for children: the Minnesota Children's Pesticide Exposure Study (MNCPES). *J Expos Anal Environ Epi*. 2000;10:145-158

Adgate JL, Kukowski A, Stroebel C, Shubat PJ, Morrell S, Quackenboss JJ, Whitmore RW, Sexton K. Pesticide storage and use patterns in Minnesota households with children. *J Expo Anal Environ Epidemiol*. 2000; 10(2):159-67.

Adgate JL, Clayton CA, Quackenboss JJ, Thomas KW, Whitmore RW, Pellizzari ED, Lioy PJ, Shubat P, Stroebel C, Freeman NC, Sexton K. Measurement of multi-pollutant and multi-pathway exposures in a probability-based sample of children: practical strategies for effective field studies. *J Expo Anal Environ Epidemiol*. 2000; 10:650-61.

Rigas ML, Okino MS, Quackenboss JJ. Use of a pharmacokinetic model to assess chlorpyrifos exposure and dose in children, based on urinary biomarker measurements. *Toxicol Sci*. 2001; 61:374-381.

Adgate JL, Barr DB, Clayton CA, Eberly LE, Freeman NCG, Lioy PJ, Needham LL, Pellizzari ED, Quackenboss JJ, Roy A, Sexton K. Measurement of children's exposure to pesticides: analysis of urinary metabolite levels in a probability-based sample. *Environ Health Perspect*. 2001; 109:583-590.

Freeman NCG, Jiminez M, Reed KJ, Gurunthan S, Edwards RD, Roy A, Adgate JL, Pellizzari ED, Quackenboss JJ, Sexton K, Lioy PJ. Quantitative analysis of children's microactivity patterns: The Minnesota Children's Pesticide Exposure Study. *J Expo Anal Environ Epidemiol*. 2001; 11(6):501-509.

Clayton C, Pellizzari E, Whitmore RW, Quackenboss JJ. Distributions, associations, and partial aggregate exposure of pesticides and polynuclear aromatic hydrocarbons in the Minnesota Children's Pesticide Exposure Study (MNCPES). *J Expo Anal Environ Epidemiol*. 2003; 13(2):100-111.

Pellizzari ED, Smith DJ, Clayton CA, Quackenboss JJ. Assessment of data quality for the NHEXAS - Part II: Minnesota children's pesticide exposure study (MNCPES). *J Expo Anal Environ Epidemiol*. 2003; 13(6), 465–479.

Clayton CA, Mosquin PL, Pellizzari ED, Quackenboss JJ. Limitations on the Uses of Multimedia Exposure Measurements for Multipathway Exposure Assessment–Part I: Handling Observations Below Detection Limits. *Quality Assurance*, 10(3-4):123-59, 2004.

Clayton CA, Michael L, Pellizzari ED, Quackenboss JJ. Limitations on the Uses of Multimedia Exposure Measurements for Multipathway Exposure Assessment–Part II: Effects of Missing Data and Imprecision. *Quality Assurance*, 10(3-4):161-75, 2004.

6.3.2 Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP)

The CTEPP study (Morgan et al. 2004; Wilson et al., 2004) is the largest children's exposure study undertaken to date. It examines the aggregate exposures of 257 preschool children, ages 18 months to 5 years, to environmental chemicals commonly found in their everyday environments. The major objectives of this three-year pilot study were to quantify the children's aggregate exposures, apportion the exposure routes, and identify the important exposure media. Participants were recruited randomly from selected homes and daycare centers in six North Carolina and six Ohio counties. Monitoring was performed over a 48-h period at the children's homes and/or daycare centers. Samples collected included soil, dust, air, diet, dermal wipes, surface wipes, and urine. The samples were analyzed for over 50 pollutants from such chemical classes as pesticides, polycyclic aromatic hydrocarbons, phthalates, phenols, and polychlorinated biphenols.

The CTEPP study has been completed, and it has provided important data on the exposures of preschool children to chemicals commonly found in their daily environments. Results of the CTEPP study indicate that low levels of many chemicals were found in both homes and day care centers. Chemicals found at these locations include pesticides, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), phthalates, and phenols. The most frequently detected chemicals were those that are commonly used in the home, products found in the home, or from common processes such as combustion. Many of the chemicals were detected in air, dust, solid food, and/or on hand wipes. Analysis of the urine samples indicated that several of the chemicals studied were absorbed into the bodies of the children and adult caregivers. For the children, food was the dominant route of exposure to the most frequently detected chemicals. In particular, dietary intake accounted for >50% of the children's pesticide exposures to chlorpyrifos, diazinon, *cis*-permethrin, *trans*-permethrin, and 2,4-D in both states.

CTEPP was one of the first exposure studies to analyze dietary samples and other environmental media (i.e., air, carpet dust, and surface wipes) for two OP pesticide metabolites that are urinary biomarkers of exposure in humans. For the OP insecticides, chlorpyrifos and diazinon, their specific urinary biomarkers of exposure are 3,5,6-trichloro-2-pyridinol [TCP] and 2-isopropyl-6-methyl-4-pyrimidinol [IMP], respectively. TCP and IMP were measurable in several environmental media including food, air, dust and wipes at both the homes and daycare centers in both states. An interesting finding was that median TCP concentrations were 12 and 29 times higher than chlorpyrifos concentrations measured in the solid food samples collected at the NC homes and day care centers, respectively (Morgan et al., 2005). Therefore, the study results suggested that some of the TCP found in the CTEPP subject urine samples may have come from dietary TCP rather than from the metabolism of chlorpyrifos. From this observation we learned that when trying to compare urinary metabolite concentrations to exposure measurements, it is necessary to consider exposure to the metabolite as well as exposure to the parent chemical.

The CTEPP exposure data and associated study information are anticipated to be publicly available on the Human Exposure Database System (http://www.epa.gov/heds/) by summer 2006.

References:

Chuang, J.C., Wilson, N.K., Morgan, M.K., Lordo, R.A., Chou, Y.L., and Sheldon, L.S., "Polycyclic Aromatic Hydrocarbon Exposure of 257 Preschool Children." *(in preparation, scheduled for 2006)*

Morgan**,** M.K., L.S. Sheldon, C.W. Croghan, J.C. Chuang, R.A. Lordo, N.K. Wilson, C. Lyu, M. Brinkman, N. Morse, Y.L. Chou, C. Hamilton, J.K. Finegold, K. Hand, and S.M. Gordon., "A pilot study of children's total exposure to persistent pesticides and other persistent organic pollutants (CTEPP)." EPA/600/R-041/193 (2004)

Morgan**,** M.K., Sheldon, L.S, Croghan, C.W., Jones, P.A., Robertson, G.L., Chuang, J.C., Wilson, N.K., and Lyu, C.W., "Exposures of preschool children to chlorpyrifos and its degradation product 3,5,6-trichloro-2-pyridinol in their everyday environments." *Journal of Exposure Analysis and Environmental Epidemiology* 15: 297−309 (2005)

Morgan, M.K., Sheldon, L.S., Croghan, C.W., Jones, P.A. Chuang, J.C., and Wilson, N.K., "Exposures of preschool children to *cis*- and *trans*-permethrin at their homes and daycare centers in North Carolina and Ohio." *Environmental Health Perspectives (submitted 9/05).*

Morgan, M.K., Sheldon, L.S., Croghan, C.W., Jones, P.A. Chuang, J.C., and Wilson, N.K., "Exposures of young children to 2,4-dichlorophenoxyacetic acid at their homes and daycare centers in North Carolina and Ohio." *(in preparation, scheduled for 2007)*

Wilson NK, Chuang JC, Lyu C., « Levels of persistent organic pollutants in several child day care centers." *J Expo Anal Environ Epidemiol.* 11(6):449-58. 2001

Wilson NK, Chuang JC, Lyu C, Menton R, Morgan MK., "Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home." *J Expo Anal Environ Epidemiol.* 13(3):187-202. (2003)

Wilson NK, Chuang JC, Iachan R, Lyu C, Gordon SM, Morgan MK, Ozkaynak H, Sheldon LS., "Design and sampling methodology for a large study of preschool children's aggregate exposures to persistent organic pollutants in their everyday environments." *J Expo Anal Environ Epidemiol.* 14(3):260-74. (2004)

Wilson, N.K., Chuang, J.C., Lordo, R.A., Morgan, M.K., and Sheldon, L.S., "Exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare." *(in preparation, scheduled for 2006)*

6.3.3 First National Environmental Health Survey of Child Care Centers

EPA, in collaboration with the US Department of Housing and Urban Development and the US Consumer Product Safety Commission, characterized young children's potential exposures to pesticides, lead, and allergens in a randomly-selected nationally representative sample of licensed institutional child care centers. Multi-stage sampling with clustering was used to select 168 child care centers in 30 primary sampling units across the US. Child care centers were recruited into the study by telephone interviewers. Samples for pesticides, lead, and allergens were collected at multiple locations in each child care center by field technicians. Wipe samples from indoor surfaces (floors, tabletops, desks, etc.) and soil samples were collected at the child care centers. A wide variety of pesticides were detected in the environmental measurements with chlorpyrifos (0.004-28 ng/cm^2 of surface; 4-1154 ng/g of soil), diazinon (0.002-18 ng/cm^2 of surface; 1-110000 ng/g of soil), and *cis*- (0.004-90 ng/cm^2 of surface; 4-128 ng/g soil) and *trans*- (0.004-219 ng/cm^2 of surface; 4-136 ng/g of soil) permethrin detected in >54% of the child care centers. Based on the questionnaire responses, pyrethroids were the most commonly used pesticides among child care centers applying pesticides. Furthermore, among the 63% of centers reporting pesticide applications, the number of pesticides in each center ranged from 1 to 10 and the frequency of use ranged from 1 to 107 times annually. By participating in this study, the EPA gained a better understanding of pesticide use practices in the nation's child care facilities and an understanding of the potential exposures of young children (less than 6 years of age) to pesticide residues in child care facilities.

References:

Rogers, J, Zhou, JY, Tulve, NS, Viet, SM, Marker, D, Fraser, A, Jones, PA, Croghan, CW, Jacobs, D, Cave, CJ, Friedman, W. Lead, allergens, and pesticide use results in child care centers in the United States. (*In preparation, anticipated submission Dec 05*).

Tulve, NS, Jones, PA, Fortmann, RC, Croghan, CW, Zhou, JY, Friedman, W, Fraser, A, Cave, C, Nishioka, M., "Pesticide measurement results from the first national environmental health survey of child care centers." (*In preparation, anticipated submission Nov 05*).

6.3.4 Agricultural Health Study Pesticide Exposure Study

The Agricultural Health Study is a collaborative effort between the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (U.S. EPA). This prospective epidemiological study was designed to address the limitations observed in previous epidemiological studies of farm applicators. It was also designed to quantify the cancer and non-cancer risks in the agricultural community and to study the relationship between agricultural pesticide exposures and disease. The larger AHS study uses questionnaires to provide information regarding pesticide use, work practices, and other agricultural exposures, as well as information on other activities that may affect either exposure or risk for a large (more than 89,000) cohort of licensed agricultural pesticide applicators and their spouses in Iowa and North Carolina. In support of the larger AHS objectives, NERL planned and conducted the AHS Pesticide Exposure Study (PES) to assess the exposure-classification procedures developed from the AHS questionnaire data and to better understand factors leading to pesticide exposures for agricultural pesticide applicators and their families. The AHS PES was an exposure-measurement field study for a relatively small subset of agricultural pesticide applicators (~100 farm applicators) and, where they volunteered, participating family members in the larger AHS cohort. The study was designed to provide real-world exposure data for improving exposure and risk assessments for agricultural pesticide applicators and their families by:

- Improving survey questionnaires and the exposure-classification procedures based on data from the questionnaires;
- Increasing the power of the AHS epidemiological study through improved exposure assessments;
- Assessing critical exposure pathways and factors influencing applicator exposures to agricultural pesticides;
- Assessing how exposures for families of agricultural pesticide applicators compare to exposures for the general population.

The research results will be used to improve health-risk assessments in the larger AHS epidemiological study. The results may also provide information on how pesticides can be handled more safely to reduce the exposure risks to farm-workers and their families. Study findings will be used by pesticide-safety educators to improve training programs for agricultural pesticide applicators and other pesticide handlers. Data analyses are near completion and science journal articles describing results for farm pesticide applicators and farm family members are in preparation for journal submission in late 2005.

References:

Jones, M., Thomas, K., Gordon, S., Reynolds, S., Nishioka, M., Raymer, J., Helburn, R., Lynch, C., Knott, C., Sandler, S., Dosemeci, M., and Alavanja, M. "Summary of biological and environmental monitoring results from the agricultural health study/pesticide exposure study." 5th International Symposium of Rural Peoples, Saskatoon, Saskatchewan, Canada October 19-23, 2003.

Sheldon, L., Thomas, K., Chapa, G., Gordon, S., Jones, M., Raymer, J., Sandler, D., Hopping, J., Dosemeci, M., Blair, A., and Alavanja, M.. "Results from the Agricultural Health Study - Pesticide Exposure Study." North American Pesticide Applicator and Certification and Safety Education Workshop in Madison, WI, August 18, 2005.

Thomas, K.W., Sheldon, L.S., Sandler, D.P., Dosemeci,M., and Alavanja, M.C.R. "Agricultural Health Study/Pesticide Exposure Study: Study Design and Preliminary Biomarker Results." International Symposium on Agricultural Exposures and Cancer, Oxford, U.K., November 17 - 22, 2002.

6.3.5 American Healthy Homes Survey

In June 2005, NERL, in collaboration with the US Department of Housing and Urban Development (HUD), initiated a survey of US residences (public and private) designed to examine key physical parameters related to the US residential housing stock and the spatial and temporal concentrations of selected environmental pollutants within these residences. Approximately 1100 residences will be randomly selected out of the total population of US residences. Each residence will be visited one time for the collection of various questionnaire and environmental samples. Indoor floor surface wipe samples will be collected in each residence and analyzed for the identical suite of pesticides and other persistent pollutants reported in the CTEPP study. An inventory of household pesticides will also be collected. Soil samples collected in the yard and near wood structures will be analyzed for lead and arsenic. Indoor dust samples will also be analyzed for lead and arsenic. Where available, the homeowners' vacuum cleaner bags will be collected and the vacuumed dust analyzed for targeted mold species by via an innovative PCR technique developed by NERL researchers (Vesper et al.,). The dust in the homeowner vacuum cleaner bags will also be analyzed for other persistent pollutants. The PCR results will be compared to the HUD reported mold concentrations from indoor residential dust samples analyzed via traditional culturing techniques. The study results will provide EPA with high quality occurrence data describing pesticide use and occurrence data across the US for a single point in time. The study results will also provide EPA with an understanding of the range of concentrations for other important environmental pollutants found in US residences by region. The data collected in this study will be used to develop new distributions of exposure and risk, and to examine changes in the occurrence and magnitude of these exposures and risks over time, where baseline data is available. The sample collection is scheduled to be completed in January 2006 with the initial reports planned for June-August 2006. Numerous EPA peer reviewed publications are anticipated from the study results with many providing the Agency with distributions of pesticides and other pollutants in US residences.

References:

U.S. Department of Housing and Urban Development (HUD), Draft Protocol and Sample Design Report: American Healthy Homes Survey, Washington, D.C. 20410, December 2003

Meklin, T., Haugland, R.A., Reponen, T., Varma, M., Lummus, Z., Bernstein, D., Wymer, L. J. Vesper, S. J. Quantititive PCR analysis of house dust can reveal abnormal mold conditions. Journal of Environmental Monitoring. 6:615-620. (2004)

6.3.6 Children's Environmental Exposure Research Study

The Children's Environmental Exposure Research Study (CHEERS), formally titled the "Longitudinal Study of Young Children's Exposures in Their Homes to Selected Pesticides, Phthalates, Brominated Flame Retardants, and Perfluorinated Chemicals," was designed, based on the Draft Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways (EPA, 2001), as a two-year longitudinal field measurement study of very young children's (aged 0 to 3 years) potential exposures to environmental contaminants routinely found in US residences. Very little data is currently available that describes residential exposures or the key factors influencing residential exposures for children of this age group. CHEERS was an observational field monitoring study designed to fill these critical data gaps. The targeted list of study analytes included current-use pesticides and selected phthalates, polybrominated diphenyl ethers, and perfluorinated compounds, compounds reportedly measured in residential environments by many researchers throughout the international scientific community. Environmental, biological, personal, activity pattern, and questionnaire data were to be collected for up to six data collection events for the same participating families over the two-year study period. The study was to be conducted in Duval County, Jacksonville, Florida. Jacksonville was selected as the study location for a variety of reasons: 1) the earlier NOPES data suggested Jacksonville residential pesticide levels may be relatively high compared to other selected locations; 2) available pesticide use data suggested that environmental sample levels would be above the calculated detection limit for the proposed sampling media; and 3) past collaborative research relationships with Duval County Health Department. Sixty very young children were to be recruited into this study into two approximately equal cohorts: 1) children who were less than 3 months of age at the time of enrollment, and 2) children who were approximately 12 months of age at the time of enrollment. The data collection events at the participant households were to correspond to changes in the participant child's age, corresponding with the EPA's Risk Assessment Forum (RAF) proposed developmental age bins: 3, 6, 9, 12, 18, 24, 30, and 36 months. Each data collection event was to last for five days, during which visits were to be made on a daily basis to collect samples. The study data, along with other exposure research data, would be used to evaluate the draft RAF age bins. The field study was cancelled for perceived ethical issues. Nonetheless, numerous standard operating procedures, methods, and protocols were developed in support of this study (see Methods and Protocols section above) and that these science documents are readily available for exposure assessment researchers to assist them in the design and conduct of all aspects of an aggregate exposure study.

6.4 Data Analysis Activities to Inform Future Research

NERL has initiated several activities to analyze the results from multiple studies. Summaries of these activities are provided below:

6.4.1 Analysis of available children's mouthing data

Young children may be more likely than adults to be exposed to pesticides following a residential application as a result of hand- and object-to-mouth contacts in contaminated areas. However, relatively few studies have specifically evaluated mouthing behavior in children less than 5 years of age. Previously unpublished data collected by the Fred Hutchinson Cancer Research Center (FHCRC) were analyzed to assess the mouthing behavior of 72 children (37 males/35 females). Total mouthing behavior data included the daily frequency of both mouth and tongue contacts with hands, other body parts, surfaces, natural objects, and toys. Eating events were excluded. Children ranged in age from 11 to 60 months. Observations for more than 1 day were available for 78% of the children. The total data set was disaggregated by gender into five age groups (10-20, 20-30, 30-40, 40-50, 50-60 months). Statistical analyses of the data were then undertaken to determine if significant differences existed among the age/gender subgroups in the sample. A mixed effects linear model was used to test the associations among age, gender, and mouthing frequencies. Subjects were treated as random and independent, and intrasubject variability was accounted for with an autocorrelation function. Results indicated that there was no association between mouthing frequency and gender. However, a clear relationship was observed between mouthing frequency and age. Using a tree analysis, two distinct groups could be identified: children ≤24 and children >24 months of age. Children ≤24 months exhibited the highest frequency of mouthing behavior with 81±7 events/h (mean±SE) (n=28 subjects, 69 observations). Children >24 months exhibited the lowest frequency of mouthing behavior with 42±4 events/h (n=44 subjects, 117 observations). These results suggest that children are less likely to place objects into their mouths as they age. These changes in mouthing behavior as a child ages should be accounted for when assessing aggregate exposure to pesticides in the residential environment.

Reference:

Tulve, NS, Suggs, JC, McCurdy, T, Cohen Hubal, EA, Moya J., "Frequency of mouthing behavior in young children." *Journal of Exposure Analysis and Environmental Epidemiology*. 12:259-264. (2002)

6.4.2 A Relative Comparison of Indoor Air Concentrations of Organochlorine, Organophosphate and Pyrethroid Pesticides in the US Over Twenty Years

Pesticides used to control indoor pests have transitioned across the chemicals classes of organochlorine, organophosphate, and pyrethroid compounds from the 1980's to the present. Research was performed to summarize and compare the pesticide concentrations measured from the indoor air of homes from four studies sponsored by the US EPA. The studies included are the Non-Occupational Exposure Study (NOPES) (EPA 1990, Whitmore et al., 1994), the National Human Exposure Assessment Survey (NHEXAS-Maryland) (Macintosh et al, 2000), the Minnesota Children's Pesticide Exposure Study (MNCPES) (Clayton et al., 2003), and the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) (Morgan et al., 2004) study and were conducted during the periods of 1988-89, 1995-96, 1997 and 2000-01, respectively. In general, the detection frequencies for DDT, DDE, chlorpyrifos, diazinon, and permethrin increased from 1988 to 2001, due to increased method sensitivity. Pesticides were commonly measured from residential air in all studies. Mean airborne concentrations show highly variable heptachlor levels, while chlordane appears to have declined from 1988 levels. DDT and DDE were present at measurable concentrations from indoor air. The concentrations were remarkably similar and exhibited only slight variation across all studies. All organophosphate concentrations were lower than those measured in the NOPES-FL. Permethrin concentrations were variable and none was measured in NOPES-MA. Results demonstrate the high degree of variability across studies associated with indoor air concentrations measured from homes. Overall, the findings suggest decreasing concentrations for some pesticides over time. Finally, the use of standardized techniques has strengthened the comparability of airborne concentrations between studies, but comparability could be significantly improved by collecting additional airborne measures in the same cities or states as these studies.

References:

USEPA. (1990) Final Report: EPA/600/3-90-003.

Whitmore R. W., Immerman F.W., Camann D. E., Bond A. E., Lewis R. G., Schaum J.L. (1994) Arch. Environ. Contamin. Toxicol. 26: 47-49.

Macintosh D. L., Kabiru C., Scanlon K. A., Ryan P. B. (2000) J. Exp. Anal. Environ. Epidemiol. 10: 1053-4245.

Clayton C. A., Pellizzari E. D., Whitmore R. W., Quackenboss J. J., Adgate J., Sexton K. (2003) J. Exp. Anal. Environ. Epidemiol. 13: 100-111.

Morgan M. K., Sheldon L. S., Croghan C. W. (2004) Report: EPA/600/R-04/193.

6.4.3 The Results for EPA's Workshop on the Analysis of Children's Measurement Data

An integral component to any research program is the analysis of the results in light of the study objectives and the genesis of new research hypotheses. While researchers attempt to use the data from other studies in their analyses and interpretation, the ability to examine data across studies is hampered by the difficulty in obtaining all the validated data for those studies. The objective of this research activity was to examine the results of all the NERL studies to identify trends, major findings, and identify future research needs.

NERL sponsored a workshop on September 27-28, 2005, to:

- review the results of the NERL-sponsored children's pesticide exposure studies that had been conducted since the implementation of FQPA
- propose analyses of these study data, along with other study data that could be made available by the scientific community, to examine the results from across studies
- identify where sufficient research has been performed to reduce uncertainty in a selected are and where are the future research needs

Exposure researchers from within and outside EPA were invited to participate in this workshop and assist NERL in accomplishing the objectives.

A draft report "Summary and Comparisons of Data Collected in NERL's Children's Pesticide Exposure Studies" (Egeghy et al., 2005) was developed to promote the workshop discussions. The final workshop report is scheduled for early 2006 and will include a variety of data analysis activities that will ultimately result in peer reviewed scientific publications. In the interim, the draft report provides new insights for risk assessors resulting from each individual NERL-sponsored studies. It also provides risk assessors with a clearer understanding of the quality and quantity of the available children's exposure data, the key factors influencing children's exposures to pesticides, and the remaining critical gaps.

<u>Reference:</u>

Egeghy, P.,Croghan, C., Fortmann, R., Jones, P., Melnyk, L., Morgan, M., Sheldon, L., Stout, D., Tulve, N., and Whitaker, D. "Summary and Comparisons of Data Collected in NERL Children's Pesticide Exposure Studies," NERL/EPA Report September 2005.

7. EXPOSURE AND DOSE MODELING RESEARCH

Computational models, both exposure and dose, along with their supporting databases, comprise the third major category of exposure research products NERL has produced to support children's pesticide-exposure assessments. Exposure models simulate human exposure or contact with environmental media that contain the chemical(s) of interest, and the transfer of these chemicals to the person. Dose models simulate the absorption of chemicals into the exposed human and describe the adsorption, distribution, metabolism and elimination (ADME) of the target compound or its metabolite. Over the past 10 plus years, NERL's exposure and dose modeling research has focused on developing and refining appropriate algorithms and modeling modules, and linking these model capabilities to address real-world FQPA issues. In addition, modeling approaches have been used to assist NERL researchers in developing and testing hypotheses, identifying areas of greatest uncertainty, and developing future research study designs.

7.1 Exposure Modeling Research

NERL's principal exposure model for simulating children's aggregate exposure to pesticides is the Stochastic Human Exposure and Dose Simulation (SHEDS) model. SHEDS uses human activity pattern data from the NERL-developed database the Consolidated Human Activity Database (CHAD), discussed later in the Database section. Although the data in CHAD are not limited to the activities of children nor to residential pesticide-related activities, the data in CHAD include those of children in residences. CHAD is an important resource for conducting children's pesticide exposure assessments. CHAD and documentation about it are available from EPA's Internet site at http://www.epa.gov/chadnet1/

The initial development and application of the SHEDS model (see framework section), was for the assessment of children's residential exposure to chlorpyrifos via the dermal and non-dietary ingestion exposure pathways (Zartarian et al. 2000). This initial application of SHEDS provided variability distributions for modeled exposure and dose within the simulated sub-population for different post-application time periods.

The second generation SHEDS-Pesticides model is a 2-stage Monte Carlo aggregate model, including the inhalation, dietary ingestion, dermal, and non-dietary ingestion routes. After the initial chlorpyrifos application for dermal and non-dietary ingestion exposure assessment, the SHEDS model was enhanced by incorporating two-dimensional variability and uncertainty distributions of model inputs and outputs. This feature was added to address an important scientific area of concern regarding exposure modeling – variability in the expected population's distribution of exposures and the distribution of uncertainty around those variability distributions. The second generation SHEDS model was used to model chlorpyrifos exposures for selected NHEXAS participants (Buck et al., 2001) and children from the EOHSI home study (). The modeled results compared favorably with the measured urine results, demonstrating the robustness of the model.

In October 2001, ORD/NERL, at the request of OPP/HED, hosted a scientific Aggregate Residential Exposure Model Comparison Workshop in Research Triangle Park, NC, which included the second generation SHEDS-Pesticides model. The workshop focused on four aggregate human exposure models being developed for the Food Quality Protection Act of 1996 (FQPA): Calendex (Novigen Sciences, Inc.), CARES (American Crop Protection Association), Lifeline (The Lifeline Group), and SHEDS (EPA ORD's National Exposure Research Laboratory). The primary objective of the workshop was to advance the science of aggregate exposure modeling. The primary goal of the workshop was to demonstrate, compare, and contrast the outputs and capabilities of the four models given the same input scenarios. Specific goals of the workshop were to:

- identify similarities and differences among the four models, and where different outputs are produced for the same scenario, to identify the source(s) of differences;
- identify strengths and weaknesses of current modeling approaches relevant to OPP's needs under FQPA;
- identify the most critical parameters and default assumptions in the four models; and
- identify and prioritize specific data needs necessary to improve the performance and the application of these aggregate exposure models.

The major conclusion of the model-comparison exercise was that the four exposure models provided generally similar outputs for a given scenario. The differences observed were attributed primarily to how the respective model developers interpreted and assigned the input variables. The workshop provided valuable insight into future modeling and data requirements for human exposure assessment, and helped to further guide the development of the SHEDS-Pesticides model.

The third generation SHEDS-Pesticides model is currently being developed to enhance version 2 to include pet, broadcast, and fogger application scenarios; co-occurrence algorithms using the REJV (Residential Exposure Joint Venture) pesticide usage survey data; and separate source-to-concentration and exposure-to-dose modules. The options for the source-to-concentration module include probability distributions or user input of time series data for post-application concentrations indoors and outdoors, treated and untreated rooms, and different surface types. To generate time series data for indoor pyrethroid application scenarios, NERL and its collaborators (Battelle/Harvard) developed another pesticide exposure-related model to simulate indoor residential concentrations of pesticides that result from indoor pesticide application. This model employs the chemical principle of fugacity to estimate transfer rates of pesticide between air and solid-surface compartments within the modeled residence. Compartments in the model include air and various types of surfaces (such as vinyl, carpet, and walls) within both the pesticide-treated zone and the adjacent, non-treated zone. This so-called “indoor fugacity model” was described in published papers (Bennett et al. 2002; Bennett and Furtaw 2004). The model software has recently been coded for incorporation into SHEDS. When the indoor fugacity model is run together with SHEDS, it will provide modeled air and surface concentrations that SHEDS can use in its exposure simulations. The options for the exposure-to-dose module include using a simple pharmacokinetic model or exporting SHEDS-generated exposure time series to PBPK models such as ERDEM. Preliminary interfacing between SHEDS and ERDEM has been conducted. This third version of SHEDS-Pesticides will be applied to estimate residential pyrethroid exposures. The dietary module for SHEDS-Pesticides version 3 was applied in June 2005 to assist OPP/HED with their dietary assessment for carbamate. NERL exposure modelers worked closely with OPP to compare SHEDS dietary estimates with those from CARES and Lifeline models, and found the results to be very consistent.

At the request of OPP’s Antimicrobials Division in 2001, major modifications were made to the SHEDS-Pesticides model by NERL researchers to develop a scenario-specific version of SHEDS (SHEDS-Wood; also with 2-dimensional Monte Carlo capabilities) for simulating children’s exposures and doses to arsenic and chromium from chromated copper arsenate (CCA)-treated wood playsets and decks, and soil surrounding these structures. The SHEDS-Wood model methodology was presented to OPP's FIFRA SAP in August 2002, and the application of SHEDS-Wood was reviewed favorably by the SAP December 2003. The draft and final reports were delivered by NERL to OPP's Antimicrobials Division (Zartarian et al., 2003; Zartarian et al., 2005) and several journal articles have been submitted to the journal of Risk Analysis. This application of the SHEDS model was conducted over several years with extensive interaction between scientists from NERL and from OPP's Antimicrobials Division. The results of the SHEDS-Wood CCA exposure assessment provided the basis for OPP's risk assessment for CCA-treated wood structures. For this SHEDS model application, skin contact with, and non-dietary ingestion of, arsenic in soil and wood residues were considered for the population of children in the United States who frequently contact CCA-treated wood playsets and decks. Model analyses were conducted to assess the range in population estimates and the impact of potential mitigation strategies such as the use of sealants and hand washing after play events. The results include the following:

- Predicted central values for lifetime annual average daily dose values for arsenic ranging from 1E-6 to 1E-5 mg/kg/day, with predicted 95th percentiles on the order of 1E-5 mg/kg/day
- There were several orders of magnitude between lower and upper percentiles
- Residue ingestion via hand-to-mouth contact was determined to be the most significant exposure route for most scenarios
- Variables associated with these routes for which limited data are available (e.g., average number of days per year children play around CCA-treated playsets; average fraction of non-residential time a child plays on/around CCA-treated playsets) should be the focus of future data collection efforts towards wood preservative exposure assessments
- Results of several alternative scenarios were similar to baseline results, except for the scenario with greatly reduced residue concentrations through hypothetical wood sealant applications; in this scenario, exposures were lower, and the soil ingestion route dominated
- The model results compare well to those from other deterministic CCA exposure assessments.

A general description of SHEDS can be found at: http://www.epa.gov/heasd/emrb/emrb.htm. Various technical reports and users guides for SHEDS are available upon request from Dr. Linda Sheldon (Sheldon.Linda@epa.gov) or at 919-541-2454. The EPA Council for Regulatory Environmental Modeling (CREM) provides guidance for the development and application of EPA models. Information regarding SHEDS and other related models can be found at: http://cfpub.epa.gov/crem/knowledge_base/knowbase.cfm

References

Bennett, D.H., Furtaw, E.J.Jr., and McKone, T.E., "A fugacity-based indoor residential pesticide fate model." Paper presented and published in the Proceedings: Indoor Air 2002, July 2002, Monterey, CA.

Bennett, D.H. and Furtaw, E.J.Jr., "Fugacity-Based Indoor Residential Pesticide Fate Model." *Environ. Sci. Technol.* 38(7): 2142 - 2152. (2004)

Buck, R.J., Ozkaynak, A.H., Xue, J., Zartarian, V., and Hammerstrom, K. Modeled estimates of chlorpyrifos exposure and dose for the Minnesota and Arizona NHEXAS populations. Journal of Exposure Analysis and Environmental Epidemiology 11 (3):253-268 (2001). EPA/600/J-02/228.

Lioy, P.J., Hore, P., Zartarian,V., Xue, J., Ozkaynak, H.,Wang, S.Yang, Y., Chu, P, Sheldon, L, Robson, M, Needham, L., and Barr, D., "Children's Residential Exposure to Chlorpyrifos: Application of CPPAES Field Measurements of Chlorpyrifos and TCPy within MENTOR/SHEDS Pesticides Model." *Science of the Total Environment* (to be submitted)

Zartarian, V., Ozkaynak, A.H., Burke, J.M., Zufall, M.J., Rigas, M.L., and Furtaw, Jr., E.J., "A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and non-dietary ingestion." *Environmental Health Perspectives* 108 (6):505-514 (2000). EPA/600/J-01/112.

Zartarian, V.G., Xue J., Özkaynak H., Dang W., Glen G., Smith L., Stallings C., " Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks Using the Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Exposure Scenario (SHEDS-Wood)," Draft Preliminary Report, prepared for EPA Office of Pesticide Programs FIFRA (Federal Insecticide, Fungicide, Rodenticide Act) Science Advisory Panel (SAP) meeting, December 3-5, 2003. EPA/600/X-04/089.

Zartarian V.G., J. Xue, H. A. Ozkaynak, W. Dang, G. Glen, L. Smith, and C. Stallings., "A Probabilistic Exposure Assessment for Children Who Contact CCA-treated Playsets and Decks Using the Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Scenario (SHEDS-WOOD)" Final Report. U.S. Environmental Protection Agency, Washington, DC, EPA/600/X-05/009. (http://www.epa.gov/heasd/sheds/caa_treated.htm)

V. Zartarian, J. Xue, H. Ozkaynak, W. Dang, G. Glen, L. Smith, C. Stallings. "A Probabilistic Arsenic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks: Part 1. Model Methodology, Variability Results, and Model Evaluation." *Risk Analysis* (submitted; review comments being addressed)

Xue, J., V. Zartarian, H. Ozkaynak, W. Dang, G. Glen, L. Smith, C. Stallings, "A Probabilistic Arsenic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks: Part 2. Model Methodology, Variability Results, and Model Evaluation." *Risk Analysis* (submitted; review comments being addressed)

7.2 Dose Modeling Research

NERL researchers have developed a physiologically-base, pharmacokinetic (PBPK) modeling system for simulating the dose of chemicals that enter the body as a result of exposure. The Exposure-Related Dose-Estimating Model (ERDEM) contains approximately 30 compartments corresponding to various physiological organs, tissues, and fluids. ERDEM has the ability to model aggregate exposure by simulating chemical inputs to the organism via several different portals, including inhalation, ingestion, dermal absorption, and injection. This latter portal is available so that laboratory-animal injection dosage experiments can be simulated.

ERDEM is described in an EPA Report (Blancato et al., 2004). This report is available on EPA's Internet site: http://www.epa.gov/heasd/erdem/erdem_report.pdf.
A version of the ERDEM software is available for download from EPA's Internet site: http://www.epa.gov/heasd/erdem/erdem.htm. Users can download this software free of charge and actually conduct modeling runs using ERDEM. However, prospective users are cautioned that using this model is a complex process that requires many user-provided inputs to produce meaningful results.

ERDEM has been used in several different pesticide applications supporting OPP science needs. These include:

- multiple-organophosphorus insecticides for simultaneous exposure via several pathways;
- malathion application as a head-lice treatment;
- the carbamate insecticide carbaryl and the on-going N-methyl carbamates cumulative risk assessment; and,
- the on-going work to model dose from exposure to pyrethroid insecticides in support of the pyrethroids cumulative risk assessment.

One application of ERDEM was for simultaneous exposure via multiple routes of exposure to three organophosphorus (OP) insecticides - chlorpyrifos, isofenphos, and parathion. This application simulated multiple-pathway pesticide exposure, and it also ventured into the complex pharmacokinetics and pharmacodynamics of "cumulative effects". In the language of the FQPA, "cumulative effects" refers to the health effects of multiple chemicals that share a "common mechanism of toxicity" (FQPA, Section 408). In this case the cumulative effect is cholinesterase inhibition. Results from this modeling work were presented at an International Society for Exposure Analysis (ISEA) conference in 2001. Electronic copies of the presentation are available through Dr. Linda Sheldon (Sheldon.Linda@epa.gov).

Another recent pesticide application of ERDEM was for the assessment of malathion used for head-lice treatment. This model application was developed in close cooperation with OPP personnel. In this application, ERDEM was used to model the exposure, dose, and cholinesterase-inhibition effect due to this usage of malathion. This work is described in the draft EPA report "Malathion Exposures During Lice Treatment: Use of Exposure Related Dose Estimating Model (ERDEM) and Factors Relating to the Evaluation of Risk" (Dary et al., 2004).

A third major pesticide-related application of ERDEM is for the risk assessment of carbaryl. This is the first member of the carbamate family to be modeled in ERDEM. A poster was presented at the March 2005 Annual Meeting of the Society of Toxicology. An EPA report has also been prepared (Okino, et al, 2005). The intention is to eventually to conduct cumulative dose and effect modeling in ERDEM for the other N-methyl carbamates. This class of compounds has the common mechanism of toxicity of cholinesterase inhibition. Electronic copies of the presentation are available through Dr. Linda Sheldon (Sheldon.Linda@epa.gov).

The fourth and on-going pesticide application of ERDEM is for the pyrethroid insecticides. This work is a collaborative project including scientists from NERL, ORD's National Health and Environmental Effects Laboratory (NHEERL), ORD's National Center for Environmental Assessment (NCEA), and OPP. This pyrethroid-modeling research will consider cumulative effects of multiple-pyrethroid exposures; hence like the OP and carbamate dose modeling described above, this work goes beyond aggregate exposure to one chemical, and considers cumulative effects from several related chemicals. The ERDEM pyrethroid modeling approach for addressing pyrethroids cumulative risks was presented at a seminar on the use of PBPK models in risk assessment at the OPP offices in Washington, DC in August 2004. This seminar provided prospective users with information on the ERDEM family of PBPK models. Many of the presentations were on the pesticide applications of ERDEM, but the seminar also included a presentation on the use of ERDEM for assessing exposure and dose of volatile organic compounds from contaminated water. Electronic copies of the presentation are available through Dr. Linda Sheldon (Sheldon.Linda@epa.gov).

The development and improvement of the ERDEM family of PBPK models continues. One enhancement that is currently being developed is referred to as Cellular Modeling. This technique will incorporate diffusional processes into many of the organ and tissue compartments within ERDEM. This will make the physiological representation of movement of chemicals (both parent compounds and metabolites) into and through tissues more mechanistically realistic, thus improving the scientific basis of ERDEM. A draft report is currently being prepared that describes both this Cellular Modeling, and the implementation of enzyme inhibition within the ERDEM.

References

Blancato, J.N., Power, F.W., Brown, R.N., Dary, C.C., "Exposure Related Dose Estimating Model (ERDEM) for Assessing Human Exposure and Dose," EPA Report EPA/600/R-04/060 December 2004.

Dary, C.C., Power, F.W., Blancato, J.N., "Malathion Exposures During Lice Treatment: Use of Exposure Related Dose Estimating Model (ERDEM) and Factors Relating to the Evaluation of Risk," draft EPA Report EPA/600/R-04/xxx July 2004

Okino, M.S., Power, F.W., Tornero-Velez, R., Blancato, J.N., Dary, C.C., "Assessment of Carbaryl Exposure Following Turf Application Using a Physiologically Based Pharmacokinetic Model," draft EPA Report EPA/600/R-05/xxx December 2005

"Exposure Related Dose Estimating Model (ERDEM), Implemention of Cellular Modeling", NERL, August 2005.

8. EXPOSURE DATABASES

Two electronically available databases, the Consolidated Human Activity Database (CHAD) and the Human Exposure Database System (HEDS), have been developed to store, maintain, retrieve and disseminate the validate results of NERL's exposure measurements research program. These databases also store and maintain key input data that are used to develop and evaluate exposure and dose models. Extensive research has been conducted to develop these two robust databases and to ensure they provide the scientific community with consistent input data for the exposure and dose models and to warehouse and make publically available the validated results of NERL's exposure research measurement and modeling activities. Brief descriptions of these databases are provided below.

8.1 Consolidated Human Activity Database (CHAD)

Past exposure monitoring and modeling study research demonstrated the importance of activity pattern data in explaining and predicting variation in human exposures to environmental pollutants (McCurdy 1994, 1995, 1997a). These studies also have demonstrated that aggregated time-activity pattern data developed from general population studies often have little scientific value in understanding activity patterns, exposures experienced, or dose received of children or any other population subgroup (Graham & McCurdy, 2004; McCurdy & Graham, 2003, 2004). Factors such as age, mobility, dermal-oral transfer, habitual daily activities, lifestyle (e.g., propensity of exercising frequently), residential and worksite locations, and mode of transportation used on a daily basis influence the intensity (magnitude), frequency, duration, and pattern of pollutant exposure (McCurdy 1997c).

The Consolidated Human Activity Database (CHAD) has attempted to address these concerns by assembling data from 13 existing human activity databases and making them easily accessible to the public via http://www.epa.gov/chadnet1/ (McCurdy et al., 1990). CHAD includes data from EPA-funded random-probability activity surveys, including the 1992-1998 National Human Activity Pattern Survey (NHAPS), and the Denver and Washington DC surveys undertaken in the mid-1980s. CHAD includes a national random-probability study undertaken by the Institute of Social Research at the University of Michigan that includes over 5,000 person-days of children's activities. CHAD also includes data from a Cincinnati survey funded by the Electric Power Research Institute; a survey of activities in Valdez, Alaska funded by Alyeska, a consortium of petroleum companies; two small panel activity surveys in Los Angeles undertaken by the American Petroleum Institute; and the two large random-probability studies of Californian's activities conducted by the State's Air Resources Board in the early 1990s. Finally, CHAD includes EPA's panel study of elderly inhabitants of an apartment complex in Baltimore MD.

A common set of activity and location codes was developed so that the separate formats used by the original databases could be easily accessed by exposure analysts. There are 140 activity codes and 114 location codes arranged in a hierarchal structure in CHAD, and the database developers attempted to retain as much detail in the original surveys as possible. A common format for handling time also was established, so that all of the individual diary days of activity start and end at midnight. This facilitates computer modeling, because code "translations" no longer have to be used to bring together the data. A unique feature of CHAD is that a distribution of physiologically-based ratios of personal energy expenditure to basal metabolism (called a MET) is provided for every activity coded in the database (McCurdy 2000). Since inhalation, water consumption, and food ingestion can be related to the MET indicator, CHAD facilitates multi-route exposure/uptake dose modeling.

Over 22,000 person-days of data are included in the database. About one half of these data focus on children (~ 10,100 person-days of data). CHAD provides a synoptic basis for undertaking multi-route, multi-media exposure and dose assessments. The data can be accessed by age, gender, location of the country, housing characteristics, and/or socioeconomic factors. The significant portion of these data which focus on children's activities represent a valuable contribution to understanding children's time-activity patterns, exposure, and risk, and to developing multi-route exposure and dose models.

References:

McCurdy, T. (1994). "Human exposure to ambient ozone," pp. 85-127 in: D.J. McKee (ed.) Tropospheric Ozone. Ann Arbor MI: Lewis Publishers

McCurdy, T. (1995). "Estimating human exposure to selected motor vehicle pollutants using the NEM series of models: Lessons to be learned." J. Exp. Anal. Environ. Epidem. 5: 533-550

McCurdy, T. (1997a). "Comparison of cumulative inhaled ozone dose estimates using a disaggregated, sequential approach and alternative recommended approaches." Paper presented at the 7th Annual Meeting of the International Society of Exposure Analysis

McCurdy, T. (1997b). "Human activities that may lead to high inhaled intake doses in children aged 6-13." Environ. Tox. Pharm. 4: 251-260

McCurdy, T. (1997c). "Modeling the dose profile in human exposure assessments: ozone as an example." Rev. Tox.: In Vivo Tox. Risk Assess. 1: 3-23

McCurdy, T. (2000). "Conceptual basis for multi-route intake dose modeling using an energy expenditure approach." J. Expos. Anal. Environ. Epidem. 10: 86-97

McCurdy, T., Glen, G., Smith, L., and Lakkadi, Y. (2000). "The National Exposure Research Laboratory's Consolidated Human Activity Database." J. Exp. Anal. Environ. Epidem. 10: 566-578

McCurdy, T. and Graham, S. (2003). "Using human activity data in exposure models: Analysis of discriminating factors." J. Exp. Anal. Environ. Epidem. 13: 294-317

McCurdy, T. and Graham, S. (2004). Analyses to Understand Relationships Among Physiological Parameters in Children and Adolescents Aged 6-16. Research Triangle Park, NC: U.S. Environmental Protection Agency (EPA/600/X-04/092)

McCurdy, T. and Xue, J. (2004). "Meta-analysis of Physical Activity Index data for US children and adolescents." J. Child. Health 2: 297-319

Graham, S.E. and McCurdy, T. (2004). "Developing meaningful cohorts for human exposure models." J. Expos. Anal. Environ. Epidem. 14: 23-43

8.2 Human Exposure Database System (HEDS)

NERL has established an electronically available repository for the validated exposure research data, the Human Exposure Database System (HEDS), available at http://www.epa.gov/heds/. The HEDS website provides information about the studies as well as information on how to use the database system. HEDS is a web-enabled data repository for validated human exposure studies. It provides the validated data sets, supporting documents (protocols, SOPs, etc.), and other important metadata for human exposure studies that can be easily accessed and understood by a diverse set of users. Although the data are provided about human exposure, NERL strives to protect the confidentiality of all study participants. 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. Currently the validated NHEXAS are readily available for exposure researchers on HEDS. The validated CTEPP and Arizona Border study results are anticipated to be electronically available by the end of FY 2006.

9. GENERAL CONCLUSIONS

Significant progress has been made in children's pesticide exposure research since the passage of FQPA in 1996. The results of NERL's research have filled numerous data gaps and provided risk assessors with refined methods, knowledge, data and models for estimating children's exposures to pesticides.

A brief summary of areas where important progress has been made is highlighted below.

- Those pesticides that are most frequently used for residential pest control have been identified. Information on the occurrence and co-occurence of pesticides in the environmental (air, dust, soil, and surface wipe) and personal exposures measured via hand wipe and urine samples has also been developed.
    - The pyrethroid pesticides are currently the most frequently used insecticides for indoor applications. Their use is expected to become more widespread since the discontinuation of registrations for indoor use of chlorpyrifos (2001) and diazinon (2002).
    - *cis- and trans*-Permethrin and cypermethrin were the most frequently detected pyrethroid pesticides in environmental samples. Chloropyrifos is still the most frequently detected pesticide in residential environmental samples despite its discontinued residential indoor use.

- High quality data are now available documenting pesticide concentrations in environmental and personal samples for children. These data will be used to substantially improve future exposure assessments.
    - Concentrations distributions of pesticides in environmental and personal samples have been measured for a number of populations across the country. Results for these general population and nationally representative occurrence studies gives information on background levels since pesticide applications are intermittent and monitoring is not targeted to any particular monitor application event in these studies.
    - Data on the temporal and spatial distribution of pesticides after applications have also been generated. Preliminary results suggest that pyrethroid pesticides accumulate in the dust and may be persistent in the home for much longer time periods than were reported for organophosphate pesticides. Thus residential applications may result in chronic exposures to these pesticides.
- Pesticides can be categorized as either semivolatile (i.e., chlorpyrifos, diazinon) or nonvolatile (i.e., pyrethroids) based on their vapor pressure. The volatility characteristics of a given pesticide will have a substantial impact on the fate and transport of pesticides in residential environments, as well as routes and pathways for exposure.
    - Semivolatile pesticides are present primarily in the air and as residues on surfaces. Nonvolatile pesticides are primarily bonded to dust particles in the home. These factors change the transfer characteristics and efficiency for pesticides.
    - Particles can transfer more efficiently from one media to another. Thus, nondietary exposure through surface-to-hand and hand-to-mouth activities should be considerably greater for the nonvolatile particle-bound pesticides compared to the semivolatile pesticides.
    - Dermal exposure is expected to be less for the nonvolatile pesticides because the particle-bound pesticides are likely to stay on the particles rather than transfer to and through the skin surface.
- An understanding of the relative magnitude of exposure by different routes has been developed. This information will allow us to apply route specific PBPK models to more accurately predict target tissue dose, biomarker levels, and health outcomes. It also will provide focus for future exposure monitoring and epidemiological studies and will allow model sensitivity analysis to be framed based on the most important exposure routes.
    - Inhalation - Even when semivolatile pesticides such a chlorpyrifos are measured at relatively high concentrations in air samples, there appears to be little impact on absorbed dose as estimated by urinary biomonitoring data. These results suggest that chlorpyrifos may be poorly absorbed through the lung and inhalation may not be an important exposure route in residential settings.
    - Dermal Absorption – Calculations using skin loading measurements and default assumptions for dermal penetration rates give very low values for absorbed dose compared to aggregate absorbed dose estimated by biomonitoring. Additional research is needed in the areas of dermal absorption and biomonitoring.
    - Nondietary Ingestion – this appears to be an important route of children’s exposure for nonvolatile pesticides such as the pyrethroid pesticides.

        - Nondietary ingestion can account for ~25% of aggregate exposure in areas that have moderate residential pesticide use. This includes states such as Ohio and North Carolina where the CTEPP study was conducted.
        - In high pesticide use areas such as Florida, nondietary ingestion could be substantially higher.
        - Methods need to be improved to accurately estimate exposure by this route.
    - Dietary – for most pesticides, especially in moderate use areas, this is the predominant exposure pathway. For some pesticides, the dietary route accounts for greater than 90% of aggregate exposure.
        - Methods for measuring dietary exposure must be improved – better analytical methods, refinements in duplicate diets sample collections, and methods for estimating the impact of preparation and handling in the home are needed.
        - Models for estimating dietary exposure need to be refined and evaluated against existing data on both foods consumed and measured intake levels.
- Based on reported biomonitoring data, there are areas of the country where children have substantially higher exposures to pyrethroid pesticides. This appears to be due to high residential use. Additional information is needed to understand the sources, routes, and pathways for children's exposures in these areas.
- Longitudinal Exposures – few studies have addressed longitudinal exposures and relate these to lifestage and activities. Additional research is needed.
- Biomonitoring is a useful tool for understanding exposures and absorbed dose especially when comparing across populations. Substantial research has been conducted to understand the limitations and to improve the methods for using biomarkers to estimate exposure and absorbed.
    - For some pesticides, high levels of degradation products are in the environment. This is a potential confounder especially for risk assessments.
    - Quantitative exposure estimates require measures of urinary output rather than concentration. Collection methods, including diaper collection methods for young children, have been refined so that urinary output rates can be calculated.

Progress has been made in many areas and we are beginning to understand the environment that children live in, their activities, and the resulting exposures. However, research is still needed to adequately characterize the magnitude, routes and pathways of exposure. We still need to understand the key factors that influence the dermal transfer and indirect ingestion of pesticides. We need to be able to more accurately assess dietary exposure. In order to evaluate exposure models, we must be able to quantify the relationships between and among environmental concentrations of pesticides in various media, children's activities, and the results of biomarkers of exposures as measured in urine and/or blood. Exposure models outputs that include the timing and route of exposure need to be linked to PBPK models in order to develop accurate assessment of target tissue dose. Research, especially model development, needs to extend beyond single chemical aggregate exposures and dose to include exposures and risks that accumulate across chemicals and over time.

10. SUMMARY

Since 1996, NERL has conducted significant research to develop and provide tools and data for use in assessing children's aggregate exposure to pesticides. High quality research products have been provided to Agency risk assessors to address FQPA-related issues, including: publications describing a framework for systematically conducting related research; measurement methods for sampling and analysis of environmental media to which humans are exposed; data from numerous studies of children's pesticide exposure; and the development and application of exposure and dose models for simulation of aggregate (and in some cases cumulative) pesticide exposure and dose.

This report has compiled a list of NERL research activities and available technical products that have already been used in selected cases, and that can be used in the future by Agency exposure and risk assessors in conducting scientifically sound pesticide exposure and dose assessments. The NERL researchers realize the complexity associated with conducting these assessments, and of employing newly developed state-of-the-art knowledge tools in conducting risk assessments. NERL encourages risk assessors to contact the individual researchers and/or senior NERL leadership to find opportunities for collaboration in using these tools to address key scientific problems associated with children's risk. The NERL researchers invite and encourage pesticide exposure assessors and risk assessors to contact Dr. Linda Sheldon (Sheldon.linda@epa.gov, or 919-541-2454)) to obtain assistance in the usage of these products.