United States Environmental Protection Agency

The U.S. EPA National Exposure Research Laboratory's (NERL's) Workshop on the Analysis of Children's Measurement Data

Workshop Summary Report

RESEARCH AND DEVELOPMENT

EPA 600/R-06/026
March 2006

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By

Nicolle S. Tulve[1], Jeff Driver[2], Peter E. Egeghy[1], Jeff Evans[3], Roy C. Fortmann[1], John Kissel[4], Nancy McMillan[5], Lisa J. Melnyk[6], Marsha Morgan[1], James Starr[1], Daniel M. Stout II[1], Mark Strynar[1]
[1]US EPA, Office of Research and Development, National Exposure Research Laboratory, Human Exposure and Atmospheric Sciences Division, Research Triangle Park, NC 27711
[2]infoscientific.com, Inc., Manassas, VA 20111
[3]US EPA, Office of Pesticide Programs, Health Effects Division, Washington, DC 20460
[4]University of Washington, Department of Environmental and Occupational Health Sciences, Seattle, WA 98195
[5]Battelle, Columbus, OH 43201
[6]US EPA, Office of Research and Development, National Exposure Research Laboratory, Microbiological and Chemical Exposure Assessment Research Division, Cincinnati, OH 45268

National Exposure Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC, 27711

Notice

The U.S. Environmental Protection Agency, through its Office of Research and Development, National Exposure Research Laboratory, sponsored the workshop described in this report. It has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. This report was prepared as a general record of the discussions held during the U.S. EPA National Exposure Research Laboratory's (NERL's) Workshop on the Analysis of Children's Measurement Data (September 27-28, 2005). This report captures the main points and highlights of the meeting. It is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the collective views of the workshop participants. None of the statements should be used to infer official positions or policy of the EPA.

Executive Summary

The U.S. EPA National Exposure Research Laboratory's (NERL's) Workshop on the Analysis of Children's Measurement Data was held on September 27 and 28, 2005. A group of recognized experts in the fields of exposure and health assessments, toxicology, statistics and biostatistics, modeling, analytical chemistry, and biomarker measurements was assembled to discuss three themes regarding measurements data from recent children's exposure studies conducted or funded by NERL. To facilitate the two-day discussions, a summary document containing information on the recent studies of children's exposure was compiled and distributed to all attendees. The summary included data from laboratory and observational field studies that had been conducted or funded by NERL over the previous years. The studies took place in the EPA Research Test House, in child care centers, and in private residences. The field studies were observational measurement studies. No chemicals or other products were introduced by EPA into the homes or day care centers, and participants were asked to follow their normal daily routines while the environmental samples and other types of information were collected. The workshop attendees were assigned to one of four groups to discuss the themes as presented and any additional ideas that were identified. The groups were evenly mixed with Program Office, Industry, Academia, and Government researchers.

Workshop participants were asked to consider the following themes during their discussions:

Theme 1: Major trends in the data across children's exposure studies

a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?
b. Identify the major factors that influence children's exposures to the pesticides.
c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

Theme 2: Additional hypotheses that should be tested using existing data

a. Provide a list of the major hypotheses that could be tested on existing data.
b. Why are these considered to be important hypotheses?
c. How suitable are the existing data? What is still missing?

Theme 3: Additional statistical analyses that can be performed on these data to better understand children's exposures to chemicals at homes and daycare centers? Provide a list of statistical analyses that could be performed on the accrued data. For each proposed analysis, please specify

a. What data gap are you addressing?
b. What key hypothesis are you testing?
c. What result do you expect to find?
d. What is the likelihood of success, given the limitations of the data?

At the conclusion of the meeting, each group produced a summary document that captured their theme discussions. There were many similar observations recorded for the groups. For example, all groups recognized the importance of diet as a route of exposure. It was also recognized that adequately capturing

children's activities is critically important to understanding and evaluating their exposures. The need for more statistical evaluations that incorporate the questionnaire data was deemed highly important. Many additional hypotheses and statistical analyses were proposed during the workshop.

This workshop report lists a summary of the observations related to each theme. These results will be used to generate a detailed statistical analysis plan that will be implemented using the available data.

Contents

Acknowledgements

The authors would like to thank all the workshop participants for their valuable contributions to this report.

Chapter 1
Introduction

Background

The U.S. Environmental Protection Agency (U.S. EPA) has pledged to increase its efforts to provide a safe and healthy environment for children by ensuring that all EPA regulations, standards, policies, and risk assessments take into account special childhood vulnerabilities to environmental toxicants. Children are behaviorally and physiologically different from adults. Their interaction with their environment, through activities such as playing on floors, mouthing of hands and objects, and handling of food, may increase contact with contaminated surfaces. Proportionally higher breathing rates, relative surface area, and food intake requirements may increase exposure. Differences in absorption, metabolism, storage, and excretion may result in higher biologically-effective doses to target tissues. Immature organ systems may be more susceptible to toxicological challenges. Windows of vulnerability, when specific toxicants may permanently alter the function of an organ system, are thought to exist at various stages of development.

Children are commonly exposed to a wide variety of chemicals in their daily lives in their homes, schools, day care centers, and other environments that they occupy. The chemicals to which they are exposed may originate from outdoor sources, such as ambient air contaminants, and indoor sources such as building materials and consumer products. One category of consumer products to which children may be exposed is pesticides that are used to control roaches, rats, termites, ants, and other vermin. Despite widespread residential and agricultural use of pesticides, little is known about the actual levels of pesticide exposure among children and the factors that impact children's exposures to pesticides. The Food Quality Protection Act (FQPA) of 1996 requires EPA to upgrade the risk assessment procedures for setting pesticide residue tolerances in food by considering the potential susceptibility of infants and children to both aggregate and cumulative exposures to pesticides. Aggregate exposures are exposures from all sources, routes, and pathways for individual pesticides. Cumulative exposures include aggregate exposures to multiple pesticides with the same mode of action for toxicity. Specifically, FQPA requires that risk assessments must be based on exposure data that are of high quality and high quantity or exposure models using factors that are based on existing, reliable data.

EPA's Office of Research and Development (ORD) is responsible for conducting research to provide the scientific foundation for risk assessment and risk management and to meet the mandates of the FQPA. In 2000, ORD released its *Strategy for Research on Environmental Risks to Children* addressing research needs and priorities associated with children's exposure to environmental pollutants and providing a framework for a core program of research in hazard identification, dose-response evaluation, exposure assessment, and risk management.

The National Exposure Research Laboratory (NERL) is working to achieve three specific objectives of the ORD *Strategy* through its Children's Exposure Research Program: (1) develop improved exposure assessment methods and models for children using existing information; (2) design and conduct research on age-related differences in exposure, effects, and dose-response relationships to facilitate more accurate risk assessments for children; and (3) explore opportunities for reducing risks to children. After an exhaustive review of the volume and quality of the data upon which default assumptions for exposure factors are based (Cohen Hubal *et al*., 2000a), a framework for systematically identifying the important sources, routes, and pathways for children's exposure was developed (Cohen Hubal *et al*., 2000b).

This framework (see Figure below), based on a conceptual model for aggregate exposure, provides the foundation for a protocol for measuring aggregate exposures to pesticides (Berry *et al*., 2001) and for developing sophisticated stochastic models (Zartarian *et al*., 2000). Using the framework, four priority research areas, representing critical data gaps in our understanding of environmental risks to children, have been identified:

(1) Pesticide use patterns;
(2) Spatial and temporal distribution in residential dwellings;
(3) Dermal absorption and indirect (non-dietary) ingestion (including micro- and macro-activity

approaches); and
(4) Direct ingestion.

Several targeted studies were designed and conducted to address these research needs. These include laboratory studies, small pilot field studies, and large collaborative field studies. These studies aimed to

(1) evaluate methods and protocols for measuring children's exposure.
(2) collect data on exposure factors to reduce the uncertainty in exposure estimates and risk assessments.
(3) collect data for use in exposure model development and evaluation.

The studies took place in the EPA Research Test House, child care centers, and private residences. The field studies were observational measurement studies. No chemicals or other products were introduced by EPA into the homes or day care centers. Participants were asked to follow their normal daily routines while the environmental samples and other types of information were collected. Organophosphate and pyrethroid pesticides and their metabolites were measured in environmental samples (e.g., air, surface dust residues, diet) representing multiple routes and pathways of exposure and in biological fluids (e.g., urine). Time/activity and other questionnaire data were also collected. The primary participants in the field studies were children ranging in age from 8 months to 12 years.

References

Berry, MR, Cohen Hubal, EA, Fortmann, RC, Melnyk, LJ, Sheldon, LS, Stout, DM, Tulve, NS, Whitaker, DA. 2001. Draft Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways. EPA/600/R-03/026. Office of Research and Development, Research Triangle Park, NC.

Cohen Hubal, EA, Sheldon, LS, Burke, JM, McCurdy, TR, Berry, MR, Rigas, ML, Zartarian, VG. 2000a. Exposure assessment for children: a review of the factors influencing exposure of children, and the data available to characterize and assess that exposure. *Environmental Health Perspectives* 108(6):475-486.

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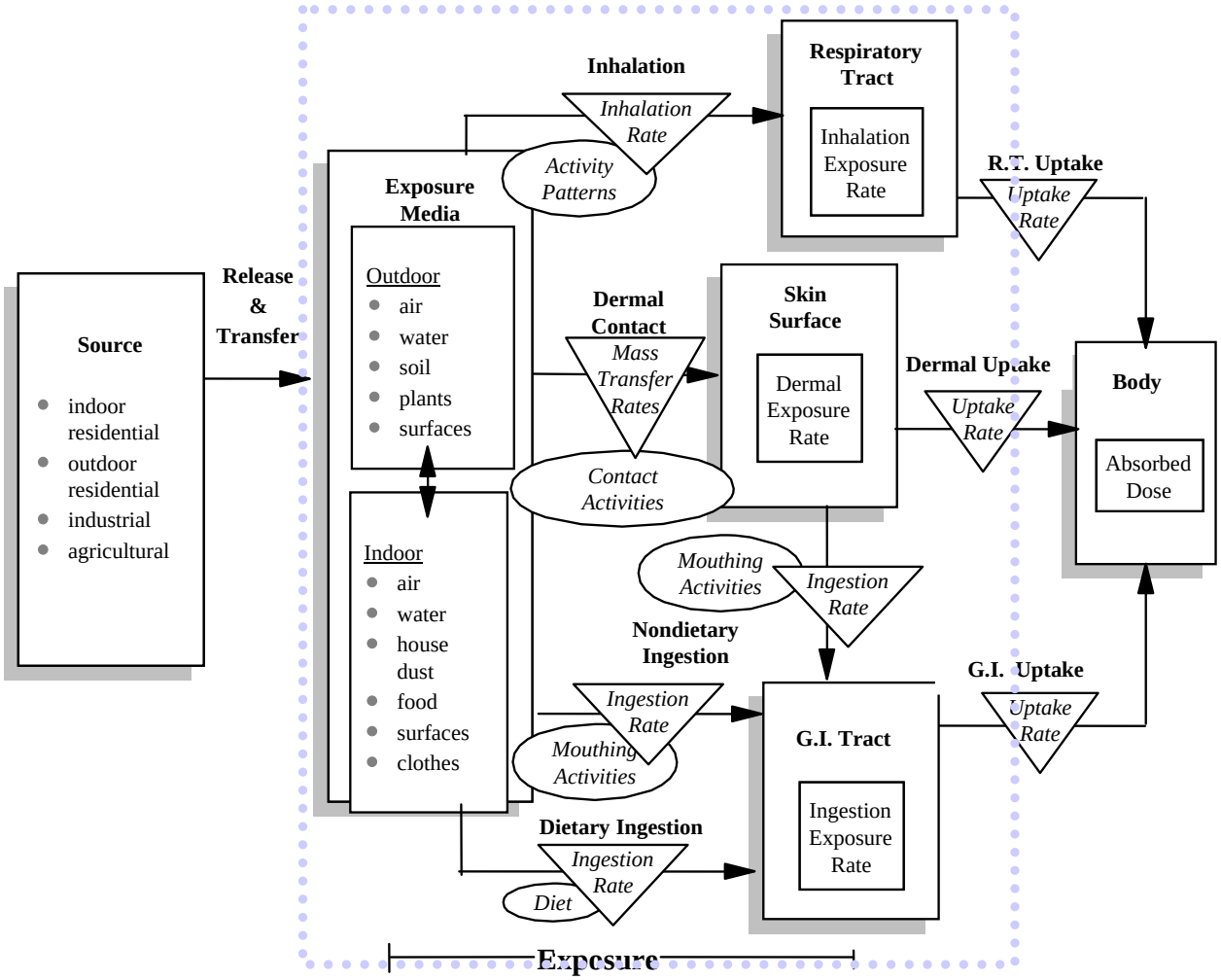
Zartarian, VG, Ozkaynak, H, Burke, JM, Zufall, MJ, Rigas, ML, Furtaw, EJ Jr. 2000. A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and nondietary ingestion. *Environmental Health Perspectives* 108(6):505-14.



Modeling framework for children's pesticide exposure from Cohen Hubal *et al*. (2000b).

Goal of the Workshop

The U.S. EPA National Exposure Research Laboratory's (NERL's) Workshop on the Analysis of Children's Measurement Data was held on September 27 and 28, 2005 in Research Triangle Park, NC.

Workshop participants were provided with a summary document that contained the following information:

- Descriptions of recent children's exposure studies conducted or funded by NERL, including descriptions of the parameters measured and the measurement methods;
- Concentration data and summary statistics for comparisons of the studies;
- Simple comparative analyses; and,
- Highlights of the results of the studies.

The goal of the workshop was to assemble a group of recognized experts in the fields of exposure and health assessments, toxicology, statistics and biostatistics, modeling, analytical chemistry, and biomarker measurements to discuss the major trends in the data, additional hypotheses, and additional statistical analyses that should be undertaken with the data (Chapter 1), using the summary document and an overview presentation by Dr. Linda Sheldon as the bases for discussions. The results of the two-day workshop have been captured in this report (Chapter 2, Appendices A and C). An important outcome from this workshop will be a research plan for additional statistical analyses of the collected children's measurement data in order to improve our understanding of the relevant factors affecting children's exposures to pesticides.

Report Structure

The preliminary text contains an Executive Summary. Chapter 1 includes a brief discussion of the background for the research, a description of the purpose of the workshop, the meeting agenda, the charge questions, and biographical information on the guest presenters. Chapters 2 and 3 provide summaries of the charge questions and the discussion on collaborative ideas. Appendix A contains the individual group discussion materials. Appendix B contains the list of attendees with contact information. Appendix C contains the overview presentation given by Dr. Linda Sheldon, Acting Director of the Human Exposure and Atmospheric Sciences Division, and the presentations given by the guest presenters during day one of the workshop.

Agenda

Day 1: Tuesday September 27, 2005	
8:00 am – 9:00 am	**Continental Breakfast (Camillia Room)**
9:00 am – 9:30 am	**Registration**
9:30 am – 10:00 am	**Welcome** ***Breaks on your own** **Overview Presentation (Camillia Room)** **Presenter: Dr. Linda Sheldon (Acting HEASD Director, EPA)**
10:00 am – 12:00 noon	**Presentations by Guest Speakers (20 min. each)** **Speaker 1 – Bob Lordo (Battelle)** **Speaker 2 – Richard Fenske (University of Washington)** **Speaker 3 – Robin Whyatt (Columbia University)** **Speaker 4 – Haluk Ozkaynak (USEPA/ORD)** **Speaker 5 – Jeff Evans (USEPA/OPP)**
12:00 noon – 1:00 pm	**Lunch *on your own.***
1:00 pm – 3:00 pm	**Theme 1: Major Trends in The Data** ***Groups (A, B, C, or D) - assigned rooms**
3:00 pm – 4:00 pm	**Theme 2: Additional Hypotheses**
4:00 pm – 5:00 pm	**Report Out for Themes 1 and 2** ***All Groups - Camillia Room**
5:00 pm	**Adjourn** *Dinner on your own – suggestions will be provided.*
Day 2: Wednesday, September 28, 2005	
8:00 am – 8:30 am	**Continental Breakfast (Camillia Room)**
8:30 am – 9:00 am	**Overview of Today's Agenda (Camillia Room)** **Presenter: Dr. Linda Sheldon**
9:00 am – 11:00 am	**Theme 3: Additional Statistical Analyses**
11:00 am – 12:00 noon	**Report Out for Theme 3**
12:00 noon – 1:00 pm	**Lunch *on your own.***
1:00 pm – 2:30 pm	**Future Collaborations (optional)**
2:30 pm – 3:00 pm	**Closing Remarks** **Presenter: Dr. Linda Sheldon**
3:00 pm	**Adjourn**

Charge Questions

To facilitate the two-day discussions, charge questions were used to focus the group discussions and are reproduced here.

Charge Questions for the U.S. EPA NERL's Workshop on the Analysis of Children's Measurement Data

NERL has conducted and/or funded many children's exposure studies involving pesticides over the past several years. We have summarized the information from a number of these studies in the provided draft report entitled "Summary and Comparison of Data Collected in NERL Children's Pesticide Exposure Studies".

For this workshop, NERL would like to have open discussions with fellow researchers on the data and results from these studies. In addition, we encourage fellow scientists to share their data and findings from their children's exposure studies as well.

We have divided the workshop members into four assigned groups A, B, C, or D. The charge for each group is to provide your input and comments on the following research themes:

Theme 1: Major trends in the data across children's exposure studies

a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?
b. Identify the major factors that influence children's exposures to the pesticides.
c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

* *Two hour time limit*

Theme 2: Additional hypotheses that should be tested using existing data

a. Provide a list of the major hypotheses that could be tested on existing data.
b. Why are these considered to be important hypotheses?
c. How suitable are the existing data? What is still missing?

* *One hour time limit*

Theme 3: Additional statistical analyses that can be performed on these data to better understand children's exposures to chemicals at homes and daycare centers

Provide a list of statistical analyses that could be performed on the accrued data. For each proposed analysis, please specify

a. What data gap are you addressing?
b. What key hypothesis are you testing?
c. What result do you expect to find?
d. What is the likelihood of success, given the limitations of the data?

Please prioritize the proposed analyses.

* *Two hour time limit*

Presentations by Guest Speakers

During Day 1 (September 27, 2005) of the workshop, five guest speakers were asked to discuss the importance of the data contained in the summary document with respect to their research. Presentation summaries and speaker biographies are captured below. Speaker presentations can be found in Appendix C.

Speaker 1: Dr. Robert Lordo, Battelle

Title: Major findings and recommendations based on the outcome of statistical analysis of children's exposure data from the CTEPP study

Description of Presentation: EPA has recently completed an observational pilot study of Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP), in which environmental monitoring, personal exposure, and biomarker data were collected on selected pesticides and other pollutants from the homes and day care centers of 257 preschool children, in order to investigate their aggregate exposures to these pollutants. Statistical modeling techniques were used to characterize how personal exposure levels may differ among different types of environments (e.g., urban vs. rural, day care vs. stay-at-home children) and which exposure routes were most dominant for a particular pollutant. In addition, analysis of chlorpyrifos and chrysene data from the CTEPP study were recently performed using novel statistical techniques, including structural equations modeling and hierarchical Bayesian modeling, in order to evaluate the utility of selected exposure biomarkers in understanding potential exposure pathways to children. Important findings and conclusions from the analyses performed on these data will be presented, along with questions and issues that remain unresolved and, therefore, could impact the design of future children's exposure studies.

Dr. Robert Lordo has served as an environmental statistician at Battelle for the past 17 years. His primary research focus has been in areas of exposure assessment and risk analysis, using statistical modeling techniques to evaluate the extent to which sensitive subpopulations are exposed to toxic chemicals and to characterize the pathways of exposure within various environmental media and ultimately to human biomarkers. For several years, he has provided statistical support to EPA's Lead Program, characterizing exposures of lead-based paint hazards and their statistical link to elevated blood-lead levels in children. He recently served as principal statistician on EPA's pilot study of Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP).

Speaker 2: Dr. Richard A. Fenske, University of Washington

Title: How can we improve the accuracy of children's measurement data?

Description of Presentation: This presentation will focus on the strengths and limitations of several approaches to characterizing children's exposure to pesticides: the use of urinary metabolite monitoring in conjunction with environmental and personal sampling; the potential for saliva monitoring to provide a better understanding of internal dose; and the value of global positioning system instruments for improving our understanding of children's macro (time-location) activities. Examples will be drawn from laboratory and fields studies conducted by University of Washington researchers.

Dr. Richard A. Fenske, PhD, MPH, is a professor in the Industrial Hygiene and Safety Program in the Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington. He has served as director of the NIOSH-supported Pacific Northwest Agricultural Safety and Health Center since its establishment in 1996. His research interests include exposure assessment and intervention studies in the workplace and in communities. His current studies included reducing children's exposure to pesticides in agricultural communities, using fluorescent tracers for pesticide safety education, improving risk communication methods, and developing novel exposure assessment methods. He teaches courses in environmental sampling and analysis, and environmental risk analysis. He is a member of the U.S. Environmental Protection Agency's Science Advisory Board, and a member of the National Academy of Sciences/Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. From 1994-2004 he served on the National Advisory Panel of the National Cancer Institute's Agricultural Health Study, a prospective epidemiological study of pesticide applicators and their families.

Speaker 3: Dr. Robin Whyatt, Columbia Center for Children's Environmental Health, Columbia University

Title: Validating biomarkers of prenatal insecticide exposure. Will this help resolve conflicting epidemiologic findings?

Description of Presentation: Three recent epidemiologic studies have examined the relationship between prenatal organophosphate exposures and birth outcomes (see EHP, 112, 2004). Results are not consistent. Associations reported include decreased birth weight and length (Whyatt et al.); decreased head circumference with levels of paraoxonase 1 activity as a modifier (Berkowitz et al.) and decreased gestational age (Eskenazi et al.). Differences in exposure patterns and in the biomarkers used (chlorpyrifos in cord blood versus chlopyrifos metabolites in maternal prenatal urine) have been identified as factors that could have contributed to the discrepant findings (Needham, EHP, 113, 2004). Between 2001-04, we undertook a validation study nested within one of the cohorts to examine relationships between these biomarkers and measures of external exposure. 85% of the women report using some form of pest control during pregnancy and 46% report using higher toxicity methods. The organophosphates chlorpyrifos and diazinon and the carbamate, propoxur were detected in 99.6%-100% of repeat two-week integrated indoor air samples (n=354 samples) collected from 102 homes during pregnancy. There was little within home variability in the indoor air concentrations; between home variability accounted for 92% of the variance in chlorpyrifos levels, 94% in diazinon levels and 87.7% in propoxur levels ($p<0.001$, mixed model). Chlorpyrifos levels in repeat indoor air samples were significantly correlated with levels of 3,5,6-trichloro-2-pyridinol (TCPY) in repeat prenatal maternal spot urine samples ($r=0.3$, $p<0.01$) but not with levels of chlorpyrifos in maternal or umbilical cord blood. TCPY levels in postpartum meconium were significantly correlated with TCPY levels in maternal prenatal urine samples ($r=0.4$, $p<0.001$) and with chlorpyrifos levels in maternal and umbilical cord blood collected at delivery ($r=0.35$-0.44, $p=0.001$). Chlorpyifos and TCPY in the environmental and biologic samples declined significantly following the U.S. EPA 2000-2001 regulation action to phase out residential uses. Results suggest that organophosphate metabolites measured in meconium may provide an alternative dosimeter for examining effects of prenatal exposure on birth outcomes.

Dr. Robin Whyatt is Associate Professor of Clinical Environmental Health Sciences at the Mailman School of Public Heath at Columbia University and is Deputy Director of the Columbia Center for Children's Environmental Health. Her research focus is on the effects of environmental exposures on women and children, including the developing fetus. This has included molecular epidemiologic research on prenatal exposures to ambient air pollution and cigarette smoking in Poland and research on the effects of environmental exposures among African American and Dominican mothers and newborns from New York City. Dr. Whyatt's particular focus is the effects of prenatal exposure to non-persistent pesticides (organophosphates, carbamates and pyrethroids) and phthalates among this minority population. She is principal investigator on a number of federal research grants including studies to validate biomarkers of prenatal pesticide exposure; to assess exposures to the newer use insecticides and to evaluate effects of phthalate exposures during pregnancy. She is also collaborating with the Center for Disease Control on the validation of biomarkers of prenatal exposure to contemporary-use pesticides. Dr. Whyatt has published widely on research using biologic markers in studies of prenatal exposures and has served on a number of federal committees. She currently serves on a National Academy of Science Committee on Human Biomonitoring for Environmental Toxicants and is co-chair of the chemical exposure workgroup for the National Children's Longitudinal Cohort Study.

Speaker 4: Dr. Halûk Özkaynak, USEPA's National Exposure Research Laboratory

Title: Modeling Children's Exposure to Pesticides: Issues and Challenges

Description of Presentation: This presentation provides an overview of issues and challenges encountered in modeling children's exposures to pesticides. Opportunities for reducing model and input uncertainties are discussed. In particular, areas where field measurement data are especially important for model evaluation and refinement are identified. Recent pesticide exposure modeling studies indicate that major uncertainties in model results stem from data gaps for critical factors, including information on pesticide usage; the pattern and frequency of touching surfaces; hand- to-mouth and object-to mouth activity patterns; pesticide residue concentrations at different post-application times; residue transfer to the skin surface upon contact; where people spend their time in relation to where residues exist in the residential environment; and factors related to intake and uptake into the human body after exposure. As more exposure measurements data become available and collectively analyzed, uncertainties in the exposure model results should be reduced. By the same token, as model refinements progress, models will help define critical areas where further survey and measurement research are needed.

Dr. Halûk Özkaynak is a Senior Scientist at U.S. EPA's National Exposure Research Laboratory (NERL) in the Office of Research and Development (ORD). The principal responsibilities of his position includes developing and applying new exposure analysis and modeling methods for the assessment of population health risks in order to improve risk assessment and management decisions of EPA, by active collaboration with scientists from different ORD Laboratories, Centers and various EPA Program Offices. Dr. Özkaynak is presently the co-chair of the EPA Workgroup on Probabilistic Risk Analyses. He is also a member of the World Health Organization's International Programme on Chemical Safety (WHO's IPCS) Uncertainty in Exposure Assessment and EPA's Integrating Scientific Information Workgroups. Recently, he has served as the co-chair of the Chemical Exposure Workgroup of an interagency study in the US for the planned National Children's Study (NCS). Prior to joining EPA in 1998, Dr. Özkaynak was a Lecturer at the Department of Environmental Health of Harvard School of Public Health in Boston. His research at Harvard included directing a multi year environmental epidemiology study in Russia, and participating in various exposure assessment and community studies, including the National Human Exposure Assessment Survey (NHEXAS) and the Kanawha Valley Health Studies, both sponsored by the U.S EPA. Dr. Özkaynak is a former President of the International Society of Exposure Analysis (ISEA).

Speaker 5: Mr. Jeff Evans, Office of Pesticide Programs, Health Effects Division

Title: OPP Regulatory Perspective

Description of Presentation: This presentation will focus on how EPA can best use the data developed by ORD in the day-to-day regulation of pesticides. What has worked, what has not? What do we still need?

Mr. Jeff Evans is a Senior Exposure Assessor for occupational and consumer uses of pesticides, member of the Division's Risk Assessment Review Committee, and Chair of the Exposure Science Advisory Counsel. He is involved in the development of Standard Operating Procedures for Residential Exposure, Occupational and Residential Exposure Study Guidelines, and Cumulative Exposure Assessments for the Organophosphate and Carbamate Pesticides.

Chapter 2
Summary of the Workgroup Reports

Individual workgroup reports can be found in Appendix A. This section describes the common ideas, by theme, that were independently developed in each workgroup.

Theme 1: Major trends in the data across children's exposure studies.

a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?

- Evidence suggests that diet is one of the major sources of exposure to pesticides.
- Indirect ingestion may be an important route of exposure to pyrethroid pesticides.
- Inhalation may be an important route of exposure to organophosphate pesticides.
- Drinking water was not considered an exposure source for most children.
- In general, beverages other than pure fruit juices can be dismissed as an exposure source.
- Other potentially important sources and routes of exposure that were identified included: "excess dietary" ingestion (i.e., added contamination to foods from hands and residential surfaces during eating), prenatal/gestational/lactational exposures, indoor residential pesticide usage, other indoor environments where young children spend time, outdoor applications on the lawn, agricultural areas, mosquito control, occupational take-home exposures, pets, and personal care products.
- While risk assessments must account for all routes of exposure, further analyses should be undertaken to investigate if chemical class membership or physicochemical properties can be exploited in determining the dominant route of exposure for individual pesticides.

b. Identify the major factors that influence children's exposure or dose to the pesticides.

- Non-dietary ingestion, especially hand-to-mouth activity.
- Diet.
- Children's activities and behavioral patterns, including hand washing and bathing.
- Food handling behaviors.
- Bioavailability of the pesticide.
- Chemical specific exposure factors such as volatility, water solubility, degradation, and toxicokinetics.
- Specific product use characteristics, including numbers and types of pesticides applied in the indoor environment.
- Spatial and temporal variability in the indoor environment.
- Other exposure factors including demographics, specific food consumption patterns, physiological factors.

c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

- In general, the observations presented in the NERL studies are consistent with results from other studies and with current assumptions.
- All groups noted the importance of gaining a better understanding of the levels of pesticide metabolites in environmental media and how those levels influence the interpretation of urinary biomarker data.

Theme 2: Additional hypotheses that should be tested using existing data?

The workshop participants were asked to propose additional hypotheses that should be tested using the existing data. More often than not, the discussions generated a series of important research questions, but not necessarily research questions that could be tested using NERL's existing data. In theme 2, section a, we list many of the research questions that were raised during the two-day workshop.

a. Provide a list of the major research questions that could potentially be tested on existing data.

- Are the algorithms correct?
- What are the best inputs to use in the algorithms to assess children's exposures to pesticides? How can the algorithms be refined?
- Are the toxicokinetics similar for classes of chemicals?
- How do we reduce the uncertainty in the most important exposure factors, such as hand-to-mouth transfer?
- Is peak exposure or average exposure the most important metric with respect to health effects?
- Is indirect ingestion a significant route of exposure? How do we accurately estimate indirect ingestion? What is the magnitude of intra- and inter-personal variability? Are there discernable characteristics associated with the magnitude of the indirect ingestion?
- Can creatinine levels in children be used as a proxy for activity level?
- How is pesticide fate and transport different now that we are using less volatile pesticides? What is the relationship between volatile/less volatile pesticides?
- Does changing the resolution of sampling time affect the correlation with urine?
- Do biomarkers correlate better with peak exposures than with average exposures?
- Are there behavioral measurement tools currently used in other fields that we can adapt to help us gain a better understanding of the activity/behavioral/pesticide exposure relationship?
- Are there alternative approaches that utilize behavioral categories that can be used instead of the micro-environment approach and can these be related to transfer coefficient estimates? Is grouping children by macroactivity classification more descriptive as a model input than using microactivity classifications?
- Would removing the dietary contribution allow a clearer understanding of the remaining pathways and an enhanced sensitivity analysis?
- How do results from high exposure situations (e.g., post-application scenarios or identified high-use populations) compare to the overall population's environmental and biological levels?
- Does input of OPP transfer coefficients (and related assumptions regarding absorption) give results consistent with observations?
- For studies where dermal transfer coefficients can be calculated, are the values consistent with the values used by OPP?
- What are the impacts of sampling methods on measured dose calculations? Are different answers obtained based on the specific methods used?
- Which environmental media contribute significantly to urinary biomarker levels?
- Do one or more environmental measurement parameters correlate with absorbed dose distributions for biomarkers?
- Are urinary biomarker levels significantly increased due to crack and crevice applications?
- What is the significance of total versus vapor-phase inhalation exposures?
- Do individuals who consume large amounts of leafy vegetables have higher exposures to pesticides?
- Does accounting for direct intake of the metabolite improve modeled estimates of absorbed dose?
- Are there spatial distributions in the indoor environment? How do we effectively capture these distributions?
- Are there regional differences in the magnitude of the residential exposure?

- What alternative biomarkers of exposure should be considered? Are urinary biomarkers really the most appropriate?

b. Why are these considered to be important hypotheses?

Testing these hypotheses will help to determine the following:

- How to better understand and capture children's activities.
- How to apportion the routes of exposure based on relative importance; whether the route apportionment is related to the physico-chemical characteristics of the chemicals; whether chemicals can be evaluated as a class.
- How to use biomarkers of exposure to understand and interpret children's exposure.
- How to reduce the default values that are being used in the algorithms, models, and regulatory risk assessments.
- Whether the algorithms need to be refined, and, if so, how.

c. How suitable are the existing data? What is still missing?

The following were identified as data gaps or issues with the existing data:

- Temporal dimension.
- Data on very young children (under 3 years).
- Missing data elements (e.g., dietary information for young children).
- Measurement methods and method detection limits (MDLs) differ. The treatment of non-detects has not been consistent across studies.
- Time activity data and pesticide use information limited and of questionable accuracy.
- Scenario specific measurements from food handling establishments.
- A thorough mining of the questionnaire data. Analysis of the questionnaire data to determine the information that contains predictive ability.
- Unification/standardization/normalization of methodologies and QA/QC procedures.
- A comparison of the studies to national trends or the larger population.
- Aggregated/uniform data sets of larger studies.
- Parent/metabolite relationships in environmental media.

Theme 3: Additional statistical analyses that can be performed on these data to better understand children's exposures to chemicals at homes and daycare centers?

Provide a list of statistical analyses that could be performed on the accrued data. For each proposed analysis, please specify

a. What data gap are you addressing?
b. What key hypothesis are you testing?
c. What result do you expect to find?
d. What is the likelihood of success, given the limitations of the data?

The discussions on additional statistical analyses that could be performed on the accrued data were not as developed as we had hoped. In many instances, additional statistical analyses were discussed, but the data gap being addressed, the key hypothesis, the result expected, or the likelihood of success were not discussed in relation to the statistical analysis proposed. The following list of bullets highlights the various statistical analyses proposed by the workgroups.

- Create a data warehouse where all the data from these studies can be housed for statistical analyses and model evaluation. Perform more multivariate analyses using all available environmental measurements and questionnaire data to describe the relationships between the measurements and the biomarker over time. Pathway analysis should be included in these

analyses. Model testing should be included with these analyses. Evaluate the relationship between the environmental concentrations and the biomarkers. For example, ANOVA, Bayesian hierarchical analysis, sensitivity analysis.

- Statistically analyze the data set to estimate the parameters that go into the mechanistic models.
- Evaluate the relationship between the variability in the biomarker data and the dietary data.
- Normalize the data based on age, gender, and body mass.
- Compare the NERL data to other available data.
- Use the principal component analysis as a method for dealing with the interdependence of the environmental measurements.
- Apply pharmacokinetic data to adjust the dose estimates.
- Examine the currently applied assumptions to investigate the disparity between the environmental and urinary concentrations.
- Pharmacologically adjust the calculated dose based on the previous days environmental measurements (when the environmental and biomarker sampling schedules are temporally coherent).
- Develop exposure estimates based on OPP methods and compare to biomonitoring results.
- Cluster analyses.
- Compare the inventory data collected with the Residential Exposure Joint Venture (REJV) national survey.

Many research questions and statistical analyses were proposed in themes 2 and 3. The following is the authors' prioritized list of the research questions and statistical analyses that we believe we can successfully evaluate with the data.

Research questions:

- Can creatinine levels in children be used as a proxy for activity level?
- Does changing the resolution of sampling time affect the correlation with urine?
- Do biomarkers correlate better with peak exposures than with average exposures?
- Would removing the dietary contribution allow a clearer understanding of the remaining pathways and an enhanced sensitivity analysis?
- Does input of OPP transfer coefficients (and related assumptions regarding absorption) give results consistent with observations?
- For studies where dermal transfer coefficients can be calculated, are the values consistent with the values used by OPP?
- Do one or more environmental measurement parameters correlate with absorbed dose distributions for biomarkers?
- Do individuals who consume large amounts of leafy vegetables have higher exposures to pesticides?

Statistical analyses:

- Evaluate the relationship between the environmental concentrations and the biomarkers.
- Evaluate the relationship between the variability in the biomarker data and the dietary data.
- Normalize the data based on age, gender, and body mass.
- Compare the NERL data to other available data.
- Use the principal component analysis as a method for dealing with the interdependence of the environmental measurements.
- Examine the currently applied assumptions to investigate the disparity between the environmental and urinary concentrations.
- Develop exposure estimates based on OPP methods and compare to biomonitoring results.

Chapter 3
Summary of the Open Discussion on Collaboration

- Linda Sheldon opened the session. She indicated that this should be an informal discussion of ways that exposure researchers could collaborate on data analysis efforts.
- Janice Sharp (Valent BioSciences) is currently the chair of the Non-Dietary Exposure Task Force (NDETF), a group that represents the pyrethrin and pyrethroid pesticide supplier/manufacturer industry. Janice discussed the research-related work of the Task Force and the potential availability of data. NDETF has done a lot of research on the pyrethroids. This includes laboratory testing on pesticide degradation and transfers to surfaces (e.g., hand presses). She was concerned that a lot of the studies they have done may be considered dosing studies by EPA under the new rulemaking. Much of the data has been provided to OPP. She may be able to make some of it publicly available.
- The pesticide industry has performed the Residential Exposure Joint Venture (REJV), a survey of pesticide use in the U.S. They have made the data available to EPA/OPP and EPA/ORD.
- Curt Lunchik indicated that industry is very interested in sharing data. There was a discussion of how the process would work for EPA to obtain industry data. Data can be shared as confidential business information. It was suggested that HEASD take a lead in trying to move this effort forward.
- Elaine Cohen Hubal suggested that the best way to move collaborations forward to maximize the utility of data collected by different organizations would be to identify one to three questions of greatest importance and try to answer these. If there is a hypothesis to be tested, we can then determine what data are needed, who has the data, and pull the data together from all available sources for the analyses.
- Rich Fenske suggested that the Pesticide Handler Exposure Database (PHED) was an example of how this has worked in the past. Curt and others indicated that the Agricultural Handler Exposure Database (AHED), the successor to PHED, is the current example.
- A number of researchers discussed potential questions/research areas that could be used to start the collaborations.
- Curt Lunchik, with agreement from a number of others in the group, suggested that the first area could be analyses of existing biomonitoring data to look at the relationship of pesticide metabolite levels and measurements of the parent pesticide(s) in environmental media. There are many groups that have urinary metabolite levels and other measurements. Linda Sheldon suggested that we needed to start small with a "doable" project. Roy Fortmann suggested that the project should start with the pyrethroid pesticide metabolites because there is some data and they are the current-use pesticides. He suggested that the analyses of chlorpyrifos/TCPy relationships may be more difficult and less relevant. There is an International Life Sciences Institute (ILSI) workgroup headed by Linda Sheldon that might consider this as a project. The group suggested that Linda's workgroup pursue this effort.
- The second potential area, suggested by Lisa Melnyk, was quantifying behavior/activity. There was agreement that this is an important area, one in which a number of researchers have worked, but the approaches to collect information on activities and behavior, as related to children's exposures, have been highly variable. Researchers in industry, academia, non-profits, and government have collected data. There was discussion about forming an Activity Workgroup that would evaluate what data are available and determine how to proceed. Lisa Melnyk was drafted by acclimation to chair the workgroup.
- Carry Croghan suggested that an effort should be made to compile available methods, SOPs, and questionnaires from children's exposure studies. Roy Fortmann objected, considering this to be too large of an effort that was not justified unless a clear purpose was identified for this database.
- Asa Bradman discussed potential intervention studies that should be considered. These included (a) a removal study where participants are moved to a pesticide-free home, you control for diet, and collect urine samples to measure exposure, (b) a deep cleaning home study, (c) a fasting study,

and (b) food elimination studies where certain classes of foods are not included in the diet. There was not extensive discussion on this topic.

- The session was closed, having identified the following areas in which to initiate collaborations and leads on these efforts:

    1. Linda Sheldon's ILSI group to take a look at analyses of existing biomonitoring data to look at the relationship of pesticide metabolite levels and measurements of the parent pesticide(s) in environmental media starting with the pyrethroid pesticide metabolites, and,
    2. Lisa Melnyk to start an Activity Workgroup to study how best to quantify and measure the effect of behavior/activity on children's exposure to pesticides.

Appendix A
Individual Workgroup Materials

GROUP A:

In an effort to provide a safe and healthy environment for children, EPA has conducted research to provide a scientific foundation for risk assessment and risk management to meet mandates of the FQPA. NERL has designed and conducted several field studies to address these needs. The studies have been summarized and presented to a panel of exposure assessors and modelers in government, industry, and regulatory fields during a workshop held September 27 – 28, 2005. Four groups were formed to evaluate the data and discuss additional research needed to better understand the linkages between the exposure data and risk associated with an event. The groups were each given 3 themes with some charge questions. A summary of Group A responses and discussion are given here.

Theme 1: Major trends in the data across children's exposure studies.
a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?

b. Identify the major factors that influence children's exposures to the pesticides.

c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

Discussion
a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?

All sources and routes were identified as being important depending on the event, i.e., following application or no application. Diet was recognized as being significant based on the data from CTEPP, but drinking water was not a concern if it came from a public water supply system. Beverages were demonstrated to not be an important source, but the group was unwilling to completely dismiss the collection due to possible contamination in fruit based drinks, e.g., apple juice. An important aspect that was not completely understood was the contribution of handling of food prior to consumption and the influence on overall dietary exposure. The small data available did not allow for much discussion on the influence of surface-to-food and surface-to-hand-to-food to overall exposure and resulting biomarker measurements. It was shown that low levels on hands did not account for levels on food, but, again, based on a small number of sample results.

Non-dietary ingestion was recognized as a highly possible source of exposure. Hand-to-mouth activity measurements were difficult to interpret. Replenishment of contamination could not be assessed with the data presented. Influences of behavioral aspects on overall exposure were difficult to determine with the datasets. This source is of great interest to the regulatory community since it directly affects their risk calculations. Food handling could also fall into this category (changing term to indirect ingestion). More information is needed in this area to better understand the contributions of non-dietary route to overall exposure taking into consideration the extreme variability of the class of compound, application time, activities that influence the measurement or estimation, etc. (ex. 3PBA and TCP in environmental samples vs. pesticide exposure). Three reasons for the difficulty in determining non-dietary exposure were given and need to be addressed to adequately understand this route: 1) the difference between extractable vs. absorbed contaminant on the hand, 2) the difference between bioavailability of contaminant on dust vs. food, 3) transfer efficiency unknown.

A concern raised for the ingestion route was the unknown bioavailability of the contaminant. An experiment that was identified was to evaluate the difference in body burden between spiked food vs. spiked matrix ingestion (dust). Also largely unknown was the transfer efficiency from the hand to the

mouth. Many associated exposure factors come into play when trying to determine hand-to-mouth measurements. In addition to understanding the hand wipe data, methodology issues were identified. What solvent do you use to estimate this (methanol, saliva simulant)? How do you address the inability to measure source strength (hand loading)?

Inhalation seemed to be adequately addressed, but the concern was whether or not it is an important route of exposure for pesticides currently in use. Questions were raised about the adequacy of the measurement, importance, and whether the exposure changes from particle bound to free contaminant. Importance of the inhalation route is compound dependent, location specific (indoor vs. outdoor), and dependent on the health concern. It was recognized that inhalation is well characterized and may not be a major contributor.

Dermal exposure can be measured well for applied levels, perhaps not for real world samples. This is the major route of exposure after pesticide is applied, although this was not based on the data presented. Passage through skin to blood may be affected by additives (surfactants, inerts, formulations). Producers try to minimize dermal adsorption in formulation.

The discussions on routes and sources led to a focus on overall exposure. Low level chronic exposure and episodic events both contribute to overall exposure. Acute exposure vs. chronic and resulting health effects were raised as a concern. Does it vary compound to compound? We know more about acute than chronic health effects. Acute effects are required to be listed for a new pesticide, chronic are not. Chronic exposure may be a string of high level exposures.

To summarize all the sources and routes with their importance, a table was constructed. All routes need to be addressed. The relative contribution differs based on the type of study and particular pesticide addressed.

Study Type	Route of Exposure			
	Dietary	*Non-dietary	Inhalation	Dermal
After application			√ Possible (class dependant) ex. DDVP	√
Chronic	√ +	√ +		

*need non-dietary measurement research to better quantify
√ = effected route; √ + = greatly affected route

The central concern that pulls all of the exposure data together to address risk is the results of the biomonitoring. However, the link between exposure measurement and health effect is critical. This is obtained through a better understanding of bioavailability. Dietary ingestion seems to be well accepted as complete adsorption. Other routes are not well understood. Being able to measure a contaminant does not necessarily mean that it's bioavailable. This relationship needs to be better understood, maybe through PBPK modeling.

b. Identify the major factors that influence children's exposures to the pesticides

The discussion of this question is folded into the responses for question a.

c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

In general, the trends in the NERL studies for measured absorbed dose were consistent with other information; however, there are many studies and the data do not seem to be compiled to address absorbed dose. The information in the summary should be presented in a more useful format so that all the information can be digested. It was understood that each study had its own objectives and goals which may make the combining of data difficult, especially with differing measurement methods used.

It was suggested that potential routes of exposure could be eliminated as not being a major contributor based on planned study results and not speculation. The group questioned the worth of the effort to measure exposure rather than trying to determine what led to the absorbed dose.

Theme 2: Additional hypotheses that should be tested using existing data?
a. Provide a list of the major hypotheses that could be tested on existing data.
b. Why are these considered to be important hypotheses?
c. How suitable are the existing data? What is still missing?

Discussion

Group A came up with three hypotheses that were worth studying with the existing data:

1. What are the impacts of sampling methods on measured dose calculation? Do you get a different answer based on what method you use?
For example, Alcohol wipe vs. bologna for surface concentrations.
Which environmental monitoring technique has a better correlation to concurrently monitored absorbed dose (biomarker/exposure)?
Many techniques to be evaluated (many media).

Why? So we can use the data that we have with assurance of its reliability to improve study guidelines and to develop consistent measurement protocols.

Data suitable? Yes.

2. Which environmental media contribute significantly to absorbed dose?

Why? So we can focus on the appropriate and most effective media to monitor and to look for mitigation approaches.

Data suitable? No.

3. Refine risk algorithms.

Data suitable? Yes.

Theme 3: Additional statistical analyses that can be performed on these data to better understand children's exposures to chemicals at homes and daycare centers?
Provide a list of statistical analyses that could be performed on the accrued data. For each proposed analysis, please specify
a. What data gap are you addressing?
b. What key hypothesis are you testing?
c. What result do you expect to find?
d. What is the likelihood of success, given the limitations of the data?
Please prioritize the proposed analyses.

Discussion

This proved to be the most difficult task for Group A. Some of the discussion centered on the phenomenon of biomarker concentrations not explained by exposure measurements. It was theorized that a problem exists in the route/pathway algorithm; either a pathway is missed, the algorithms are off, or some exposure scenarios are missed. If there were only a 2-fold difference between exposure and biomarker, the producer of the pesticide would be satisfied. That is rarely the case. It was suggested that the algorithms need some work. The assumptions may or may not be correct. For example, the current assumption for hand loading is 100% absorption. This may not be accurate.

Time is one of the biggest factors on which to focus. Too much emphasis is placed on hours when days would be more appropriate. Hours are too short of a time frame to analyze exposure. One bad assumption is the linearity of the additive model. Exposure and biomarker output are not linear and treating them as such results in more questions than answers. It appears that a more systematic way to understand the data is needed.

After a long discussion about the value of the current data set, the group agreed on the first statistical analysis.

1) More multivariate analyses using all available environmental measurements to describe the relationships between the measurements and the biomarker over time. Pathway analysis is part of this. Other suggested techniques include, ANOVA, Bayesian hierarchical analysis, and sensitivity analysis on the current data set.

This will help us understand the relationship between the biomarker and the environmental measurements. For each individual study, correct statistical analyses the first time is critical, and then try to put the studies together. Pay attention to application events versus non-application. Results should be aggregated separately for application and non-application studies. Look at logs closely. Meta-analysis across population-based studies should be evaluated. Meta-analysis across application studies should be evaluated separately.

Urine analysis was the most common biomarker measurement. The sampling procedure and analysis varied by study. Understanding the best method for collection and analysis of the biomarker is essential. Two groups can be defined for analysis; exposed and non-exposed. The ultimate goal is to get an algorithm to give an accurate estimate of absorbed dose. Three or four exposure measurements that are good predictors of absorbed dose would be ideal. There was much debate over creatinine correction and whether to trust this data. Can a first void and spot urine collection be compared?

It was suggested that sensitivity analysis be performed on individual measurements to determine the kind of distribution that can be assigned. Variability is associated with every measurement, so all have distributions. This is a huge task to tackle. However, understanding the contribution of each source by route will lead to better exposure estimates.

2) Statistical analysis of data set to estimate parameters that go into the mechanistic models

A large data set should be used to test SHEDS. The data could be used to validate the model and its algorithms to test the predictions against the measured exposure; although there was no consensus on this point.

This suggestion would give us distributions of mechanistic model parameters after previous comments are incorporated, especially with time and linearity. More focused analysis of the data could be performed.

3) How much variability in biomarker is explained by dietary data?

Since most of the data points show ingestion as the major route of concern, Group A suggested looking more closely at the diet. The DIYC study was specifically designed to look at exposed vs. not-exposed,

and coordinated the timing of the biomarker with the exposure measurements. It was suggested that the USDA study in which dietary exposure was controlled should be reviewed to determine if the trends are the same as the data presented.

4) Normalize based on age, gender, body mass?

Time ran out during the discussion of this last recommendation for new statistical analyses. It was determined that CTEPP may not be the best data to evaluate this idea. It was hoped that this would explain more of the variability in the biomarker measurements. However, a danger exists in losing the specifics.

GROUP B:

Theme 1: Major Trends in the Data

Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?

1A Major Sources / Routes

- Diet
    - There is compelling evidence that diet is one of the major sources of exposure for pesticides
        - Curl et al. (2003) reported a median total dimethyl phosphate metabolite concentration approximately six times higher for children with conventional diets than with organic diets.
        - Lu's dietary intervention study (in press) found that the median urinary concentrations of the specific metabolites for malathion and chlorpyrifos decreased to the non-detect levels immediately after the introduction of organic diets and remained non-detectable until the conventional diets were re-introduced.
        - CTEPP estimates (based on multimedia samples) found dietary to be the dominant route for chlorpyrifos and permethrin exposures.
        - CPPAES study found no detectable increase in urinary metabolite concentration following crack and crevice application, even with air and surface levels hundreds of times higher than levels measured in CTEPP.
        - Consistent lack of correlation between usage questionnaires and measured metabolites indirectly supports diet hypothesis.

In summary, group consensus suggested that the organic diet study was sufficiently compelling to warrant additional investigation and validation.

    - However, the group was not ready to accept that it is all dietary or that other routes can be completely de-emphasized.
        - Additional intervention studies are needed to validate findings.
        - Diet does not explain elevated biomarker levels observed in high-use areas such as Jacksonville, FL.
        - Results of DIYC study suggest that "excess dietary" ingestion is a highly important factor.
        - Studies in which diet is controlled are needed to investigate the other routes.
        - Great uncertainty exists in algorithms used to estimate route-specific doses.
        - Formal sensitivity analysis of route-specific contributions appears to be lacking, but remains to be clarified.
        - Must account for all relevant pathways for risk assessment.
    - Diet needs to be addressed properly in future planning for community-based cumulative risk research.

In summary, although it was generally agreed that diet is a significant contributor of pesticide exposures, the group felt that all pathways must be considered. The risk assessors strongly indicated that all pathways, based on current assessment approaches, must be accounted for and measured inputs provided.

- Prenatal/gestational/lactational exposure as a major route of exposure for fetus/child.
    - Extent of breastfeeding is culturally-dependent.
    - Evidence of differences in pharmacokinetics during pregnancy.
    - The group recommended more research on prenatal exposure.
    - Since mother's exposure routes are different than the child's, must not limit measurements to only those relevant to young children.
    - Characterize the mother's exposure across all routes and it may be different than that of the child.

In summary the group agreed that prenatal measures were important for determining the cause of some health impacts. The association shown between cord blood and both birth outcomes and developmental milestones merits further research. In addition, the use of cord blood may circumvent difficulties related to blood draws from children.

- Indoor Residential Pesticide Usage
    - Columbia researchers found a correlation between insect infestations and pesticide use.
    - Berkley researchers found that pesticide usage is highly dependent upon individual tolerances for insects.
        - They found a 60% cockroach infestation rate, but only a 50% insecticide use rate.
    - Self-reported pesticide use may not be accurate.
    - Dust/indoor air concentration ratio determined by a pesticide's physical properties.
    - Non-persistent pesticides appear to persist in the indoor environment longer than previously believed.
    - Hygiene differences between licensed and non-licensed applicators.

In summary, elucidation of indoor pesticide usage is complex and entwined with human behavior. Research should continue to understand occupant perceptions of pests, pesticide usage, and safety.

- Lawn and Garden Residential Pesticide Usage
    - Anecdotal evidence suggests that garden pesticides are used in quantities exceeding label recommendations.
    - Increasing use of pesticides on lawns for purely aesthetic reasons.
    - Track-in of outdoor pesticides has been observed in previous studies.

- Residential Contamination by Agricultural Pesticides
    - Many agricultural pesticides have been measured indoors, with persistent pesticides measured more frequently.
    - Classifying residential exposure to non-persistent agricultural compounds is difficult, but is required for risk assessment purposes.
    - Occupational exposures may result in the take-home of pesticide residues and subsequent exposures for farm families.
    - Berkeley researchers have measured elevated levels of the pyrethroids in dust in agricultural communities.
    - Spray drift is not seen as a major source for exposure.

- Occupational Take-Home Exposures
    - The Agricultural Health Study has documented exposures to spouses.
    - The Washington studies found a correlation between levels of agricultural pesticides in automobiles and in homes.
    - Compliance with hygiene interventions among field workers has been low. For example, work clothing is often used repeatedly without washing.

In summary, occupational exposures contribute to familial exposures. There are opportunities through educational efforts (using appropriate, verifiably effective communication techniques) to provide interventions and reduce potential exposures to the families of the occupationally exposed.

- Pets
    - Little is known about the role of pets in children's exposures.
    - Few published studies are available.
    - Results from the Pet Pilot Study suggest that active pets may serve as an important vehicle for transport of turf-applied pesticides into dwellings.

In summary, the group felt that pet borne exposures might be important, but a lack of familiarity with the data prevented the group from developing solid conclusions.

- The "Missing Other"
    - There are clearly many sources of exposure that remain unidentified or unmeasured.
    - Includes pesticide use in institutional and retail settings.
    - Individuals are likely to be unknowingly exposed.
    - Prophylactic applications
        - Performed in retail food handling establishments (e.g., markets, restaurants) for sanitation reasons.
        - Performed in daycare centers/schools for licensing reasons.

In summary, the group felt strongly that other scenario-specific exposures were worth investigating. In order to understand total exposure it was considered important to quantify the contribution of locations other than the home.

1B Major Factors

- Measurement Issues
    - Are we measuring the right things?
        - Are the correct pesticides being measured? Columbia researchers found high levels of carbamates indoors, but these are not included in the EPA children's studies because of low reported usage.
        - We need to be careful in assuming that all important pesticide exposures are from non-volatile pyrethroids. The semi-volatiles may not be as dead as assumed.
        - Studies show that pesticides no longer used remain at measurable concentrations indoors.

In summary, researchers need to be aware of the breadth of pesticides present in indoor environments. The group would like more pesticides measured in future studies.

    - Are we measuring pesticide exposures correctly?
        - Are we using the correct items from the "measurement toolbox?" Are the measures adequate?
        - There is a clear lack of standardization of measurement methods. Different surface measurement methods result in greatly different loading estimates.

In summary, the group strongly felt that there was a lack of standardization among the approaches and methods employed in human exposure studies. Unanimously it was believed the comparability between studies would be enhanced by either standardizing approaches or showing the relationship between different methods.

- Exposure Variability
    - Intrinsic variability may not be accounted for, leading to substantial measurement error and exposure misclassification.
    - Temporal variability in environmental concentrations remains largely uncharacterized.
        - Believed to be compound-dependent.
        - Longer measurements or increased numbers of random measurements may be necessary to accurately quantify exposures.
    - High spatial variability was observed in focused studies (e.g., Test House). Expert judgment is often used to select surfaces to be sampled; are we capturing the full range of surface loadings with which children come into contact?
    - We may not know where the current resolution (either temporal or spatial) is insufficient. There is a need for additional laboratory experiments to determine the resolution required.
    - High temporal variability observed in urinary biomarker measurements.
        - Spot and 24-h samples are correlated, but samples separated by 3-day intervals are poorly correlated.

        - Temporal aspects are multi-factorial (including environmental and pharmacokinetic).
        - Environmental levels do not change as rapidly as biomarkers, pointing to important effect of activities.
        - Higher urinary excretion has been observed in post-partum period.
            - Need experiments on lipid storage during pregnancy.
            - Are pesticides being selectively released after birth; is there a higher level of metabolism?
            - How do you interpret biomarker measures from pregnant females?

In summary, temporal and spatial variability merits additional considerations. The variability over space and time may influence biomarker concentrations. In addition, standardized approaches for sampling surfaces are required to insure that samples are representative of the actual distribution.

- Exposure Metrics
    - Exposure peaks may be more important than average levels for certain important outcomes. Episodic events can also influence exposures and may be more important for outcomes. Exposure spikes may be critical for vulnerable and susceptible subpopulations, such as developing fetuses.
    - There is a tendency to measure blindly. We should first do back-of-the-envelope calculations and determine if we could actually capture a measure or determine what that measure might be (a sensitivity analysis).

In summary, the group felt that peak exposures might be more important for certain outcomes. However, the evidence for capturing peaks is not well supported particularly when considering generalized outcomes. Peaks might be difficult to capture and nebulous across multiple media.

- Exposure Classification: Epidemiology *vs.* Risk Assessment
    - Differences exist between epidemiological and risk assessment needs.
    - NERL's focus has been on links among exposure, uptake, and dose.
    - Risk assessors want distributions.
    - Risk assessment may benefit from methods used by Homeland Security.
- Classification of Exposure-related Behaviors
    - Exposure variability across individuals is thought to be influenced to a large degree by individual behaviors.
    - What is the theoretical basis for the supposition that higher activity levels lead to greater exposure?
        - Fenske's GPS data of child on bicycle suggests that greater area covered increases chances of contacting contaminated areas.
        - Daycare study found a correlation between qualitative assessment of relative activity levels and bodysuit loadings.
        - Group discussed anecdotal evidence that seemed to suggest that the children who moved the fastest accumulated the least amount of dermal loading (e.g., "a rolling stone gathers no moss").
    - We have not approached behavior systematically; have not explored other disciplines for their experiences.
    - The activity questionnaire approach may not be the best or get us where we want to go. Categories of active and passive may not be appropriate.
    - Perhaps we cannot capture exposure-related activities mechanistically (hand-to-mouth counts).
        - Instead of distilling down to touches, move to more general factors. Counting is not practical for capturing behavior, thus some other type of metric is needed to effectively describe behavior-dose relationships.
    - Are there ways to more accurately classify behavior with respect to exposure? The influence of personality and psychological factors on exposure needs to be explored.

        - Apply existing instruments like the "Child Behavior Check List" for appropriate ages.
        - Use existing instruments that characterize temperament or personality.
        - Other factors like attention span and tactile proclivities may be important.
        - Some personality factors may be linked to physical factors; for example, hyperactive children may have higher respiration rates.
        - The field of Environmental Anthropology should be consulted.
        - Group discussed how this could be incorporated into scenario specific distributions required by risk managers for assessments.

The risk assessor present clearly indicated that he had specific needs in order to estimate risk. It should be noted that the attending risk assessor was somewhat skeptical of several concepts introduced in this section. The introduction of individual behavior and quantification of behavior are not easily incorporated into the risk assessment process.

- Reliance on Biomarkers
    - Route-specific contributions do not seem to add up to what is excreted.
        - Estimated dose exceeds the various routes.
        - Are there unaccounted for sources?
        - Are algorithms sufficient?
        - Are assumptions accurate?
    - Creatinine adjustments specific to different age groups are not available.
    - There is a current emphasis on interpreting biomarker data.
        - For persistent compounds we have a good feel for their meaning, though perhaps not for kids.
        - Captures general population but not the tails.
    - Interpretation muddled by uncertainties in the parent-metabolite relationship.
    - Why not focus on parent compounds?
        - Parent compounds must be measured in blood, but getting blood from kids is difficult.
        - Sufficient volumes are difficult to obtain in order to be able to analyze for pesticides.
        - One idea is to use umbilical cord blood. Parent compound makes it through to baby, but metabolite does not.

In summary, due to the lack of association between urinary biomarker concentrations and multimedia, multi-route exposure measures, there was some doubt that the contribution of environmental concentrations had been fully explored and sources properly identified. We do not know enough about creatinine excretion in children and fetus/parent relationship to fully integrate exposure to biomarker relationships. The group considered whether focusing on parent compound might be a better approach than the metabolite.

- Type of Applications
    - Potential exposure implications of licensed applicator *vs.* home applications.
    - The data to test this hypothesis is currently available in the large regional studies presented as part of this workshop.
- Chemical Class
    - Dust is a reservoir for pesticides that have been applied indoors or have intruded from outdoor sources.
    - Physical properties are believed to affect transfer from surfaces to skin, and may affect route-specific contributions.
    - Predominant routes of exposure are distinctly affected by the unique properties of an individual pesticide, particularly vapor pressure.
    - Exposure to carbamates has been largely ignored, but there are a few carbamate insecticides registered for use indoors.
- Transfer efficiency
    - Needs to be clarified and is likely an important factor.

In summary, the determination of transfer efficiencies is complex and driven by multiple factors (e.g., surface concentration, maximal dermal loading, removal, physico-chemical properties of the active ingredient, etc.). Additional work is required to integrate complex factors in order to derive a meaningful value. However, it was clear that the risk assessors desired a value as part of the risk assessment process.

- Age
    - In CHAMACOS, an agricultural effect was only seen in kids less than 12 months old.
    - Major sources and routes of exposure change with a child's age.
    - Diet complexity changes with age.
- Culture
    - Influences breast feeding rate and duration. The Berkeley researchers found no difference in urinary biomarker levels between bottle- and breast-fed babies.
    - Determines types of take-home exposures. For example, some cultures remove shoes prior to entry.
    - Diet varies markedly among some cultures.
- Pets

1C. Consistent with Current Assumptions?

- CTEPP nicely demonstrates that residues in food are important.
- The group did not identify inconsistencies with currently held assumptions.

<u>Theme 2. Additional Hypotheses that Should be Tested</u>

2A List of Major Hypotheses

- Does changing the resolution of sampling time affect the correlation with urine?
- Do biomarkers correlate better with peak exposures than with average exposures?
- Would changing the resolution of sampling periods result in improved correlations?
- Would averaging environmental concentrations over longer periods of time improve biomarker correlations?
- Are there behavioral measurements, for example "temperament", that we can use to test an effect on the transfer to the child?
- Are there alternative approaches that utilize behavioral categories that can be used instead of the micro-environment approach, and can these be related to transfer coefficient estimates?
- Would removing the dietary contribution allow a clearer understanding of the remaining pathways and an enhanced sensitivity analysis?
- How do results from high exposure situations compare to the overall populations' environmental and biological levels?
- Are dermal transfer factors from the JAX study consistent with values used by OPP?

2C What is still missing?

- Scenario specific measures from food handling establishments.
- A thorough mining of questionnaire data.
- Unification/standardization/normalizations of methodologies and QA/QC procedures.
- A comparison of the studies to national trends or the larger population.
- The treatment of non-detects has not been consistent across studies.
- Aggregated/uniform data sets of larger studies.
- Parent-metabolite relationships in environmental media.
- Is urinary metabolite really the best marker? If not, what are alternative biomarkers (e.g., saliva, blood, cord blood)?

Theme 3: Additional Statistical Analyses

Rough Ideas:

Compare Data to Other Available Data

- Comparisons to other studies (e.g., occupational vs. non-occupational). What is the scale of exposure compared to occupational exposure (sense of magnitude)?
- Compare studies that applied pesticides to the survey studies.
- How do real measures relate to the model predicted exposures?

Crosswalk: Environmental Concentrations to Biomarkers

- Transfer factor successful in agriculture because of fairly standardized work practices such as time in field, duration of exposure, limited compounds, repetitive activities, etc. relative to residential environment.
- There are many different methods employed for determining transferable residues in residential studies, however, there are fewer and standardized approaches for agricultural assessments.
- Might not be realistic to expect to reconcile exposure and biomarkers measures.

Analysis Methods

- Use principal component analysis as a method for dealing with interdependence of environmental measurements.
- Apply pharmacokinetic data to adjust dose estimates.
- Perform comparisons of dose with other exposure metrics, such as: amount applied, time in home, number of family members, eating out vs. home, transportation, weather, un-mined questionnaire data, all pair-wise comparisons.
- Examine the currently applied assumptions to investigate the disparity between environmental and urinary concentrations (i.e., breathing rate, soil ingestion, etc.).
- Incorporate existing measurement and variability data into probabilistic models.

Prioritized Additional Statistical Analysis:

Define Expectations

- Define our expectation for correlation.
    - Consult lead (Pb) research to determine what the best association that we can hope for is.
    - Look at variability in children's blood lead measurements and environmental measurements and see what is achievable.
- Hypothesis: Data we have collected is as good as it is going to get.
- Expectation: Low correlation coefficient.
- Success: Lowering expectations is likely to be highly successful.

Dietary Background Normalization

- Perform a rank adjustment of biomarker levels using data from organic *vs.* conventional diet study, then correlate with environmental measurements.
    - Use post-intervention values from Lu's organic diet intervention study.
    - Subtract out dietary contribution.
- Hypothesis: Correlation exists between non-dietary routes and biomarkers, but dietary contribution must first be removed.
- Results: Better correlation between biomarker and environmental measurements.
- Success: Probable.

Adjust for Temporal Lag

- Pharmacologically adjust calculated dose based on previous day's environmental measurements.
    - Incorporating chemical ½-life.
    - Use pharmacokinetic derived dose.
    - Incorporate temporal lag in biomarker.

    - Stratify by age.
- Hypothesis: Urine is more related to previous exposures than contemporaneous exposures.
- Expect: Better correlation (or confusion).
- Success: Indeterminate.

Apply OPP SOPs

- Develop exposure estimates based on OPP methods and compare to biomonitoring results.
- Normalize sampling techniques.
- Purpose: Testing algorithms.
- Hypothesis: Current algorithms are very health protective.
- Expect: Health protective estimates.
- Success: High likelihood.

Other Analyses

- Compare dose against other metrics and all available data (questionnaires, weather).
- Take another look at assumptions.
    - Breathing rate
    - Soil ingestion
- Larger "Taking stock of exposure data" by including other available datasets.
- Employ Principal Component Analysis (PCA) to deal with interdependence of environmental measurements.
- Compare magnitude of our results to other available results (occupational, etc.).

GROUP C:

THEME 1 - Major Trends in the data across children's exposure studies

a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?

Historically, research regarding potential "personal" exposures in and around homes, including those to children, focused on airborne pollutants. Increasingly, however, studies have focused on microenvironments (indoors, outdoors, in-transit), sources (consumer products, combustion appliances, outdoor sources), media (food, air, water, surface residues, soil, dust), and unique pathways that contribute to total exposure for a given chemical. Non-dietary incidental ingestion resultant from children's mouthing behavior, for example, has been the subject of many hypotheses and studies regarding children's exposure to chemicals such as pesticides. However, pesticide exposure studies, including those that are the subject of this workshop, demonstrate that direct dietary intake is potentially the most significant source of exposure to infants and children. Dietary exposure alone, however, does not explain a significant fraction of total exposure for some subpopulations. For example, in the case of pyrethroid insecticides, non-dietary ingestion may be an important pathway of exposure to children; whereas, with organophosphates, the inhalation route appears to contribute more significantly to total or aggregate exposure. Additional research is needed to better characterize children's total (aggregate) exposure and the underlying source/pathway attribution. Further, the unique behavioral characteristics and patterns of children (e.g., toddlers) require further study to discern the impact to exposures experienced in specific microenvironments (e.g., indoor residential, outdoor residential, day care centers). Research involving urinary biomarkers of exposure (e.g., TCPy, 3-PBA) show considerable promise in this regard, but require concurrent measures of environmental media-specific residues to investigate the array of exposure sources and their respective attribution to the total personal exposure levels observed via biomonitoring. It is important to recognize that direct exposure to biomarkers (degradation products of pesticides) can occur in the environment, suggesting that in some cases, concurrent environmental measurements of the biomarkers themselves are important. Finally, it is important to recognize that estimation of parent-equivalent absorbed dose levels from biomarker measurements (e.g., urinary) requires a prior understanding of parent compound and biomarker toxicokinetics. The major sources and related factors that appear to influence children's exposure to pesticides are outlined below.

b. Identify the major factors that influence children's exposure to pesticides

Based on the existing studies, which focused on insecticides such as OPs and pyrethroids, the following observations can be made:

- Key sources of potential exposure to children include
    - Food (dietary; note: food-form contribution analyses are critical for children) (highest source)
    - Residential and other environments
        - Consumer products (microenvironments, e.g., day care centers, playgrounds, indoor surfaces, outdoor surfaces, pets, etc.)
        - Professional products (see above)
    - General area applications (e.g., agricultural areas adjacent to residential or institutional (such as schools) environments, geographic area mosquito control methods (such as aerial application, lawn)
    - Water (residue source strength and consumption depends upon the specific form, groundwater or drinking water, tap, bottled, wells, surface; there are important chemical and site-specific considerations that impact magnitude of potential residues in water; generally, water-related sources appear to be associated with low exposure potential; it is important to note that because of low residue concentrations and analytical limitations, contribution of water-related exposures from beverage consumption is often difficult to determine)
    - Personal products (e.g., head lice shampoos)

- Key exposure routes include
    - Oral ingestion (direct; diet)
    - Indirect ingestion (non-dietary)
    - Dermal (very complex exposure route/pathway; requires additional investigation using controlled studies; chemical-specific and behavioral-related factors are involved; relationship to incidental ingestion via hand-to-mouth behavior requires concurrent measurements of hand and environmental surface residue levels)
    - Inhalation (source and chemical-specific characteristics must be considered; e.g., respirable particles versus vapor-phase)
    - Role of dust (requires further investigation, e.g., pathways of exposure such as re-suspension and resultant particle size distribution)
    - Relative significance of each route requires further investigation
        - Chemical versus behavioral determinants (intra- and inter-person variability; source/route contribution variability for individuals)
        - Sensitivity analyses
    - Route-specific bioavailability is a key component (e.g., often assume 100% oral absorption of ingested residues; for example, residues associated with dust)
- Key chemical-specific exposure factors include
    - Functional group(s)
    - Volatility
    - Water solubility
    - Degradation (e.g., hydrolysis and photolysis)
    - Route-specific toxicokinetics
    - Chemical-specific product use characteristics (equipment, rates, directions)
- Key general exposure factors include
    - Demographics
    - Product use patterns (generalized, e.g., pesticide user versus non-user status; types of products being used; misuse patterns)
    - Temporal food consumption for specific populations
        - Where are the biggest uncertainties
        - Food frequency
        - Recipes (model evaluation opportunities)
        - Processing factors and degradation products (preparation, cooking)
        - Alternative analyses for non-detects; development of more sensitive analytical methods
        - Focused residue monitoring programs
    - Temporal children's activity patterns
    - Behavioral factors (e.g., surface and body-part-specific contact patterns and frequency; hand loading and mouthing patterns and frequencies as a function of activity level)
    - Physiological factors (e.g., body-part specific surface contact frequency, breathing zone location, inhalation rate, etc.)

c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

- Consistency with results from other studies should be further evaluated with respect to
    - Study design similarities/differences (demographics, product use information, if known, methodologies)
    - Review/confirm consistency of how existing studies address non-detect (ND) values
    - Must be specific regarding statistical metrics used to determine "consistency" (descriptive statistics, distributional characteristics)
    - Comparison at central tendencies versus specified percentiles
    - What to compare? (environmental media, route-specific exposure estimates, absorbed dose via biomarkers)
    - Consideration of outliers/data censoring

    - Population-based biological monitoring studies appear to be reasonably consistent (e.g., EPA-sponsored studies versus CDC data involving the same biomarkers); factors that may impact comparability can include urinary collection and analysis methods, intake of the biomarker itself, demographic differences, seasonal differences, geographic differences, unique dietary practices such as the potential role of imported foods in the diets of some sub-populations of children
    - Differences between scenario/situation-specific short-term measurements and population-based measurements of "steady-state", background exposures are apparent; further, results from studies involving specific "user" sub-populations may vary significantly; additional situational studies with specific user sub-populations recommended
- Consistency with current assumptions and children-specific exposure assessment methods (e.g., EPA Office of Pesticide Programs "Standard Operating Procedures" (SOPs) for Residential Exposure Assessment and related policy documents such as "Policy 12")
    - Time to revisit SOPs; coordination with EPA/ORD scientists (e.g., indirect, incidental ingestion)
    - Role of biological monitoring and guidance regarding protocols and interpretation of biomonitoring data (e.g., spot urine/first void and relationship to 24-hr excretion; review of historical literature/publications)

THEMES 2 and 3 – Additional hypotheses that could be tested using existing data (Theme 2) and Additional statistical analyses that can be performed on these data to better understand children's exposures to chemicals (Theme 3)

-- Provide a list of the major hypotheses that could be tested on the existing data.

- Major hypotheses that could be tested using existing data include the following:
    - Do one or more environmental measurement parameters correlate with absorbed dose distributions for biomarkers?
        - Practical, economical measures; assists with contribution analyses; provide measurement guidelines and protocols
        - Consider non-parametric versus parametric statistics (bivariate and multivariate)
        - Ongoing SEM and Bayesian analyses – consider including metabolites in SEM and HBM analyses
    - Are absorbed dose distributions significantly increased relative to "background" following indoor crack and crevice applications?
        - Needed to support regulatory safety determinations given high occurrence of the product types/exposure scenario
        - Sample size limitations; lack of pre- and post-urine samples
        - Combine CTEPP and JAX?
    - Cluster analyses – Environmental Measurements
        - CTEPP (e.g., air, soil measurements, etc.) – Do chemicals and/or media cluster
            - Addresses similarities/differences regarding environmental partitioning
            - Addresses co-occurrence in environmental media
    - Cluster analyses – Questionnaire Data
        - Identification of most important factors (e.g., associated with "higher" measurements for dietary sources)
        - Consolidation of questionnaire results to increase statistical power
    - What is the significance of total versus vapor-phase inhalation exposures?
    - Is indirect ingestion a significant route of exposure (hand-to-mouth, object-to-mouth, dust ingestion)? What is the magnitude of inter- and intra-individual variability? Are their discernable characteristics associated with the magnitude of indirect ingestion?
        - Sensitivity analyses with multiple "models" including concurrent measurements of house dust, hand wipe, surface transferability and assumptions, e.g., dust ingestion rates, hand-to-mouth frequency, surface area of hand
        - Comparison to EPA SOP algorithm

        - Relative importance of exposure route; support evaluation of related factors (surface area involved, frequency of events)
    - Do individuals who consume large amounts of leafy vegetables have higher exposures to pesticides?
        - Look at food diaries
    - Does accounting for direct exposure/intake of key metabolites improve modeled estimates of absorbed dose?
        - Model evaluation; relative importance of exposures and bioavailability of biomarkers
        - Multivariate stuff
    - Characterize spatial distributions of surface residues in indoor residential microenvironments (Are there spatial distributions in indoor environments?)
        - JAX, Test House data sets (intra-site variability)
        - Additional data sets (e.g., NDETF fogger study)
        - Significance for dermal exposure estimation
    - Are their regional differences in the magnitude of residential exposures and absorbed dose distributions?
        - What level of resolution is needed for regulatory agency decision-making?

-- Why are these considered to be important hypotheses?

-- How suitable are the existing data? Limitations?

- Limitations of existing data include
    - Temporal dimension (time series)
    - Age group specificity (e.g., under 3 yrs)
    - Missing concurrent data elements (e.g., dietary, time-activity, product use diaries)
    - Surface transferable residue measurements vary; no comparative studies to relate (e.g., specify as "indoor CA roller equivalents")
    - Source attribution for total absorbed dose
    - Data quality and accuracy evaluation (e.g., adult "shadow" reporting for children; verification of actual product used; amount applied; nominal application rate)?
    - Assumptions regarding incidental ingestion exposure
    - Comparability of dust collection methods
    - Measurement methods and method detection limits (MDLs) differ
    - Time activity and pesticide use information limited and of questionable accuracy
- Measurements that can be excluded?
    - None identified; it is noted that a study providing direct comparison of different methods of measuring surface transferable residues is required
- Other
    - Data Gap: Particle size distribution (role in inhalation exposure, role in incidental ingestion exposure); relative importance of re-suspension as an exposure pathway; importance of particle-bound chemicals
    - Existing study videography data analyses
    - Permethrin, head lice treatment incidence in JAX cohort
    - How can these data be used in conjunction with videography data (e.g., do low versus high surface contact rates correlate with dose magnitude; do low versus high hand-to-mouth rates correlate with dose magnitude)?
- Key prerequisites for combining data (Data Warehouse) is a data dictionary
    - Data dictionary for each study; common data elements that can support analyses of combined data sets and meta analyses
        - Should include selected elements of questionnaires (e.g., demographics)
        - Method equivalence (e.g., transferable residue measurements)
        - Analytical method comparability (e.g., MDL distributions)
        - What data sets "qualify" for inclusion (e.g., TCPy)

        - Methodological approach would be applicable to analyses with future data sets (e.g., pyrethroids)
- Descriptive statistics and bivariate and multivariate regression analyses
    - e.g., Surface loading versus absorbed dose
- Comparison of inventory data collected versus Residential Exposure Joint Venture (REJV) national survey
- Model evaluation case study recommended for permethrin
    - Address multiple data sets:
        - Population-based
            - CTEPP, CDC, PEPCOT
        - User-subpopulation
            - JAX, RTI Star Grant
    - Per capita probabilistic modeling
        - e.g., comparison to CARES aggregate assessment for permethrin
        - Permethrin biological monitoring versus probabilistic simulations for per capita aggregate modeling (chronic doses represented via background levels observed in the general population versus predictive estimates of LADD)
        - Permethrin scenario-specific biological monitoring versus probabilistic modeling for selected scenarios (e.g., acute, daily doses following product use events, e.g., crack and crevice)
        - Notes: the children in the JAX study had at least seven times higher levels of 3-PBA in their urine samples than children in the CTEPP-OH study; participants in the JAX study (n=9) were selected from homes that reported frequent pesticide use. Participants in the CTEPP study (n=127) were selected at random.

Theme 3: Additional statistical analyses that can be performed on these data to better understand children's exposures to chemicals at homes and daycare centers?

-- Provide a list of statistical analyses that could be performed on the accrued data. For each proposed analysis, please specify: (a) What data gap are you addressing? (b) What key hypothesis are you testing? (c) What result do you expect to find? (d) What is the likelihood of success, given the limitations of the data? Please prioritize the proposed analyses.
(Note: Prerequisite to proposed analysis is completion of a data dictionary for each study data set.)

Proposed Analysis 1: Do one or more environmental measurement parameters correlate with absorbed dose distributions for biomarkers?

- Non-parametric versus parametric statistics
- Bivariate
- Multivariate non-parametric analyses
- Comparison of inventory and use data versus REJV
- Cluster analysis (CC)
- HBM and SEM - include metabolites in SEM and HBM analyses
- Meta-analysis (analysis across the results from individual studies)
- Analysis of combined data sets (data warehouse)
- Model evaluation case studies
    - Permethrin biological monitoring versus probabilistic, per capita aggregate modeling
    - Permethrin scenario-specific biological monitoring versus probabilistic modeling
    - Focus on 3-PBA if resources are limited
    - Population-based (CTEPP, CDC, PEPCOT)
    - User-subpopulation (JAX, RTI STAR grant)

Proposed Analysis 2: Are absorbed dose distributions significantly increased due to crack and crevice applications?

- Sample size is very small
- May be inadequate data to do this analysis
- JAX 2001 biomonitoring data and questionnaire data for 200 still need to be analyzed

Proposed Analysis 3: Cluster analysis - CTEPP

- Environmental data
- Questionnaire data –identification of most important factors
- Can you do this for different percentiles (e.g., for the highly exposed – 95^{th} percentile versus 50^{th})
- Food diaries – can you identify food types that are most important?

Proposed Analysis 4: What is the significance of total versus vapor-phase inhalation exposures?

- This is a data gap, not a statistical analysis. Concern is that we may be underestimating exposure if we don't adequately address PM resuspension.

Proposed Analysis 5: Is indirect ingestion a significant route of exposure?

- Look at the assumptions that are being used; sensitivity analyses of assumptions. What are the assumptions that are driving it? Are intake assumptions correct? Which concentration measurement should you use? (house dust, surface wipes, hand wipes, PUF, etc.)
- Need to do analyses of a single data set with multiple models and assumptions to provide comparisons and uncertainty evaluations

Proposed Analysis 6: Metabolites

- Multivariate

Proposed Analysis 7: Characterize spatial distributions

GROUP D:

Theme 1: Major trends in the data across children's exposure studies.

a. Identify the major sources and routes of children's exposure to the pesticides based on the data from these and other children's exposure studies. Does this change by pesticide or class of pesticide?

In the past, we thought that children were exposed to pesticides at their homes mainly through inhalation (air) route of exposure. Today, our research has indicated that children are exposed primarily through dietary intake (solid food) of pesticides that have been applied on agricultural crops. Other important routes of exposure appear to be nondietary ingestion for the pyrethroids and inhalation for the organophosphates. The research issue is that dietary intake still only explains about 60% of the children's potential doses to pesticides in these environments. More research is needed to understand other sources (e.g., surfaces) and routes (e.g., nondietary) of children's exposure to pesticides and how their behavior impacts their exposures.

Research has recently shown that some urinary biomarkers of exposure (e.g., TCP, IMP, and 3-PBA) are quite measurable in several environmental media at children's homes and day care centers. This questions the reliability of using these urinary biomarkers of exposure to assess children's exposures to pesticides in these environments. Published research has shown that sheep orally administered TCP easily absorbed and excreted this metabolite unchanged in the urine. In addition, industry has conducted research (unpublished) showing that these degradation products (e.g., TCP) are easily absorbed in the gut and are excreted unmetabolized in the urine. This shows that degradation products can contribute to the excreted amount of metabolites in humans. Therefore in future studies, it is essential to measure for the degradation products of pesticides that are used as urinary biomarkers of exposure.

b. Identify the major factors that influence children's exposures to the pesticides.

Children's behavior and activity patterns most likely impact their exposures to pesticides at homes and day care centers. These activity patterns include hand-to-mouth and object-to-mouth activity and hygiene practices (e.g., washing hands, bathing). These activities have not been well-characterized in past studies. More research is needed to better understand how children's behavior/activity patterns influence their exposures to pesticides in these environments. We are wasting our time unless we can conduct exposure studies that link pesticide applications with children's behavior/activity patterns.

c. Are the observations in the recent NERL studies consistent with results from other studies and with current assumptions?

Generally, the NERL study results are consistent with other/previous studies.

Theme 2: Additional hypotheses that should be tested using existing data?

a. Provide a list of the major hypotheses that could be tested on existing data.

Our group felt that we needed to look at the actual data and descriptive statistics from each study before we could provide any meaningful hypotheses.

Important research needs/comments:

- We felt that the dietary and inhalation routes of exposure have been well characterized in many of these studies. However, other routes of exposure (i.e., non-dietary ingestion) have not been well characterized, particularly the best inputs (e.g., soil, dust, wipes) to use in our algorithms to assess children's exposures to these pesticides.
- We have little information on the toxicokinetics (absorption, metabolism, and excretion) of these pesticides in humans. Are the toxicokinetics similar for classes of chemicals or do we have to assess this by individual pesticides?

- There is still too much uncertainty in exposure factors. For example, use of current distributions for hand-to-mouth transfers seems to lead to very high exposure estimates.
- Do we regulate for high exposures or average exposures?
- There is still a major gap in data on transfer coefficients.
- Intra- and inter-personal variability of children's activities are important to measure.
- Group children by macroactivity levels instead of trying to describe all microactivities.
- Can creatinine levels in children be used as a proxy for activity level?
- We need to focus more on high-end exposures of children to pesticides.
- Anomaly-exposures caused by unexpected activities of children.
- Lack of specific biomarkers is an important factor limiting the use of biomarkers. Will genomics be useful? Need to have dose-response relationship and time course information (intra- and inter-person variability).
- We greatly need a research study similar to CHEERS conducted to better understand children's exposures to pesticides.
- Proximity of pesticide use (temporal and spatial) is very important when assessing children's exposure.
- Pesticide degradation (including metabolites) in the environment (time decay after application – indoors and outdoors).
- Reconcile switch from organophosphates to less volatiles; how does this affect fate and transport/bioavailability.
- Laboratory-based studies of pyrethroids versus organophosphates physico-/chemical behavior.
- Effect of vapor pressure on movement/partitioning and uptake.

Important comments:

Data from previous studies (i.e., industry) should be shared and publicly available to the scientific community. Why fund research that has already been conducted and well characterized (i.e., toxicokinetics and toxicodynamics of pesticides in humans/animals)? We need to form partnerships or have agreements of understanding with industry and other similar groups.

Research interests related to the data from these studies:

- Relationship between terminal and absorbed dose in the body.
- Review and comparison of dosimeter data and types. Dosimeters versus hand wipes: how do they reflect actual loading?
- Laboratory-based evaluations compared with field data.
- Are the Jacksonville results higher than CTEPP because of non-dietary exposure?
- Duplicate diet data compared to standard food diaries.
- SHEDS vs. CARES (or other similar models). Compare estimates using actual data input into these two models. Are they similar or different?
- Perform meta-analysis of these data – any trends?
- Re-analyze the data and look for associations with an emphasis on regulating the higher end exposures.
- Stratify existing data by application method (crack and crevice vs. broadcast) and test for differences.
- Group data by quantiles.
- Compare regulatory estimates vs. data from these studies.

Important comments:

- Can data be combined across studies to better characterize behavior and pesticide applications?
- Can information from other studies (external) be considered and included?
- Can information from studies using different methodologies be compared and included?
- Can studies using different recruitment methods be combined? Are the populations comparable?
- Can differences in dust concentrations, loading etc. be explained by physical chemical properties (e.g. Henry's law)?
- Need for standardization of methods.

- Lack of uniformity across studies.
- Do not over interpret existing data.
- Need better interaction between researchers and regulators to define hypotheses.

d. Why are these considered to be important research questions important?

We are curious, i.e., these areas have the greatest uncertainties in the distribution estimates.

Appendix B
Participant List

Participant	Affiliation	Contact Information
Amy Herring	UNC	Email: amy_herring@unc.edu Phone: 919-843-6368
Andrew Geller	EPA/NHEERL	Email: geller.andrew@epa.gov Phone: 919-541-4208
Asa Bradman	UC Berkeley	Email: abradman@socrates.berkeley.edu Phone: 510-643-3023
Beth Doyle	EPA/OW	Email: doyle.elizabeth@epa.gov Phone: 202-566-0056
Bob Krieger	UC Riverside	Email: bob.krieger@ucr.edu Phone: 951-827-3724
Bob Lordo	Battelle	Email: lordor@battelle.org Phone: 614-424-4516
Carry Croghan	EPA/NERL	Email: croghan.carry@epa.gov Phone: 919-541-3184
Chris Wible	Scotts	Email: chris.wible@scottsco.com Phone: 937-644-7012
Curt Lunchick	Bayer CropScience	Email: curt.lunchick@bayercropscience.com Phone: 919-549-2986
Dan Stout	EPA/NERL	Email: stout.dan@epa.gov Phone: 919-541-5767
Dana Barr	CDC	Email: dlb1@cdc.gov Phone: 770-488-7886
Dana Vogel	EPA/OPP	Email: vogel.dana@epa.gov Phone: 703-305-0874
David Miller	EPA/OPP	Email: miller.davidj@epa.gov Phone: 703-305-5352
Debbie Bennett	UC Davis	Email: dhbennett@ucdavis.edu Phone: 530-754-8282
Don Whitaker	EPA/NERL	Email: whitaker.donald@epa.gov Phone: 919-541-1571
Elaine Cohen Hubal	EPA/COMPTOX	Email: hubal.elaine@epa.gov Phone: 919-541-4077
Elin Ulrich	EPA/NERL	Email: ulrich.elin@epa.gov Phone: 919-541-3717
Frank Selman	Dow Agro Sciences	Email: fbselman@dow.com Phone: 317-337-5108
Haluk Ozkaynak	EPA/NERL	Email: ozkaynak.haluk@epa.gov Phone: 919-541-5172
Jacqueline Moya	EPA/NCEA	Email: moya.jacqueline@epa.gov Phone: 202-564-3245
Jane Chuang	Battelle	Email: chuangj@battelle.org Phone: 614-424-5222
Janice Sharp	Valent Biosciences	Email: Janice.sharp@valent.com Phone: 847-968-4844
Jeff Driver	Infoscientific.com	Email: ddriver448@aol.com Phone: 703-361-8449
Jeff Evans	EPA/OPP	Email: evans.jeff@epa.gov

Participant	Affiliation	Contact Information
		Phone: 703-305-7877
Jeff Morgan	EPA/NERL	Email: morgan.jeffrey@epa.gov Phone: 513-569-7738
Jim Olson	SC Johnson	Email: jjolson@scj.com Phone: 262-260-2768
Jim Raymer	RTI	Email: jraymer@rti.org Phone: 919-541-5924
Jim Starr	EPA/NERL	Email: starr.james@epa.gov Phone: 919-541-4608
Jim Xue	EPA/NERL	Email: xue.jianping@epa.gov Phone: 919-541-7962
John Kissel	U of Washington	Email: jkissel@u.washington.edu Phone: 206-543-5111
John Ross	Infoscientific.com	Email: john@infoscientific.com Phone: 916-486-6100
Linda Birnbaum	EPA/NHEERL	Email: birnbaum.linda@epa.gov Phone: 919-541-2655
Linda Sheldon	EPA/NERL	Email: sheldon.linda@epa.gov Phone: 919-541-2205
Lisa Melnyk	EPA/NERL	Email: melnyk.lisa@epa.gov Phone: 513-569-7494
Lynn Delpire	EPA/OPPT	Email: delpire.lynn@epa.gov Phone: 202-564-8531
Maria Morandi	U Texas at Houston	Email: maria.t.morandi@uth.tmc.edu Phone: 713-500-9288
Mark Strynar	EPA/NERL	Email: strynar.mark@epa.gov Phone: 919-541-3706
Marsha Morgan	EPA/NERL	Email: morgan.marsha@epa.gov Phone: 919-541-2598
MaryKay O'Rourke	U of Arizona	Email: mkor@email.arizona.edu Phone: 520-626-6835
Nancy McMillan	Battelle	Email: mcmillann@battelle.org Phone: 614-424-7942
Nicolle Tulve	EPA/NERL	Email: tulve.nicolle@epa.gov Phone: 919-541-1077
Paul Jones	EPA/NERL	Email: jones.paul-a@epa.gov Phone: 919-541-1516
Paul Lioy	EOHSI	Email: plioy@eohsi.rutgers.edu Phone: 732-445-0150
Peter Egeghy	EPA/NERL	Email: egeghy.peter@epa.gov Phone: 919-541-4103
Philip Villanueva	EPA/OPP	Email: villanueva.philip@epa.gov Phone: 703-308-8665
Richard Fenske	U of Washington	Email: rfenske@u.washington.edu Phone: 206-543-0916
Robin Whyatt	Columbia U	Email: rmw5@columbia.edu Phone: 646-459-9609
Ross Highsmith	EPA/NERL	Email: highsmith.ross@epa.gov Phone: 919-541-7828
Roy Fortmann	EPA/NERL	Email: fortmann.roy@epa.gov Phone: 919-541-1021

Participant	Affiliation	Contact Information
Ryan Williams	Clorox	Email: ryan.williams@clorox.com Phone: 925-425-4338
Sarah Winfield	EPA/OPP	Email: winfield.sarah@epa.gov Phone: 703-305-7016
Susan Schober	CDC	Email: sschober@cdc.gov Phone: 301-458-4484
Tom McCurdy	EPA/NERL	Email: mccurdy.thomas@epa.gov Phone: 919-541-0782
Zaida Figueroa	EPA/OPP	Email: figueroa.zaida@epa.gov Phone: 703-308-0015

United States
Environmental Protection
Agency

Office of Research
and Development (8101R)
Washington, DC 20460

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March 2006
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