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Workshop on Optimizing Exposure Metrics for the National Children's Study

Summary of Workgroup Discussions and Recommendations



Office of Research and Development
National Exposure Research Laboratory

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Summary of Workgroup Discussions and Recommendations

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Summary of Workgroup Discussions and Recommendations

Organizational Sponsors

U.S. Environmental Protection Agency, Office of Research and Development (ORD),
National Institute of Environmental Health Sciences (NIEHS), and National Children's Study (NCS)

Co-Chairs: Nicolle Tulve and Linda Sheldon (ORD)
Steering Committee: Sally Darney, Roy Fortmann, James Quackenboss (ORD);
Allen Dearry (NIEHS); and Michael Dellarco (NCS)

Background

The National Children's Study (NCS) will examine the relationships between environmental exposures and the health and development of 100,000 children living in the United States. The children will be followed from before birth until age 21. This is a very large, complex, and ambitious undertaking. Scientifically robust exposure metrics that are both low cost and low burden are needed to link environmental exposures to health outcomes within this study. This workshop engaged scientists from the exposure, epidemiology, and health effects disciplines with the goal of identifying the most promising and practical exposure metrics to use in a study the size and scope of the NCS. Additionally, the group discussed knowledge gaps and potential exposure research that would fill these gaps and could be used to develop and evaluate the most efficient and effective metrics. The workshop results are intended to provide operational input to NCS in the near term and to stimulate research in the U.S. Environmental Protection Agency's (EPA's) Office of Research and Development (ORD), the National Institute of Environmental Health Sciences (NIEHS), and the exposure science community to advance the national children's research agenda.

Prior to the workshop, three areas with clear chemical exposure to health outcome linkages were selected for discussion at the workshop: (1) air pollution and asthma, (2) endocrine disrupting chemicals and reproductive end points, and (3) insecticides and cognitive development. Three interdisciplinary expert workgroups, each consisting of a toxicologist, an epidemiologist, and two exposure scientists, were formed to address each of the three areas. The workgroups were charged with identifying appropriate target chemicals, time windows of susceptibility, and exposure metrics. The problem statement and charge given to the workgroups is attached, along with the workgroup memberships and their qualifications (Attachments A and B). The workgroups were challenged to review the current state of the science and to recommend a suite of exposure metrics that they considered most important for understanding the relationships between environmental exposures and the three health outcomes. Each workgroup met by conference call before the workshop to develop preliminary reports.

The workshop, held in Research Triangle Park, NC, on April 12 and 13, 2010, included the workgroup participants and invited scientists in the health and exposure fields from EPA, NIEHS, the NIEHS/EPA Children's Centers, the NCS Program Office, and the NCS Vanguard Centers (see Attachment C, Workshop Attendee List). The workgroups presented overviews of their discussions along with their recommendations (Attachment D) to the larger workshop audience. Workshop participants then discussed the workgroup proposals and recommendations with regard to scientific soundness, other schemes and options, feasibility, costs, participant burden, etc. Following all three workgroup presentations, opportunities for leveraging exposure research to evaluate proposed exposure metrics were discussed.

Concepts for Exposure Metrics

This section provides a common definition for exposure metric as it is used throughout this report. For epidemiological studies, the exposure metric is a summary variable used for exposure-response analysis. Exposure metrics can be as simple as a single measurement or they can combine or model information from several measurements or other types of data. In many cases, the exposure metrics discussed in this report will combine data from several sources rather than relying on a single measurement. Selection of the correct metric for a specific exposure/disease process

is crucial because misspecification of the metric can introduce error into the analysis and bias the outcome toward the null. The degree to which any exposure metric is correlated with the "true exposure" will determine how well it performs in conjunction with analyses of health end points. Fundamentally, the "true exposure" metric must capture the characteristics of exposure that are associated with the damaging or toxic effect being studied. However, identifying such a metric is often difficult, especially with complex diseases that have both genetic and environmental components.

Biologically relevant (BR) exposure recently was defined by Birnbaum (*Environmental Health Perspectives*, 118(4), April 2010) as a metric that can be directly associated with key events in a disease process and an individual's exposure profile. During a brief discussion at the workshop, it was proposed that BR exposure during the time window of susceptibility could be considered the "true exposure" metric. An example using urinary biomarkers is used to clarify these concepts. A biomarker in urine can serve as an exposure metric if it is correctly related to an exposure to the exogenous chemical. It is a BR exposure metric if that concentration also can be related to the concentration of the biologically active species that is available to react with the target disease pathway. It is the true exposure metric if it can be related to the concentration that is available for reaction during the entire period that the child would be most susceptible to the health outcome. Although only limited discussion occurred during the workshop around this concept, identification of a true metric is fundamentally important because it will provide the basis for evaluating proposed metrics, for identifying science gaps associated with proposed metrics, and for identifying the research needed to fill the most critical gaps.

Common Themes Throughout the Workshop

Although all three workgroups met independently beforehand, they raised several common themes, issues, and recommendations at the workshop. A summary of these themes is discussed first because of their cross-cutting nature. Table 1 highlights the common themes.

Time Periods for Susceptibility and Exposure Monitoring. All workgroups agreed that in utero and through early childhood (up to ages 3 to 5 years) were the time periods when children were most susceptible and when exposure monitoring should be conducted. At a minimum, all groups preferred to conduct monitoring during three visits, one each during the first trimester, the third trimester, and the first year. There was discussion but no general agreement about when to collect environmental samples and biological specimens during pregnancy if only one visit could be conducted. It is important to recognize that exposure variability over time will depend, in part, on the persistence of a chemical and the nature of the source. Thus, exposure monitoring approaches should take into account the nature of the sources, as well as the window of susceptibility. Regardless of the time period selected, all groups agreed on the need to demonstrate whether a given sample taken at one time in pregnancy could be used to estimate exposure at other times or windows of susceptibility. In addition, all of the groups agreed that, given the outcomes selected, fine time resolution (<1 day) for exposure estimates was not important. Again, the greater concern was whether a sample taken during a short time period could adequately represent exposure during the entire window of susceptibility, which may be months or even years long. Although the final recommendation was for two or three monitoring visits from conception through the first year, there was general agreement that

- urine samples were relatively low burden and should be collected more frequently, if possible;
- a blood sample should be collected from the mother while pregnant and from children once they are old enough to tolerate a blood draw; and
- additional monitoring should be conducted at the new residence if the participant moves.

Sample Matrices. All workgroups agreed that a preference should be given to samples that could be collected and archived for later analysis. There was also consensus that it would be most cost effective to analyze selected stored samples using a case/cohort approach after the health outcomes have been identified. Archived samples also can serve as a resource to evaluate exposures to chemicals (and other agents) that emerge as a concern in the future. Sample matrices that require immediate analysis were given a lower preference based on both logistical and cost considerations. However, there was consensus that research is needed to understand stability of archived samples.

Biological Samples—For many chemicals, blood (whole blood, serum, or plasma) would be the preferred matrix. Collecting blood from the mother during pregnancy and at birth already is planned. It was recognized that there would only be very small volumes of blood from the infant that would be in very high demand. It was considered unlikely that sufficient blood would be available for conducting multiple exposure measures. Recent advances in analyzing blood spot samples from children should be further pursued. Although urine is an alternative for some chemicals or their metabolites, there are currently problems with collecting urine from very young children. For many chemicals, recovery of metabolites from commercial

Table 1. NCS Exposure Metrics Workshop—Summary Recommendations for Data Collection in Home Visits

Data Collection During Home Visits				
Mother—Prenatal		Child		
Visit 1	Visit 2	Visit 3	Annual Visits	
First Trimester	Third Trimester	First Year after Birth	Up to Age 5 Years and at Puberty	Archive for Analyses
Blood	Blood	Blood Sample as Early in Life as Possible	Blood, If Available	Serum IgE, Persistent EDCs
Urine	Urine	Urine	Urine	Nonpersistent EDCs, Insecticide Metabolites
House Dust	House Dust	House Dust	House Dust	Allergens, Endotoxins, EDCs, Insecticides
Ambient Air Pollutants—Use available ambient monitoring data or modeled estimates	Ambient Air Pollutants—Use available ambient monitoring data or modeled estimates	Ambient Air Pollutants —Use available ambient monitoring data or modeled estimates	Ambient Air Pollutants—Use available ambient monitoring data or modeled estimates	$PM_{2.5}$, NO_2
Indoor Air Pollutants—Subset of homes	Indoor Air Pollutants—Subset of homes	Indoor Air Pollutants—Subset of homes	Indoor Air Pollutants—Subset of homes	$PM_{2.5}$, NO_2
Questionnaires: Air—Source proximity metrics; Pesticides—Use, gated pesticide questions, dietary intake; EDC—Product use and inventories; GIS (ambient sources, pesticides)	Questionnaires: Air—Source proximity metrics; Pesticides—Use, gated pesticide questions, dietary intake; EDC—Product use and inventories; GIS (ambient sources, pesticides)	Questionnaires: Air—Source proximity metrics; Pesticides—Use, gated pesticide questions, dietary intake; EDC—Product use and inventories; GIS (ambient sources, pesticides)	Questionnaires: Air—Source proximity metrics; Pesticides—Use, gated pesticide questions, dietary intake; EDC—Product use and inventories; GIS (ambient sources, pesticides)	
—	—	Breast Milk (if available)	—	EDCs, Insecticides

diapers may be poor. The diaper material contains co-extracted material that interferes with the analysis of some metabolites. Additionally, there are difficulties with contamination with feces in the diaper sample. On the other hand, urine bags are often difficult to use with very young children. Research will be required to improve methods for collecting and analyzing urine samples and for minimizing exposure misclassification because of variability or the presence of metabolites in environmental media.

Environmental Samples—All workgroups selected house dust as the highest priority environmental matrix and agreed that as much dust as possible should be collected. Dust provides an integrated sample over time and can be archived for later analysis. It was recognized that there are many different types of dust samples (e.g., vacuum, settled, surface and hand wipes) and methods for collecting these samples. It is a research priority to evaluate the current methods and then select and optimize a method for collecting, processing, and archiving dust samples for future analysis. Understanding the relationship between dust concentrations and exposure is another high-priority research need. Indoor surface wipe samples are not recommended because of the high variability of concentrations within homes.

Utility of Questionnaires. Except in a few cases, current questionnaires, diaries, and inventories have not been effective for predicting exposures. Many questions asked historically have proven to have little value—they have no variance, an "expected" answer, or no correlation with an outcome. For specific sources, selected questions may be useful for classifying exposure and for covering longer time periods than represented by direct measurements. All workgroups recommended that questionnaires be kept very short to reduce burden, and that research must be conducted to evaluate the value and validity of each question. An exposure question should be asked only if it can be used as, or directly related to, the development of a specific exposure metric.

Geographic Information System (GIS) Land Use Data. The location of a participant's home, workplace, or daycare and the characteristics of the surrounding environment are very important for understanding exposure. Currently, some of these characteristics are available through several internet links (e.g., Google Earth). It was very strongly recommended that a plan for archiving these data be developed immediately.

Exposure Variability. Exposure metrics must be capable of estimating exposure during the time periods of susceptibility. Thus, samples collected over a short time period must represent exposure over a much longer period. For most chemicals, very little is known about the variability (either within day or between days) of exposure or the exposure metric over the time period of concern. It is a priority to evaluate this variability either using existing data or collecting new data, if needed.

Discussion by Workgroup

Asthma Workgroup Recommendations. Asthma is a complex disease with known environmental etiologies and very high public health impacts. The workgroup considered that the greatest uncertainties were associated with understanding the onset of asthma, and that this should be the highest priority for the NCS. Progression of asthma (atopy and gender differences) also was considered important. Although, it is difficult to diagnose asthma before age 4, the critical window for exposures related to asthma onset is from in utero to 3 years of age. The time window for asthma progression is 3 years and beyond.

The workgroup considered that the overall goal was to minimize exposure misclassification for the NCS participants. Personal exposure measurements were considered not to be feasible in such a large study. Even with personal measurements, methods would be required to extrapolate the short-time measurement (1 day to 1 week) to the window of susceptibility (several months or years). Residential exposure metrics that represented both the indoor component and the ambient components of exposure were considered the most feasible. However, it also was considered important to gather information about where participants spent significant amounts of time, such as at work for pregnant mothers and at daycare centers or school for children, allowing researchers to relate this information to the GIS data.

Exposure metrics for testing the asthma hypotheses could be both source-based (traffic, second-hand smoke, indoor sources, and indoor swimming pools) and pollutant-based (traffic component, particulate matter [PM] components, PM size fractions, nitrogen dioxide [NO_2], phthalates, allergens, mold, and endotoxins). Exposures for source-based pollutants can be estimated primarily using proximity metrics based on questionnaires, GIS, and geo-databases. Pollutant-based exposure metrics would include a combination of measurements and models that evaluated exposures for both ambient and indoor pollutants.

Exposure to ambient pollutants (PM, ozone, and pollen) can be estimated using ambient monitoring data where available. Simple or more complex modeling approaches also can be used to estimate exposure or refine the metrics based on ambient measures alone. Where ambient data are not available, the workgroup recommended that modeling be used, rather than

attempting to collect additional ambient measurements. The workgroup recommended that modeling approaches that could be used at all of the NCS communities need to be developed and evaluated.

Exposure metrics for indoor pollutants will require measurements at the participant's home. The highest priority is to collect house dust and indoor $PM_{2.5}$ samples. House dust provides an integrated measurement for multiple pollutants of both indoor and outdoor origin, including allergens and endotoxins. House dust also can be used to identify exposures to specific sources using pattern recognition techniques. A medium priority was given to NO_2, which can be monitored using simple, low-cost methods. A low priority was given to measuring volatile organic chemicals (VOCs) and carbonyls (i.e., formaldehyde, acrolein) because of the cost of sample analysis, the requirement to analyze samples immediately, and variability of the measurements in a single residence.

A number of published and planned studies are available that can be used to develop and evaluate the exposure metrics. It is strongly recommended that follow-up efforts finalize exposure modeling approaches and evaluate them relative to these databases.

Hormonally Active Agents Workgroup Recommendations. Workgroup recommendations focused on health end points associated with reproductive effects. They also included other health effects, such as impaired neurological development, which is related to thyroid disruption during pregnancy. The critical windows of exposure for these end points may be 8 to 10 weeks gestation for reproductive effects, <20 weeks gestation for thyroid disruption effects, and the third trimester for neurological effects. The work group also felt that, for hormonally active compounds and hormonal end points, additional monitoring should be conducted close to the end point of interest. As an example, prepubertal monitoring is recommended at ages 6 to 8 years for girls and 8 years for boys.

The chemicals for consideration spanned a very large set. To prioritize the list, the workgroup considered their importance from a health perspective, along with the likelihood of exposure. The final list also included contaminants that act as confounders for neurotoxicity (pesticides, organotins, lead, mercury, and tobacco smoke), as well as endocrine disruptors. For each group of chemicals, information was provided on inclusion rationale, exposure characteristics, and exposure metric options. Exposure to most of these chemicals is through indoor sources or consumer products that may not be well known to consumers (which limits the validity of questions for these chemicals). Thus, the workgroup recommended that not only should the NCS consider the chemicals that are currently in use and recent replacements, but that future chemical replacements for specific uses be tracked for potential inclusion into the study at a later date.

Chemicals can be placed into several categories based on their physical and chemical properties and potential exposure pathways.

- Persistent and bioaccumulative chemicals, including polybrominated diphenyl ethers (PBDEs), perfluorinated chemicals (PFCs), and polychlorinated biphenyls (PCBs). Once absorbed into the body, these chemicals have long half-lives and tend to accumulate in lipid compartments. Exposure is best estimated by measuring levels of the chemical in serum or breast milk samples. For prenatal exposure, the mother's serum levels measured at most anytime during pregnancy should represent the developing embryo's exposure. Alternatively, breast milk samples collected postnatally potentially may be used to model prenatal exposure in the child. For postnatal exposures during the first year, the workgroup recommended a house dust sample (vacuum, settled, surface, or hand wipe) in lieu of infant serum. Although a blood sample would be ideal, it will be difficult to obtain. Research with PBDEs has demonstrated a relatively strong correlation between species found in vacuum dust or hand wipe samples and serum samples.
- Chemicals that are metabolized rapidly in the body with metabolites that are excreted in the urine.
  - Phthalates, bisphenol A, other phenols, and triclosan/triclocarban all are found in common indoor products. With the exception of the other phenols, urinary biomarkers are available for these chemicals and are recommended as the exposure metric. For the other phenols, a house dust sample is recommended. Some limited questionnaire information may be useful for this group of chemicals but, again, the use of questionnaires must be evaluated.
  - Phytoestrogens are found in infant soy formula. Questions regarding the use of soy formula are recommended. A urinary biomarker is available and could be considered, but only for limited use.
  - Perchlorate is found in certain water sources and in some foods. The development of an exposure metric based on the combination of community water sample data and well water sample data is recommended. A urinary biomarker is available and could be considered, but only for limited use.
  - PAH exposures are primarily from traffic, cooking sources, and certain foods. GIS systems and questionnaires can be used to evaluate exposures. Alternatively, PAHs can be measured in house dust, but this is expensive and not currently recommended.

It was stressed that, if urinary biomarkers are used to estimate exposure, it is crucial to evaluate variability of biomarkers over time to establish that a short-term biomarker measurement can be used to estimate/classify exposure over the entire time period of susceptibility. It also should be considered that these compounds show hormonal effects at very low levels, thus analytical methods that can generate high-quality data at these low levels are needed.

The primary exposure source of most of these chemicals is consumer product use. However, most adult participants cannot provide sufficiently accurate information for classifying exposures based on product use or activities. On the other hand, it may be possible to use questionnaires in developing exposure metrics for very young children because of the limited number of products that are used. Measurements were recommended as the primary metric for most chemicals. Where questionnaires are used, they need to be very carefully evaluated, as noted above in the "Utility of Questionnaires" section.

Diet is an additional source of exposure for the phytoestrogens, PFCs, PCBs, and, possibly, PBDEs. As suggested above, exposure to phytoestrogens through consumption of infant soy formula can be estimated using questionnaires. Dietary exposure to the persistent chemicals will be captured by biomonitoring, which provides an aggregate exposure estimate for these chemicals.

Insecticide Workgroup Recommendations. This workgroup focused on the association between insecticide exposures and poor neurological outcomes in children. Various time windows for neurological development were considered, such as cell proliferation, synapse development, myelination, etc. Based on this information, time windows during the first trimester of pregnancy and the first year of life were considered most important for exposure assessment. The second and third trimesters of pregnancy and up until 5 years of age were considered of high importance, and ages 5 to 10 years were of moderate importance.

The chemicals of interest were the organophosphate, pyrethroid, carbamate, and fipronil insecticides, and the synergist piperonyl butoxide. Most of these are current or recent use pesticides, whereas others appear to remain in homes at low levels long after their use has been discontinued. Future active insecticide ingredients need to be tracked and incorporated into the study based on use and likely exposure. In the general population, the primary sources for pesticide exposure are food and residential indoor use. For some groups, other sources may be important, including flea control, residential outdoor use, occupational use, other building uses (daycare, school, and workplace), proximity to agriculture, and public health treatments. Potential exposure to these latter uses may be informed by gated questions that may lead to additional questionnaire or measurement collection. Drinking water and ambient air are not considered important exposure media for the general population.

Developing exposure metrics for insecticides presents several difficult challenges. There are multiple pesticides, sources, and pathways that typically result in low and often variable exposures to multiple pesticides. Measuring pesticides in all important exposure media can be both high burden and very expensive and is generally not considered feasible for large studies. This is an especially difficult problem where diet is the major route of exposure because of the extremely high variability of pesticides in foods and high variability in dietary exposures over time. It is not feasible to collect, store, and analyze the number of duplicate diet samples that would be needed to evaluate exposure over a time period of concern. Biomarkers provide an alternative to environmental samples and provide the ability to integrate exposure over multiple routes and pathways. Unfortunately, biomarker interpretation is often difficult because of the short half-lives of biomarkers, intermittent and variable pesticide exposures, and presence of metabolites in the environments that can give false positive results. Finally, questionnaire-based approaches have limited predictive power for classifying pesticide exposure and generally lack chemical specificity.

The workgroup recommended that biological and environmental sampling at critical time periods is essential to estimate/classify exposures and to develop an index of exposures for epidemiological analyses. Core sample collection (to be held for future analysis) was recommended as follows: urine from key time points (indicated above) for the mother and young child; blood and milk for the mother at key times and blood from the child as feasible; and the best measure of residential loading, most likely a house dust, floor wipe, or vapor/settled dust measurement. Several nonmeasurement approaches also should be considered: questions on outdoor residential pesticide use, selected dietary questions (e.g., organic diet, fish consumption) to place dietary exposure into a low or high group, questions regarding the use of spray pesticide products by the pregnant mother, gated questions on pets and occupations, geographical information for residence to identify proximity to agricultural or public health pesticide applications, and time/activity location to provide information on other places where the child or mother may spend substantial amounts of time.

Given the many limitations associated with developing exposure metrics for insecticides, the workgroup made several strong recommendations for additional research.

- Current-use pesticide exposures often have a short-time frame, are intermittent, and are not persistent in the body, thus new methods are needed that can integrate exposures over time.
- For environmental samples, alternative measures need to be evaluated to determine the "best" measure of long-term residential concentrations and of individual exposure. This could be a house dust, a vapor/settled dust sample, or other house loading measurement. This also could include protein or albumin adducts as biomarkers.
- Carefully evaluate the uncertainties associated with using short-term urinary biomarkers to estimate long-term exposures. This includes understanding within-day, between-day, and over-season variability. It is also important to understand how much of the urinary metabolite is caused by exposure to pesticide metabolite in the environment rather than the pesticide itself. Again, the development of adduct biomarkers would overcome some of these problems.
- Understanding dietary exposure to specific pesticides and developing approaches to classify exposure in very broad classes based on questionnaires or diaries (e.g., to identify "high" or "low" consumers of foods likely to contain pesticide residues).
- Finally, intensive substudies were proposed to evaluate the ability of exposure metrics to estimate biologically effective exposure during the time window of susceptibility.

Areas for Future Research

Throughout the workshop, a number of knowledge gaps were identified that could impact the usefulness of the exposure metrics that were identified. Several areas were discussed for which research is needed to fill important gaps and reduce the uncertainty associated with the use of various metrics. Both near-term and longer term research needs were identified. The following list is presented according to the metrics proposed by the workgroups. The highest priority should be given to research needed to implement the recommendations of the workgroup related to house dust methods, urine sample collection, and air exposure metrics.

House Dust

- Development of methods for relating house dust loading and/or concentrations to exposure to effectively use house dust as an exposure metric in the NCS. Existing data should be analyzed from relevant studies.
- Evaluation of potential methods for estimating house dust loading of pesticides, other organic chemicals, allergens, and endotoxins. A single sample needs to be collected using a simple, but standardized method. Adequate sample needs to be collected to facilitate multiple analyses. Alternatives for consideration include vacuum dust, settled dust, and passive sampler. Conduct literature review, data analyses, and limited experimental testing. Develop protocols for sample collection for multiple analytes.
- Development of a method for the efficient and effective sampling, processing, and storage of dust samples.
- Development of protocols for documenting storage stability of dust samples for selected EDCs, pesticides, allergens, and endotoxins.

Air Exposure Metrics

- Development of the protocols and modeling approaches proposed by the asthma workgroup for the exposure metrics for onset and exacerbation of asthma. Approaches (e.g., land use regression modeling) should be developed and evaluated in ongoing studies.
- Development of a low cost, low burden method for collection of indoor PM.

Blood

- Development and evaluation of adduct techniques on blood spots to characterize infant exposures.
- Evaluation of storage stability of blood for analyses of EDCs.

Urine

- Evaluation of the relevance and applicability of short-term sampling for extrapolation to long-term exposures. Data are needed on the within-day and between-day variability of urinary metabolite concentrations. Approaches to estimate exposures during the critical windows of susceptibility need to be identified or developed. Protocols for collection of urine samples for biomonitoring of nonpersistent chemicals need to be developed based on an improved understanding of urinary variability.
- Development of new and improved methods for collecting infant urine samples (improved diaper or bag methods). Multiple analytes need be analyzed in urine samples. Methods need to address potential interferences and recovery.
- Development of alternative methods for biological sample collection for nonpersistent EDCs and pesticides.

Nonmeasurement Methods—Questionnaires, Inventories, GIS, etc.

- Development and evaluation of improved surveys for categorizing dietary exposures to pesticides.
- Evaluation of the use of questionnaires to categorize or estimate exposures to pesticides and EDCs. Analyze data from the EPA/NIEHS Children's Centers studies and other studies.
- Develop and evaluate alternative approaches for recording product use and inventories (e.g., bar code recording methods).
- Develop protocols for collecting and archiving GIS data.

Metric Evaluation

- Field studies or substudies should be conducted to evaluate the relationship between the proposed exposure metric and the true exposure metric.

ATTACHMENT A

WORKGROUP PROBLEM STATEMENT AND CHARGE

Workshop on Optimizing Exposure Metrics for the National Children's Study

Workgroup Problem Statement

Currently, the NCS has seven Vanguard centers recruiting participants and collecting multimedia samples (e.g., environmental and biological samples) and questionnaire information. These Vanguard centers are serving a critical need in regard to evaluating all aspects of this large, longitudinal study. The protocol developed for the NCS Vanguard centers includes an array of environmental and biological measures that, in combination with limited questionnaire data, were intended to form the basis for exposure classification for many chemicals of interest in the full study. However, the cost and burden of measuring all the environmental and biological media and chemicals of interest at all relevant time periods is high and may not be supportable in the full NCS. Alternative approaches and metrics are being considered for the classification of exposures to chemical contaminants in the NCS cohort. These approaches are intended to optimize the site visit assessments and provide reliable exposure estimates at critical lifestages at reduced cost and burden. Approaches that may be considered include the use of extant data where available, increased use of questionnaire and other survey information, and strategically targeted validation measurement studies to assess core exposure classification approaches. Experts in the fields of toxicology, epidemiology, and exposure assessment can provide valuable guidance for developing a resource-efficient study design that is based on the selection of appropriate exposure metrics and refined approaches for exposure classification in the NCS.

Workgroup Charge

Three expert workgroups are being organized and challenged to develop exposure classification metrics and schemes associated with different chemical exposures, critical time periods, and health outcomes. The expert workgroups are being asked to address the following specific questions.

- What environmental exposures for children, and at what lifestages, likely result in the health outcome?
- What metrics are needed to characterize the environmental exposures? If physical measurements are not available for all chemicals at all relevant time periods, what other metrics can best be used for all individuals in the cohort?
- What are the minimal metrics and approaches that can be employed for exposure classification?
- What is the best approach for employing these metrics cohort-wide for exposure classification?
- How should the proposed exposure classification approach be evaluated or verified?

ATTACHMENT B

WORKGROUP MEMBERS

Workgroup 1—Exposure to Indoor and Outdoor Air Pollution, Aeroallergens, and Asthma Risk

Patrick N. Breysse, Ph.D., Johns Hopkins University
Dr. Breysse is a professor in the Department of Environmental Health Sciences at the Johns Hopkins Bloomberg School of Public Health. He conducts research on air pollution exposure assessment, including pollutant source characterization, exposure measurement and interpretation, development, and use of biomarkers of exposure/dose/effect, and evaluates relationships between sources, exposure, doses, and disease. A major focus of research in Dr. Breysse's laboratory is on exposure assessment for studies of childhood asthma. This research includes evaluating in home and ambient exposures to PM, ozone, NO_2, airborne nicotine, allergens, and endotoxins. This research is conducted as a part of the multidisciplinary Center for Childhood Asthma in the Urban Environment. Dr. Breysse is also the Program Director for the EPA-funded Johns Hopkins Particulate Matter Research Center.

Michael Brauer, Sc.D., University of British Columbia
Dr. Brauer is a Professor in the School of Environmental Health at the University of British Columbia (UBC). He also holds associate appointments in the Division of Respiratory Medicine and the School of Population and Public Health at UBC. Dr. Brauer received bachelor's degrees in biochemistry and environmental sciences from the University of California-Berkeley (1986) and a doctorate in environmental health from Harvard University (1990). He was a visiting scientist at the Institute of Environmental and Occupational Medicine at Arhus University in Denmark (1991), at the Institute for Risk Assessment Sciences at Utrecht University in the Netherlands (2000-2001) and at the East-West Center in Hawaii (2008). Dr. Brauer's research emphasis is on the assessment of exposure and health impacts of air pollution. He has evaluated associations between air pollution and incidence of childhood asthma in birth cohorts in the Netherlands and Canada. He is an investigator in the recently launched Canadian Healthy Infant Longitudinal Development birth cohort and is currently investigating air pollution-genetic interactions in relation to asthma initiation in a combined analysis of multiple birth cohorts. He has served on advisory committees to the World Health Organization, the U.S. National Academy of Sciences and Institute of Medicine, the Royal Society of Canada, and the International Joint Commission. He is currently a member of the outdoor air pollution expert working group of the Global Burden of Disease Project, the International Scientific Oversight and Review Committees of the Health Effects Institute and chairs the external scientific advisory committee of the Mesa-Air Study.

David Diaz-Sanchez, Ph.D., EPA, NHEERL
Dr. Diaz-Sanchez is a recognized expert in the area of human asthma and allergy, as well as genes that control susceptibility of humans to air pollution. Prior to joining EPA in October 2007, he was a tenured Associate Professor in the Department of Medicine at the University of California, Los Angeles. He is currently Chief of the Clinical Research Branch of NHEERL. He is also the ORD representative for the Federal Liaison on Asthma Group, as well as the National Asthma Education and Prevention Program. He also serves on several working groups at the NHEERL, ORD, and Agency levels, including the Interagency Working Group on Climate Change and Health. In addition, he has an adjunct position as Associate Professor in the Curriculum of Toxicology at the University of North Carolina. He has served on numerous review committees for national and international agencies, including the National Academy of Sciences. He recently was nominated to serve as a standing member of the Infectious, Reproductive, Asthma/Allergy, and Pulmonary (IRAP) Conditions Study Section for NIH. Recognition of his work has come in the form of multiple requests to speak in different venues at national and international conferences (SOT, AAAI, New Trends in Allergy VII) and to different universities (e.g., Vanderbilt, Johns Hopkins). He continues to have an active research program on factors determining susceptibility to pollutants. His work has shown how specific sensitivity factors, particularly diseases like asthma, genes, and age can influence response to air pollutants. His publications have ranged from a demonstration of the role of diet in protection from air pollutants to the first report of how environmental pollutants can alter epigenetic regulation (microRNAs) to identification of novel biomarkers of air pollutant effects in asthmatics.

Jack R. Harkema, D.V.M., Ph.D., D.A.C.V.P., Michigan State University
Dr. Harkema received a B.S. (biology/chemistry) from Calvin College, an M.S. (mammalian physiology) and a D.V.M. (veterinary medicine) from Michigan State University (MSU), and a Ph.D. (comparative pathology) from the University of California-Davis (UCD). After completing an NIH-sponsored research/residency training program in comparative pathology and toxicology at the UCD, Dr. Harkema joined the scientific staff at the Lovelace Respiratory Research Institute in Albuquerque, NM, in 1985 as an experimental and toxicological pathologist. He later became the institute's project manager for pathogenesis research. In 1994,

Dr. Harkema joined the faculty of the Department of Pathobiology and Diagnostic Investigation in the College of Veterinary Medicine at MSU, where he is currently a University Distinguished Professor. He is Director of the Laboratory for Experimental and Toxicological Pathology and the MSU Mobile Air Research Laboratories. Also, he is a faculty member in MSU's Center for Integrative Toxicology and the MSU/NIEHS training program in Environmental and Integrative Toxicological Sciences. Dr. Harkema's research is in the areas of inhalation toxicology and respiratory pathobiology. His studies are designed primarily to understand the cellular and molecular mechanisms involved in the pathogenesis of airway injury and remodeling caused by the inhalation of airborne toxicants (e.g., ozone, PM, engineered nanomaterials), or other xenobiotic agents (e.g., bacteria, viruses, allergens) commonly found in both environmental and occupational settings. He is also a recognized expert on laboratory animal models of human cardiopulmonary diseases (e.g., asthma, COPD, hypertension, atherosclerosis). Dr. Harkema has authored or co-authored over 180 peer-reviewed scientific publications and has served on numerous national scientific advisory committees, including those for the NIEHS, EPA, and the NAS. Besides training graduate students, residents, and postdoctoral fellows in biomedical research, he also moderates courses in advanced general pathology, integrative toxicology, and pulmonary pathobiology. Dr. Harkema is a diplomate of the American College of Veterinary Pathologists and a member of the Society of Toxicologic Pathologists, the SOT, and the American Thoracic Society.

Lisa K. Baxter, Sc.D., EPA, NERL
Dr. Baxter is currently an Environmental Health Scientist in the EPA's NERL. She has a doctor of science degree from the Harvard School of Public Health. Her area of interest is the improvement of human exposure estimates for epidemiology studies. In large epidemiological studies, it is often impractical to collect direct quantitative measures of exposure on all subjects; therefore, reasonable proxies need to be developed. For her doctoral research, Dr. Baxter participated in the study design and collection of air pollution data for a birth cohort study, as well as developed models of air pollution exposure estimates. The study investigated the development of asthma in children because of environmental, genetic, and social factors. Although much smaller in scale, this study bears many similarities to the NCS. Her current research activities continue along the same theme of developing and improving air pollution exposure estimates for epidemiology studies. She has developed exposure models identifying surrogates that can be utilized when air pollution measurements on an entire cohort are not available. This is germane to NCS in that exposures for the entire cohort will need to be estimated based on measurements from a subset of participants.

Tim H. Watkins, EPA, NERL (Workgroup Facilitator)
Mr. Watkins is currently the acting director of the Environmental Public Health Division in the EPA ORD NHEERL. Prior to this position, He served as the deputy director of the Human Exposure and Atmospheric Sciences Division in the EPA ORD NERL. Mr. Watkins' expertise and interests lie in the area of air pollution exposure assessment, including ambient air monitoring, personal monitoring, source apportionment, and air quality and exposure modeling. He also has supported some specific collaborative activities involving monitoring and modeling. Most recently, he has supported collaborative efforts between the EPA and the Centers for Disease Control and Prevention (CDC) toward the CDC's Environmental Public Health Tracking program by providing air quality data from monitoring networks, models, and satellites for use in surveillance activities to track potential associations between air quality and public health. In addition, Mr. Watkins also served as the co-lead for the development of a cross-EPA multimedia monitoring strategy for PBTs, which focused primarily on monitoring emissions, environmental concentrations, and exposures to mercury, dioxin, and PCBs. He currently serves as the co-chair of the Scientific and Technical Subcommittee of the U.S.-Canada Air Quality Committee and as the EPA representative to the NARSTO Executive Steering Committee. Mr. Watkins also participates in the Ambient Monitoring Subcommittee of the National Association of Clean Air Agencies. He has worked with the EPA since 1990. He received his M.S. in economics from the University of North Carolina at Chapel Hill and his B.A. in economics and mathematics from Rollins College.

Workgroup 2—Nonpersistent Pesticides and Poor Neurobehavioral and Cognitive Skills

P. Barry Ryan, Ph.D., Emory University
Dr. Ryan is Professor of Exposure Science and Environmental Chemistry in the Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University. He is jointly appointed in the Department of Chemistry at Emory University. Prior to joining the faculty at Emory in 1995, he was on the faculty at the Harvard School of Public Health. He received a B.S. in chemistry from the University of Massachusetts, an M.S. in physical chemistry from the University of Chicago, and a doctorate in computational chemistry from Wesleyan University. He has been active in the exposure assessment field for more than 25 years publishing in excess of 90 peer-reviewed manuscripts and book chapters and making over 170 presentations of his work to the scientific community. His work has included both cross-sectional and longitudinal studies of community-based exposure to multiple pollutants in multiple media. Dr. Ryan is currently the PI on an EPA-funded STAR grant designed to assess the effectiveness of biological markers of exposure to organophosphate and pyrethroid pesticides. In addition, he is a PI studying the impact on the surrounding community of airport emissions of various airborne compounds and of a retrospective study of exposure to perfluorooctanoic acid in a large area surrounding a manufacturing facility using this compound. Recently, he began work assessing exposure to pesticides experienced by individuals in a community in Northern Thailand. Dr. Ryan is a member of the Executive Committee of the Emory/Battelle/Morehouse consortium for the NCS. In the recent past, he was the PI on the EPA-funded longitudinal study of exposures to pollutants known as the National Human Exposure Assessment-Maryland study, and he was co-PI of a study on health-compromised individuals assessing the impact of PM exposure on heart rate variability. He also was co-PI on a study of the impact of air pollution exposure on hiker lung health in the Great Smoky Mountains National Park. Dr. Ryan is a member of the Board of Scientific Counselors for EPA's ORD. Dr. Ryan also completed a 4-year term on the Federal Advisory Committee for the NCS being undertaken by the National Institutes of Health. He has served on numerous advisory panels for the EPA, most recently as an ad hoc member of the FIFRA SAPs on CCA-treated wood products and carbamate pesticides. Dr. Ryan also has served on several National Academy of Science panels, most recently on the panel producing the monograph *Managing Air Quality in the United States*. Dr. Ryan is a trained chemist and maintains a large laboratory facility. His website is http://www.sph.emory.edu/eoh/faculty/ryan.html.

Asa Bradman, Ph.D., UC Berkeley
Dr. Bradman is an environmental health scientist who focuses on environmental exposures to pregnant women and young children. In 1997, he helped found the Center for Children's Environmental Health Research in the UC Berkeley School of Public Health. In this capacity, he helps direct multiple biomonitoring and exposure studies investigating the relationship of environmental exposures and health in children living in the Salinas Valley, CA. Between 1987 and 1998, Dr. Bradman participated in studies of lead exposure, iron deficiency, pesticide exposure, and childhood cancer with the California Department of Health Services. He recently was appointed by Governor Schwarzenegger to the Scientific Guidance Panel for the California Environmental Contaminant Biomonitoring Program and also serves on the Science Advisory Council for the National Center for Healthy Homes and the California Childcare Health Program Advisory Committee, and has served on the Exposures to Chemical Agents Working Group for the NCS.

Virginia Rauh, Sc.D., Columbia University
Dr. Rauh is Professor of Population and Family Health at the Mailman School of Public Health, Columbia University, and Deputy Director of the Columbia Center for Children's Environmental Health. Her work focuses on the adverse impact of exposure to air pollutants, including secondhand smoke and pesticides on pregnancy and child health, and the susceptibility of disadvantaged populations to environmental hazards. Dr. Rauh has been working in the field of perinatal epidemiology since 1982. Her expertise is in the area of low birth weight and preterm delivery, particularly with respect to socioeconomically disadvantaged and minority populations. She has been principal investigator on numerous major research projects, including studies of the impact of organophosphorus insecticides and secondhand smoke on child neurodevelopment and brain abnormalities, a randomized intervention trial for low-birth-weight infants, a multisite study of lifestyles in pregnancy, a study of developmental outcomes of children born to inner-city adolescent mothers, a multilevel analysis of the impact of Head Start on New York City school children, a study of the effects of air pollutants on pregnant women and their children, and a study of links between race, stressors, and preterm birth. She has worked with other Columbia faculty to study the effects of the World Trade

Center disaster on pregnant women and newborns. Dr. Rauh is currently principal investigator for the Manhattan Site and co-investigator for the Queens Vanguard Site of the NCS. Dr. Rauh serves on numerous national committees, including the Scientific Advisory Board for the EPA.

Jane Hoppin, Sc.D., NIEHS
Dr. Hoppin is a staff scientist in the Epidemiology Branch at the NIEHS. Her research interests focus on environmental exposure assessment for environmental epidemiology studies, with particular interest in pesticides and bioaerosols. She is one of the PIs of the Agricultural Health Study (AHS), a prospective cohort study in Iowa and North Carolina of 89,000 farmer pesticide applicators, commercial pesticide applicators, and spouses of private pesticide applicators. A critical piece of the AHS is exposure assessment and characterizing exposure intensity to pesticides for applicators and farm residents. Dr. Hoppin has assessed the accuracy of self-reported pesticide use information and contributed to the development of the AHS exposure assessment algorithm and to the modification of this algorithm based on field study data. Dr. Hoppin currently is conducting a case-cohort study of asthma among 3600 participants in the AHS; this study is collecting lung function measurements, biological samples, and environmental samples (dust) that will be integrated with the previously collected exposure information. In addition to pesticide exposure assessment and epidemiological analyses in the AHS, since joining NIEHS Dr. Hoppin has been involved with helping develop protocols for biological sample collection to assess environmental exposures in the Norwegian Mother and Child Study cohort and with development of environmental sampling protocols for the Sister Study, a study of 50,000 women whose sisters had breast cancer. Specific to the topics of interest to the NCS, Dr. Hoppin has assessed the variability of urinary phthalate levels in women of reproductive age and has assessed the reliability of a detailed exposure questionnaire to predict urinary phthalate levels. She received her doctorate from the Harvard School of Public Health in 1995 in environmental health and epidemiology. She has served as a councilor for the International Society of Exposure Analysis and as an associate editor of the *American Journal of Epidemiology*. She has contributed to a number of efforts to develop exposure materials that can be applied in epidemiology studies, including the NHGRI's PhenX project and the development of standardized questionnaires for Parkinson's disease research.

Stephanie Padilla, Ph.D., EPA, NHEERL
Dr. Padilla is a neurotoxicologist in the Integrated Systems Toxicology Division of EPA's NHEERL, Research Triangle Park, NC. Dr. Padilla received her Ph.D. in Biochemistry from the Medical School of the University of North Carolina at Chapel Hill. After completing a staff fellowship with the National Institutes of Health in Bethesda, MD, she joined the EPA in 1981. Her research interests include acute and chronic toxicity of anticholinesterases and developmental neurotoxicity, specifically use of alternative species for screening chemicals for toxicity. Dr. Padilla has received numerous awards, including Scientific and Technological Achievement Awards and Silver and Bronze Medals for Commendable Service. In addition, she is an Adjunct Professor in the Curriculum in Toxicology, University of North Carolina at Chapel Hill. Dr. Padilla has served on many professional review boards, on the editorial board of the scientific journal *Neurotoxicology,* and she also has served as an officer in numerous scientific societies. Additionally, she has authored numerous book chapters and reviews and over 80 peer-reviewed publications.

Kent Thomas, EPA, NERL (Workgroup Facilitator)
Mr. Thomas is a research scientist at EPA's NERL. He has extensive experience in the development and implementation of human exposure measurement methods for environmental contaminants. His experience includes complex multimedia and multipathway studies of human exposure to VOCs, pesticides, PAHs, metals, and particles. Mr. Thomas has contributed to the development of sampling and analytical methodology for contaminants in air, water, food, dust, soil, blood, breath, and urine. Specific research experience includes the Total Exposure Assessment Methodology studies and being the field study leader for the National Human Exposure Assessment Survey in Region 5, the Minnesota Child Pesticide Exposure Study, and the Particle Total Exposure Assessment Methodology Study. Additional experience includes studies of building and residential air pollutants and human exposures. He has led research on methods for collecting personal dietary samples and analysis of dietary samples for chemical contaminants. Mr. Thomas is the EPA team leader for the Agricultural Health Study (AHS) Pesticide Exposure Study and serves as the EPA representative to the inter-agency executive committee for the AHS. He was the task leader for exposure and activity research areas under ORD's Aging Initiative research and currently contributes to the community cumulative risk and biomonitoring research tasks. Mr. Thomas has served as a government councilor for the International Society of Exposure Science, was a member of the Exposure to Chemical Agents Workgroup for the NCS, and serves on the advisory panels for two NIEHS epidemiology studies.

Workgroup 3—Hormonally Active Environmental Agents and Reproductive Development

Deborah Bennett, Ph.D., UC Davis
Dr. Bennett is an associate professor in Environmental and Occupational Health in the Department of Public Health Sciences at the University of California, Davis. Dr. Bennett's research focuses on the fate, transport, and exposure of chemicals in both the indoor and multimedia environments within the context of both environmental risk assessment and environmental epidemiology. Her work utilizes both modeling and measurement techniques, bridging the gap between these two lines of inquiry. Current research interests include exposure to pesticides from indoor uses, relating environmental measures to biological measures for flame retardants, exposures and resulting risks from hazardous air pollutants, supporting exposure assessments in autism studies, quantifying intake fraction and exposures to agricultural workers.
Dr. Bennett received her doctoral degree in mechanical engineering from UC Berkeley, worked as a scientist at the Lawrence Berkeley National Laboratory, and was a member of the faculty at the Harvard School of Public Health. Dr. Bennett received the Early Career Award from the International Society of Exposure Assessment and was an EPA STAR Fellow. She has served on both the EPA Science Advisory Board and Science Advisory Panel, as well as on other EPA committees and was a U.S. representative to OECD/UNEP Workshop on the use of multimedia models. She served as the treasurer for the International Society for Exposure Assessment.

Heather Stapleton, Ph.D., Duke University
Dr. Stapleton is an assistant professor of environmental chemistry in the Nicholas School of the Environment at Duke University. She received her Ph.D. in 2003 from the University of Maryland at College Park and joined the faculty at Duke University in 2005. Her research interests are focused on understanding the fate and transformation of emerging organic contaminants in the environment and in measuring human exposure to these contaminants in indoor environments. Her current research focuses on characterizing the sources and understanding the fate, biotransformation, and human exposure, to flame retardant chemicals that are found in consumer products (e.g., furniture, baby products, TVs, computers, etc.). Dr. Stapleton is a member of the advisory board for the U.S. CertiPur program, and she is on the editorial board for the journal *Environment International*. Professional organizations in which she is a member include the American Chemical Society and the Society of Environmental Toxicology and Chemistry.

Stephanie Engel, Ph.D., Mt. Sinai School of Medicine
Dr. Engel earned an MSPH and Ph.D. in epidemiology from the University of North Carolina at Chapel Hill. She joined the Mount Sinai School of Medicine in 2003 as a postdoctoral fellow and is currently a tenure-track Associate Professor in the Department of Preventive Medicine. Dr. Engel's research expertise is in molecular perinatal epidemiology with a focus on immune, genetic, and environmental risk factors for adverse pregnancy outcomes and neurodevelopmental impairment. She was a project PI of the Mount Sinai Children's Environmental Health and Disease Prevention Research Center and recently has published influential articles in the area of prenatal environmental exposures and child neurodevelopmental impairment.

Mike Shelby, Ph.D., NIEHS
Dr. Shelby founded the NIEHS/NTP Center for the Evaluation of Risks to Human Reproduction in 1998 and served as its Director until mid-2009. In the past 12 years, he has participated in the evaluation of the reproductive effects of over 20 substances, including industrial chemicals, pharmaceuticals, and environmental contaminants. He has been at NIEHS since 1977, serving in the office of the Associate Director for Genetics, as head of the Mammalian Mutagenesis Section, as head of the Reproductive Toxicology Group, and as Chief, Laboratory of Toxicology. Prior to joining NIEHS, he was a research associate at the Biology Division, Oak Ridge National Laboratory. He received his B.S. in biology (1966) from Central State College, Edmond, OK, and his Ph.D. in genetics (1973) from the University of Tennessee. His graduate training was in radiation mutagenesis and DNA repair. He has served as President of the Environmental Mutagen Society, the Genotoxicity and Environmental Mutagen Society, and the NIEHS Assembly of Scientists. He was an editor of *Mutation Research* from 1980 through 2009.

Vickie Wilson, Ph.D., EPA, NHEERL
Dr. Wilson is a Research Biologist and current Chief of the Reproductive Toxicology Branch of the Toxicity Assessment Division of EPA's NHEERL in Research Triangle Park, NC. She has been with the Agency for about 10 years. Dr. Wilson earned her B.S. degree from Framingham State University in Framingham, MA, and her Ph.D. in toxicology from North Carolina State University in Raleigh, NC. Her research centers on the

cellular and molecular mechanisms of toxicant-induced abnormal reproductive development utilizing in vitro, ex vivo, and in vivo models. Her research focuses on mechanisms through which environmental compounds may impact the endocrine system and, specifically, how those chemicals can impact offspring after in utero exposure. Dr. Wilson has published nearly 60 publications in this area over the past 10 years. For her work with endocrine disrupting compounds (EDCs), she has been awarded nine EPA Science to Achieve Results awards and three Bronze Medal awards from EPA ORD. Dr. Wilson is an active member of several professional societies, including SOT, the Society for the Study of Reproductive Biology, the Triangle Consortium of Reproductive Biology, and the Society of Environmental Toxicology and Chemistry. She routinely serves as a session chair, having organized several symposiums at national meetings and on workgroups within those organizations. She also routinely serves as an ad hoc reviewer for several scientific journals, as well as serving as a member of the Board of Reviewing Editors for 4 years for the journal *Biology of Reproduction*. Dr. Wilson also serves as a member of the ORD-EDC workgroup, which provides technical assistance and protocols to the program offices for their endocrine screening program. She also routinely serves on technical review panels for both OECD and NIH.

Nicolle S. Tulve, Ph.D., EPA, NERL (Workgroup Facilitator)
Dr. Tulve is a research scientist in the EPA's NERL. Her research focus includes understanding young children's exposures to chemicals (e.g., pesticides, PBDEs, PFCs, etc.) in their everyday environments. She has had lead responsibility for several projects that were collaborative efforts with academia and other government organizations and for in-house EPA research projects. She completed a detail (in 2002) with the Office of Pesticide Programs that was developed to promote collaboration between NERL researchers involved in collecting multimedia measurements and the regulatory staff in the program office. Currently, Dr. Tulve is the team lead for the children's exposure measurement research program in NERL. She graduated from Clarkson University with a Ph.D. degree in environmental engineering in 1999. She is a member of the International Society of Exposure Science (ISES) and the American Chemical Society. Dr. Tulve currently serves as a government councilor for ISES, as well as chair of its membership committee.

ATTACHMENT C

WORKSHOP ATTENDEE LIST

Workshop on Optimizing Exposure Metrics for the National Children's Study
Attendee List

Dana Barr
Emory University

Lisa Baxter
EPA

Debbie Bennett
UC Davis

Asa Bradman
UC Berkeley

Michael Breen
EPA

Patrick Breysse
Johns Hopkins University

Scott Collingwood
University of Utah

Gwen Collman
NIEHS

Lou D'Amico
EPA

Allen Dearry
NIEHS

David Diaz-Sanchez
EPA

Caroline Dilworth
NIEHS

Peter Egeghy
EPA

Michael Firestone
EPA

Roy Fortmann
EPA

Kim Gray
NIEHS

Jack Harkema
Michigan State University

Ross Highsmith
EPA

Jane Hoppin
NIEHS

Steven Kleeberger
NIEHS

Danelle Lobdell
EPA

Rob McConnell
USC

Larry McMillan
EPA

David Miller
EPA

Lucas Neas
EPA

Aaron Niman
EPA

Marcia Nishioka
Battelle

Halûk Özkaynak
EPA

Stephanie Padilla
EPA

Jim Quackenboss
EPA

Charles Rodes
RTI

P. Barry Ryan
Emory University

Pat Ryan
University of Cincinnati

Tim Shafer
EPA

Mike Shelby
NIEHS

Linda Sheldon
EPA

Heather Stapleton
Duke University

Dan Stout
EPA

Warren Strauss
Battelle

Kent Thomas
EPA

Nicolle Tulve
EPA

Eric Vigoren
University of Washington

Tim Watkins
EPA

Cliff Weisel
UMDNJ

Ron Williams
EPA

Vickie Wilson
EPA

Attendance via Webinar on April 12, 2010

Stephanie Engel
Mt. Sinai

Michael Dellarco
NCS

Marina Kleinhapel
Michigan Department of Community Health

Angela Galka

Ellen Wells
Case Western Reserve University

Elizabeth Triche

Karen Broski
Michigan State University

Margot Brown
NCS

Kelly Johnson

Dean Baker
UC Irvine

Peter Weyer
University of Iowa

Kimberly McAllister
NIEHS

Bonny Specker
South Dakota State University

Doug Thompson

David Camann
SWRI

Charles Weschler
EOHSI

Howard Wey
South Dakota State University

Roger Lewis

Dan McCormack
SouthDakota State University

Chuck Shorter
Tulane University

Sastry Isukapalli
EOHSI

Alison Caviness
Texas Children's Hospital

Xiaobin Wang
Northwestern University

Stephen Vesper
EPA

Michael Brauer
UBC

Ralph Delfino
UC Irvine

Lianne Sheppard
University of Washington

Natalie Thiex
South Dakota State University

Bill Griffith
University of Washington

Attendance via Webinar on April 13, 2010

Marina Kleinhapel
Michigan Department of Community Health

Stephen Vesper
EPA

Howie Duit

James Starr
EPA

Stephanie Engel
Mt. Sinai

Vickie Wilson
EPA

Angela Galka

Karen Broski
Michigan State University

Elizabeth Triche

Peter Weyer
University of Iowa

Dean Baker
UC Irvine

David Camann
SWRI

Margot Brown
NCS

Kim McAllister
NIEHS

Dan McCormack
South Dakota State University

Howard Wey
South Dakota State University

Chuck Shorter
Tulane University

Nigel Fields
EPA

Ellen Wells
Case Western Reserve University

ATTACHMENT D

WORKGROUP PRESENTATIONS





Exposure Metrics for NCS Asthma Investigations

Summary and Recommendations from Workgroup 1

April 12, 2010

1

Overview

- Workgroup Information
  - Members
  - Objectives
  - Approach
- Summary of Workgroup Discussions
  - Time Window of Exposure
  - Hypotheses
  - Review of Measurement Protocol
  - Alternative Exposure Metrics
  - Exposure Algorithms
  - Recommendations

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Workgroup Members

- Lisa Baxter (US EPA, ORD/NERL)
- Michael Brauer (University of British Columbia)
- Patrick Breysse (Johns Hopkins University)
- David Diaz-Sanchez (US EPA, ORD/NHEERL)
- Jack R. Harkema (Michigan State University)
- Tim Watkins (US EPA, ORD/NERL) - Facilitator

3

Workgroup Objectives

- Provide a conceptual model linking environmental exposures with critical time period(s) and health outcomes
- Provide recommendations for exposure classification schemes that range from the simplest to the best metrics and approaches for classifying chemical exposures
- Provide recommendations regarding the best data or literature available to support the proposed metrics and approaches for classifying exposure
- Provide recommendations for research needed to understand or develop the proposed approaches for classifying exposure
- Provide recommendations where validation sub-studies could be considered within the NCS and other children's research programs

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Workgroup Approach

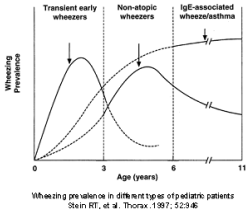
- Identified Asthma Onset as top priority (versus Exacerbation)
  - Critical Time Window
- Reviewed Environmental Measurement Protocol to prioritize relative to Asthma onset
- Discussed additional pollutants with potential to exacerbate asthma
- Discussed differences in Source-based and Pollutant-based hypotheses
  - Importance of residential information
- Reviewed alternative exposure metrics
  - Routinely available
  - Modeling
  - Low cost / novel approaches
- Discussed opportunities for validation
- Developed overall recommendations for exposure metrics

Summary of Workgroup Discussions

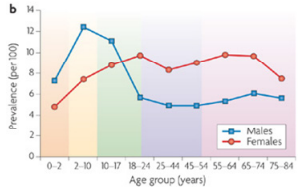
Time Window of Exposure

- Critical time window for Asthma Onset is from in-utero to 3 years
- Time window for asthma progression and exacerbation is year 3 and beyond

Asthma Phenotypes in Children



Wheezing prevalence in different types of pediatric patients
Stein RT, et al. Thorax .1997; 52:946



Ober et al. Nature Reviews Genetics **9**, 911-922 (December 2008)

Hypotheses: Asthma Onset and Exacerbation

- NCS hypotheses should focus on environmental factors leading to onset of asthma
  - Source-based
  - Pollutant-based
  - Atopic versus Non-atopic
- Hypotheses relating to the progression of asthma should also be investigated
  - Why do some children grow out of asthma?
  - Gender differences
- Hypotheses related to exacerbation of asthma are of lower priority

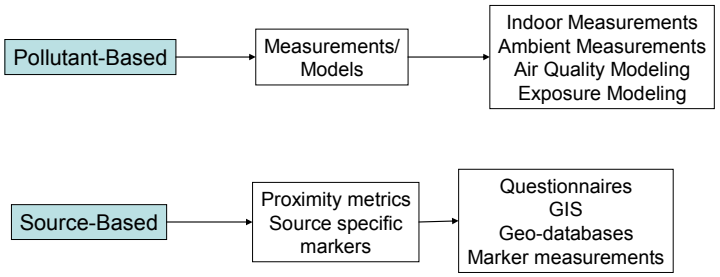


Examples of Hypotheses to be Investigated

Source-Based	Pollutant-Based
Asthma Onset	
Traffic	Traffic Components
Secondhand smoke	PM Components
Indoor Sources	PM Sizes
Indoor Swimming Pools	NO_2
	Phthalates
	Mold
	Endotoxins
Asthma Progression/Exacerbation	
	Coarse and Fine Particles
	SO_2
	Formaldehyde

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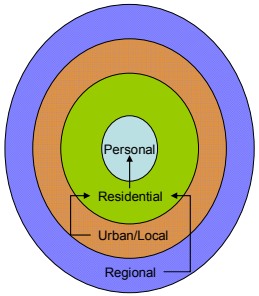
Establishing Exposure Gradients for Source-Based and Pollutant-Based Hypotheses



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Scale of Exposure

- Goal is to minimize misclassification of exposure for NCS subjects
- Personal exposure measurements for all subjects are not feasible
- Residential exposure metrics are the most realistic option for NCS subjects
  - Indoor component
  - Ambient component (including infiltration)
- Ambient exposure metrics are useful
  - Characterizing pollutant gradients in residential setting
  - Estimating infiltration into residence
- The appropriate scale for the ambient metric will depend upon the source/pollutant
  - Regional / Urban / Local



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The Importance of Tracking Residential History and Time Spent in Other Key Microenvironments

- Imperative to accurately track residential location history
- Also, important to track location of microenvironments where subjects spend significant amounts of time
  - Work (pregnant mothers)
  - Daycare/School
- The information is fundamental for developing source proximity metrics and for estimating the pollutant concentration gradients most relevant to the NCS subject
  - Need to capture archived geo-databases for historical reconstruction





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Review of Environmental Measurement Protocol

Pollutant	Priority
Indoor Measurements	
$PM_{2.5}$	High
NO_2	Medium
Ozone	Low
VOC	Lower
Carbonyls	Lower
House Dust	High
Supplemental Community Measurements are a lower priority	

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The Value of House Dust

- Highest priority indoor measurement
- Integrated measurement that can provide information on potential exposure to multiple pollutants
  - Indoor and outdoor origin
- Accumulative exposure metric
- Measure allergens, endotoxin
- Could possibly be used to identify exposures to specific sources
  - Examples
    - Hopanes may be a unique indicator of exposure to traffic pollutants
    - Nicotine is a measure of SHS exposure
- Collection Methods – vacuum, wipe
- Archivable

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Indoor Measurements versus Supplemental Community Measurements

- In general, indoor measurements are a higher priority than additional community-based measurement
  - Ambient monitoring exist in many locations
  - Ambient concentrations can be modeled
- Exception, community monitoring may be a priority if no existing measurements exist
  - Particularly for source specific impacts

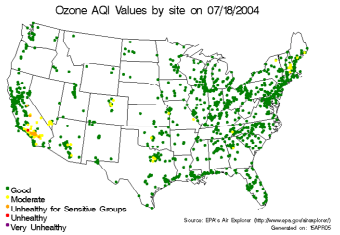




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Alternative Exposure Metrics: Ambient Concentrations (1)

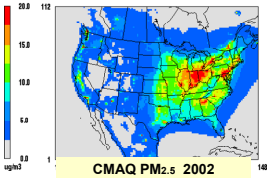
- Ambient Air Monitoring Networks
  - Reliable source of ambient air data
  - Possible near road monitoring network
- AirNOW
  - Provides a semi-quantitative estimate of exposure based on Air Quality Index for entire country
  - Need to validate for personal exposure
- Pollen Counts
  - Should be collected from available sources

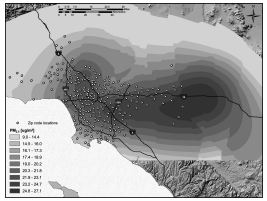


16

Alternative Exposure Metrics: Ambient Concentrations (2)

- Air Quality Modeling
  - AQ modeling could be used in NCS, but needs to be validated
  - AQ models should be related/linked to actual human exposure
- Land Use Regression
  - Provides a more spatially resolved estimate of ambient concentrations
  - Need measurements (40 min, passive) placed in key locations to capture characteristics that factor into variability





(*Jerrett et al. Epidemiology 2005; 16: 727-736*)

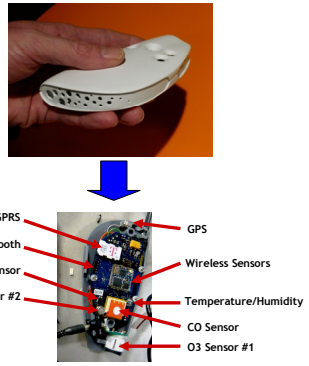
Alternative Exposure Metrics: Residential/Personal Exposure (1)

- Source Proximity
  - Relative low cost estimate exposure obtained through various approaches including:
    - Questionnaires
    - Modeling with GIS/Geo-databases
    - Archive geo-data to capture land use changes (e.g., roads, sources)
- Questionnaires
  - Provide valuable information, including:
    - Where people are
    - What they are doing
    - What was around them
    - Source proximity – sources of ambient and indoor air pollutants
  - Validation is important
    - Self reporting may not be reliable, especially with negative responses



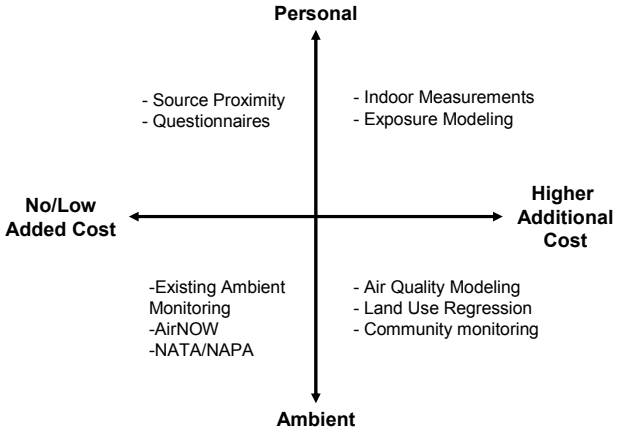
Alternative Exposure Metrics: Residential/Personal Exposure (2)

- National Air Toxics Assessment (NATA)
  - Census tract level estimate of exposure to air toxics
  - NATA will eventually become National Air Pollution Assessment (NAPA) to include criteria pollutants.
- Human Exposure Modeling
  - Should also be considered, but reliable input data is needed.
- Novel Sensor Technologies
  - Technology is evolving quickly, but not ready for immediate application.
  - NCS should allow for possible introduction at a later date.



(Source: M Jerrett & Intel Berkeley)

Trade-Offs



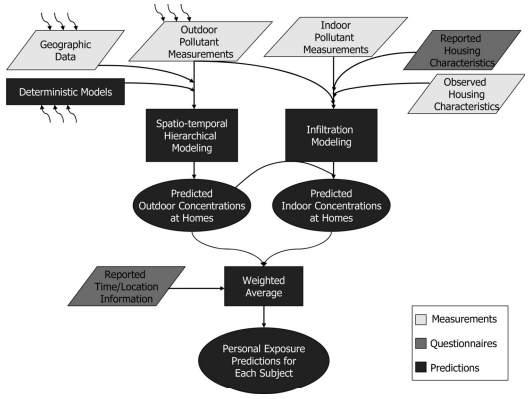
Developing Exposure Algorithms

- It may be possible to develop an "algorithm" using readily available information to provide an exposure metric
- Possible Approaches
  - Ambient Adjustment
    - Use housing characteristics (e.g., age, square footage, AC, normalized leakage) obtained from property assessment data
      - Works relatively well in winter, but not as well in summer when windows are used
  - Weighted Metric
    - Identify activities that impact exposure and assign weights to develop an exposure metric
    - Traffic Example - Assign weights to various traffic related metrics (e.g., distance from road, traffic counts, amount of diesel traffic, commuting time) to created an overall traffic exposure metric
  - Exposure Modeling
    - Use ambient metric combined with either person specific or census based information to model personal exposure estimates

Algorithms – Ongoing Research

- There is ongoing research relevant to the development of exposure algorithms
  - Ambient Adjustment
    - Normalize Leakage (LBNL)
    - Property Assessment Data (Univ of Victoria)
  - Exposure Modeling
    - EPA's Exposure Model for Individuals (EMI)
      - Provides person specific exposure estimate for use in cohort studies
      - Ambient concentration input (modeled or measured)
      - Indoor air quality model
      - Individual level activity / housing characteristic data

An Integrative Approach to Estimating Chronic Exposure to Air Pollution: MESA-Air

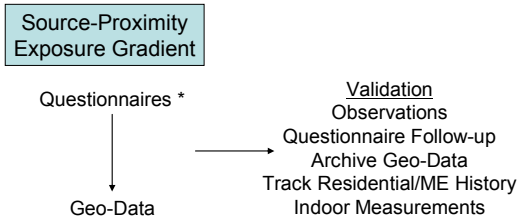


Cohen et al. ES&T 2009

Opportunities for Evaluating Exposure Metrics

- Databases
  - Relationships of Indoor, Outdoor, and Personal Air (RIOPA)
  - Detroit Exposure and Aerosol Research Study (DEARS)
  - Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP)
    - How does a dust sample relate to personal exposure?
- Planned Studies
  - Near-road EXposures to Urban air pollutants Study (NEXUS)
    - EPA Study in Detroit (with Univ of Mich) – Fall 2010 start
    - Investigating role of near road exposures in children's asthma
    - High Diesel / Low Diesel Impact
    - Exposure Metrics - Proximity, Measurements, Modeling
  - EPA RTP Near Road Study (Dates TBD)

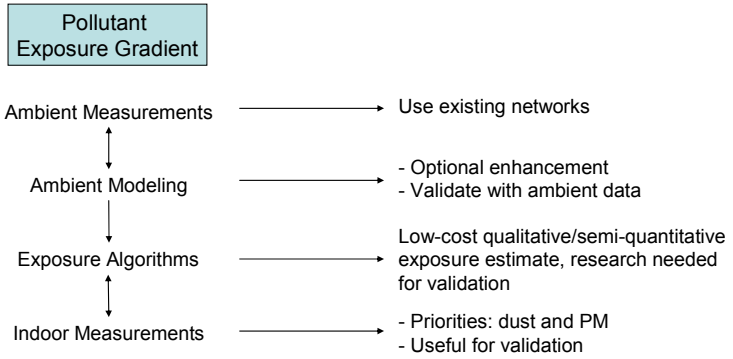
Summary Recommendations: Source-Based Hypotheses



* Note - Include source proximity questions in questionnaires

25

Summary Recommendations: Pollutant-Based Hypotheses



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Recommendations for Prioritization of Exposure Metrics

Existing Data	Level 1	Level 2	Level 3
Ambient Networks	Indoor - Dust	Indoor – PM	Supplemental Ambient Measurements
AirNOW	Source Proximity	Ambient Air Modeling	Indoor - Other
NATA/NAPA		Algorithms	
Pollen Counts		Exposure Modeling	

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Overall Summary

- Asthma onset is highest priority hypothesis
  - Critical time window of exposure – in utero to 3 years
- Residential level exposure estimate are the most realistic for NCS
- House dust is the highest priority indoor measurement.
- Source Proximity metrics can be obtained relatively easily and should be strongly considered
  - Track residential location history and locations of other key microenvironments (daycare/school).
- If additional resources are available, alternative exposure metrics should be considered.
  - Air quality modeling
  - Exposure algorithms

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Insecticide Exposure Assessment in the National Children's Study

Workgroup 2
Summary and Recommendations

April 13, 2010

Workgroup Members

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School of Public Health, Columbia University
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Rollins School of Public Health, Emory University
Kent Thomas (Workgroup Facilitator)
U.S. EPA, National Exposure Research Laboratory

Acknowledgement of Prior Work

NCS Exposure to Chemical Agents Workgroup
- White Paper on Environmental Exposure Assessment
- Journal articles on exposure assessment, including pesticides (EHP Mini-Mongraph)

NICHD, EPA, and NIEHS Sponsored Research
- Lessons learned from Children's Center research
- Design and Pilot Studies
  - Low cost/low burden sample collection
  - Validation sub-sampling
- Workshops and White Papers

NCS Program Office, Vanguard Centers, Coordinating Center
- Environmental measurements committee
- Development of draft research study design
- Development of Vanguard Center protocol
- Development of Questionnaires and Survey Instruments
- Development of Dietary Intake Instruments (with input from EPA/ORD and OPP)

Overview

- Hypothesis
- Workgroup Goals
- Pesticides of Interest
- Important Time Windows of Exposure
- Important Sources and Exposure Pathways
- Insecticide Exposure Assessment Challenges
- Summary Recommendations
- Measurement Exposure Metrics and Research Needs
- Survey-Based Exposure Metrics and Research Needs
- Measurement Sub-Sampling
- Other Considerations
- Final Workgroup Recommendations
- References

Need for Insecticide Exposure Classification in NCS

Assessing exposures to specific insecticides in the NCS is important --

The potential association between insecticide exposure and poor neurological outcomes in children remains an important public health question.

The NCS provides the best opportunity to assess multiple chemical and non-chemical exposures, genetic susceptibility factors, and neurological outcomes.

It may not be possible to fully evaluate neurological outcomes in the NCS without information on multiple risk factors, including insecticide exposures.

5

Hypothesis

Current NCS Meta-hypothesis

Repeated, low-level exposure to non-persistent pesticides, including carbamates, organophosphates, and pyrethroids, in utero or post-natally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and childhood.

6

Workgroup Goals

Provide recommendations regarding insecticide measurement approaches, considering cost/burden issues

Consider non-measurement approaches for insecticide exposure classification

Recommend research that would be needed for:

- Improving measurement approaches and interpretation
- Assessing predictive power of non-measurement metrics
- Improving non-measurement exposure assessment

Provide recommendations for measurement sub-studies within the NCS

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Chemicals of Interest

Organophosphate Insecticides
Pyrethroid Insecticides
Carbamate Insecticides
Fipronil Insecticide
Piperonyl Butoxide (synergist)
Future active ingredients

Exposure assessment and exposure classification of individual active ingredients should be a goal for the NCS.

Assumes persistent chemicals, including organochlorine insecticides, PCBs, and others will be evaluated using blood biomarker measurements.

8

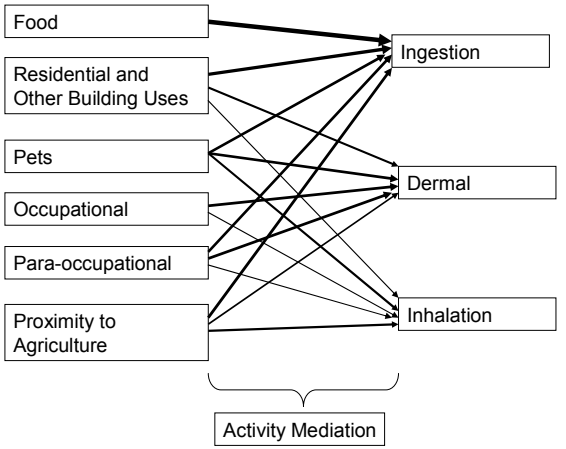
Sources of Exposure

In the general population, the primary sources of exposure are from:
- Residential indoor use
- Foods

For some parts of the population, other sources may be important
- Pet uses
- Residential outdoor use
- Occupational (direct use by parent and take-home)
- Proximity to agriculture
- Other building uses (day care, school, workplace)
- Public health treatments

Sources generally not as important for insecticides
- Drinking water
- Ambient air

Insecticide Exposure Pathways



Time Windows for Neurological Development

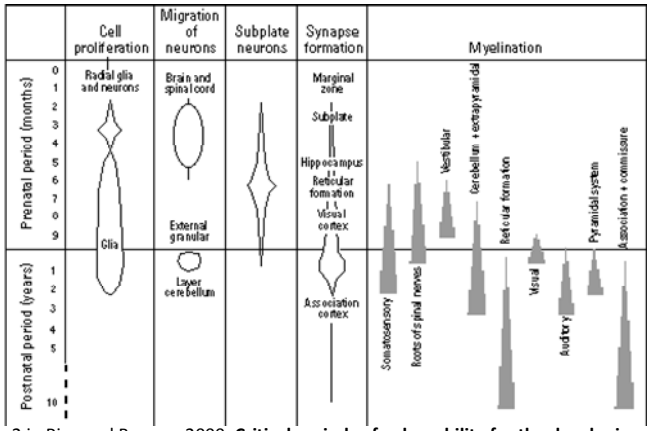
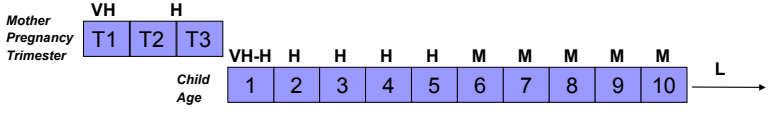


Fig 2 in Rice and Barone. 2000. **Critical periods of vulnerability for the developing nervous system**. *Environ Health Perspect* 108:511-33.

Importance of Time Windows for Insecticide Exposure Assessment



VH = very high importance for exposure assessment
H = high
M = moderate
L = low

Pesticide Exposure Classification Challenges

Multiple pesticides, sources, and exposure pathways

Typically low concentrations in food and environmental media

Short-term variability in exposures

Limited information on relationships between activities and exposures

Lack of chemical specificity in non-measurement approaches

Limited predictive power (low R^2) for survey data

Short biological half-lives for current-use pesticides

Exposure to metabolites in environmental media confounding biomarker interpretation

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Workgroup Summary Recommendations: Measurements

Biological and environmental samples are essential

Core Sample Collection

- Collect cohort-wide core samples, hold for future analysis
  - Urine from key time points for mother and young child
  - Blood & milk from mother at key times; from child as feasible
  - Best measure of residential loading (wipe, dust, or settled dust?)
- Additional research needed to support use for exposure classification

Sub-Sampling Measurements

- Random sub-sample with oversampling for some possible high/low exposure categories using multi-media and longitudinal approaches (validation)
- Consider targeted sampling based on survey information

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Workgroup Summary Recommendations: Non-Measurement Approaches

- Collect residential pesticide use information
- Collect dietary intake information most appropriate for dietary intake assessments
- Gated questions on pets and occupation
- Geographical information for residence
- Some time/activity/location information will probably be needed
- Additional research
  - Focused research needed in near term to assess predictive power of survey information; use Children's Center, Vanguard, and other recent research study data
  - Revise and focus current survey instruments – evaluate how well they result in accurate, useful information
  - Assess predictive power for outcomes as well as exposures

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Core Sample Collection

Urine for insecticide biomarker analysis
- Collect from mother at T1 and end of T2 or early T3 times
- Collect from child as often as possible through age 5
- Collect entire FMV void volume; collect previous and current void times
- Store for future analysis

Other biological samples
- Blood for parent compound and other biomarkers, store for future
  - Mother at T1, child when feasible for sufficient volume
- Mother's milk; store for future analysis

Collect an appropriate residential "loading" sample
- Select best approach: house dust, floor wipes, vapor/settled dust
- Collect at mother T1, child age 6 months or 1 year
- Collect new sample with change in residence
- If feasible, collect additional samples through age 10 (mail-in?)
- Store for future analysis

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Research Needs - Urine

Given the short-term variability in urine biomarker concentrations, will urine samples allow adequate exposure classification over longer time periods?

- Assess extant research examining this issue for OPs, and especially for pyrethroid and carbamate insecticides

- If needed, collect sufficient longitudinal samples from mothers and young children to evaluate variability over 3-month (and 1-year ?) time intervals

Urinary metabolites of pesticides may also appear as pre-formed degradates in food and environmental media; will these potentially confound exposure classification?

- Assess extant research examining this issue for OPs, pyrethroid, and carbamate insecticides

- If needed, perform measurement study to collect food, house dust, floor wipe samples and analyze for metabolites concurrently with collection of urine from home residents

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Research Needs – Residential Loading

What is likely to be the best residential metric with regard to predicting overall residential "loading"? Predicting exposure?

What type of sample has lowest cost/burden and can provide the best information on other chemicals of interest?

- Assess extant research examining this issue for OPs, and especially for pyrethroid and carbamate insecticides (AHHS, CTEPP, Children's Centers, others?)

- Analysis of Vanguard Center data

- Lessons learned from application of PUF indoor vapor/deposition sampling effort and possible further assessment

- Assess the temporal variability in residential loading measures

- Develop a participant-based sample collection and mail-in approach

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Non-Measurement Approaches

Questionnaire and other survey data collected cohort-wide could, potentially, be used as low-cost/low-burden metrics for generic insecticide exposure classification in the NCS cohort.

However, there are major limitations in the use of non-measurement insecticide exposure classification approaches in the general population.

- Pesticide use information from questionnaires has not been shown to be highly predictive of insecticide exposures in general, and for individual active ingredients in particular
- Exposure – activity relationships are still not well-defined, particularly for very young children
- Systematic analyses of survey data and exposure across recent studies are lacking
- For much of the population, dietary intake of insecticides is difficult to classify using consumption and residue information due to the infrequent occurrence of residues, variability of residue concentrations, and diet variability

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Non-Measurement Approaches

Some survey information will need to be collected for the most important sources and pathways

Proposed areas of information collection are described in the next several slides

The following slides discuss research that is needed to identify the information most highly associated with insecticide exposures

Current questionnaires and instruments will need to be refined

20

Non-Measurement Approaches: Residential Use Information

Collect basic pesticide residential use information from all participants

Focus on (*in priority order*):

- Recent use
- Frequency of use
- Duration of use
- Indoor use locations
- Outdoor pesticide and lawn chemical use
- Purpose of use

Collect information about flea and termite treatments

Product inventories may have some analytic value; need to assess time/burden for information collection

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Non-Measurement Approaches: Dietary Information

Collect dietary intake information from all participants (needed for other purposes in NCS as well)

Ensure that good information is collected for

- Potential highly exposed (high consumers of specific foods likely to contain residues)

Potential low exposed (primarily organic fruits and vegetables in diet)

Consider alternate approaches

- Collect some information outside of food instruments (organic diet details, gardening, local farmers markets)
- Community dietary sample collection and analysis
- Market basket sample collection and analysis

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Non-Measurement Approaches: Pet Use Information

Collect Qx information about presence of pets; use as gateway question for additional pesticide use information collection

Collect Qx information for

- Use of flea collars
- Use of spot-on treatments
- Use of shampoos or powders
- Treatment of bedding or outdoor areas
- Whether pets spend time indoors and outdoors

It is not clear whether enough data are available to define useful human/pet interaction activity information for improving exposure classification

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Non-Measurement Approaches Other Uses to Consider

Lice treatments

Use of impregnated materials (e.g. bedding liners for mites, clothing, etc.)

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Non-Measurement Approaches: Occupational Information

Collect information about parent occupational use of, or exposures to, pesticides

Use gateway question for collection of additional information

- Specific occupational use(s) or exposure(s)
- Whether location is same as home location (e.g. farm, nursery)
- Duration and frequency of uses or exposures
- Hygiene information (changing clothes/shoes after work, etc.)

Analyses likely to be limited by lack of chemical specificity

25

Non-Measurement Approaches: Time/Location/Activity Information

Exposures are affected by time spent in environments with pesticide residues and interaction with those environments

General information on time spent in different microenvironments will need to be collected for multiple purposes in NCS

At this time we have limited ability to apply simple activity information for improving pesticide exposure assessment

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Non-Measurement Approaches Geographical Information

General geographic region may be informative regarding exposures in one NCS PSU relative to others (higher pesticide uses in some regions)

Archival of satellite photos over time (every 2 years?)

In rural areas, information regarding proximity to agricultural pesticide use should be collected

- GIS approaches where supported by extant data
- Participant questions regarding proximity to ag use

Analyses will be limited by lack of specificity of active ingredients in most locations

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Research Needs for Non-Measurement Approaches

Systematic evaluation of extant literature, recent studies, and current studies is needed to assess predictive power of questionnaires and other survey information regarding associations with exposures and/or associations with outcomes.

Evaluation and assessment of questionnaires and other survey tools in diverse communities is needed to ensure that people can provide accurate, comparable, and consistent information.

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Research Needs for Non-Measurement Approaches

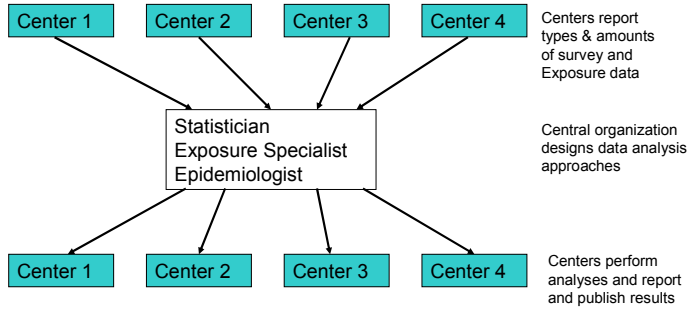
Literature Review
- Associations between survey information and environmental levels
- Associations between survey information and exposures
- Associations between survey information and outcomes

Analysis of Extant Data
- NCS Vanguard Centers
- EPA/NIEHS Children's Centers
- American Healthy Homes Survey
- Other EPA STAR grant studies
- EPA data including CTEPP, Jacksonville pilot, NHEXAS
- NHANES
- Other recent research?

Issues
- Availability
- Funding
- Short time frame to complete work

Research Needs for Non-Measurement Approaches

A possible model for systematic analysis of survey and exposure data at Children's Centers



Funding mechanism for PI or Post-docs at Centers? EPA or NIH?

Research Needs for Non-Measurement Approaches

Near-term analyses of NCS Vanguard Center data are needed

Questions regarding NCS Vanguard Center data
- Will urine and environmental samples be analyzed for pesticides or biomarkers in near term?
- Will questionnaire and dietary data be prepared for analysis in the near term?
- Will measurements and survey data be made available for analyses that could inform insecticide exposure assessment approaches?
- When would information be available?
- Who will perform analyses?

Research Needs for Non-Measurement Approaches

Other Data Sources and Analyses
- American Healthy Homes Survey (EPA/HUD)
- Other STAR Grant Recipients
- EPA Study Results
- EPA analysis of NHANES dietary intake data and PDP pyrethroid data

It is recommended that EPA devote time and resources to perform or fund analyses in near term that can inform predictive value of survey data for the NCS

Validation Sub-Sampling Measurements

Purpose
- Evaluate how well core measures and survey data predict exposures (validation, exposure misclassification assessment)
- Potentially, use results for analytical adjustments

Recommended Approach
- Random sample across NCS cohort
- Consider oversampling selected sub-groups, potentially including higher and lower exposure groups:
  - By geographic area
  - By residence type
  - By socio-economic status
  - By agricultural proximity

Sample Size
- Cost, burden, power factors
- Use of Battelle/Harvard tool

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Targeted Sub-Sampling Measurements

Purpose
- Provide measurement data for improved outcome assessment

Recommended Approach
- Use initial survey data on pesticide use and diet to select participants

- Based on likely higher or lower exposures
  - Reported residential pesticide use
  - High or low dietary intake category
  - Other use or proximity information
  - Outcome susceptibility information??

- Sampling with known probability is recommended

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Sub-Sampling Measurement Plan

The workgroup did not develop a detailed set of recommendations for the types of samples and the sub-sampling strategy

Measurements should be designed to assess the important sources and pathways
- Residential dust, surfaces, soil
- Dietary intake
- Activity levels, activities types, locations
- Urine
- Dermal
- Consider some air/inhalation measures

Frequency and duration of sampling are critical and should be based on information on variability in environmental and biological media; a repeated measures design will likely be needed for at least some media

35

Exposure Algorithm or Index

Development of an exposure algorithm or index for epidemiological insecticide exposure classification in the general population will be a difficult, time consuming task. The workgroup discussed some of the considerations for developing an algorithm:

- Expert workgroup
- Feasibility assessment
- Selection of key parameters or variables
- Evaluation of supporting data
- Combining dissimilar information
- Level of specificity needed for active ingredients (or, potentially for cumulative exposures)
- Decisions on continuous (numerical) or categorical indicator
- Peer review
- Ability to assess or validate inside or outside of NCS

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Co-Exposures

Chemical stressors other than insecticides, and other non-chemical exposures, may also result in or contribute to adverse neurological outcomes. Multiple risk factors must be considered in the NCS epidemiologic analyses.

The workgroup has not considered exposure assessment for other chemical and non-chemical stressors. Some of the important stressors may include:

- Persistent chemicals (OC pesticides, PCBs, Pb, Hg) these need to be measured in blood (or hair for Hg)
- Non-persistent chemicals not considered by this workgroup; may need to measure in biological and environmental samples
- Other exposures or conditions
  - Maternal alcohol and drug use
  - Nutrition (pre- and post-natal)
  - Social environment
  - Others?

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Lawn Care Chemicals

Herbicides are widely used, and insecticides and fungicides are sometimes used, in lawn care products and treatment programs.

Concerns have been raised regarding the use of lawn care chemicals and children's health.

While the workgroup was asked to consider exposure assessment for insecticides and neurological outcomes, the NCS could offer a platform to more broadly examine lawn care chemical use and health.

NCS information collection and chemical analyses would need to be broadened to include lawn care products and herbicides.

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Final Workgroup Recommendations

Workgroup members emphasize the need for retaining biological and environmental measurements at critical time periods for insecticide exposure assessment in the NCS.

Exposure assessment and classification of individual insecticides should be a study goal.

Sub-sampling strategies and internal and/or external research can improve insecticide exposure interpretation and classification.

The ability to use non-measurement information for general insecticide exposure classification, and particularly for individual chemicals, has not been adequately demonstrated. More research is needed in the near term to improve survey questions and tools.

39

1

ENDOCRINE DISRUPTING COMPOUNDS: EVALUATION FOR NCS

Deborah Bennett, Stephanie Engel, Mike Shelby, Heather Stapleton, Vickie Wilson

Workgroup Facilitator: Nicolle Tulve

Outline

2

- Health Endpoints
- Process
- Compound List
- Guidance by chemical
- Decisions still needed to be made
- Available and needed research

Health Endpoints

3

- In addition to reproductive effects, it is important to include other health effects related to hormonally active compounds
- Thyroid disruption during pregnancy impacting neurological development
- Critical window to capture will depend on the exposure and outcome of interest:
  - Thyroid < 20 weeks' gestation possible sensitive window
  - Surge in brain development starting 3rd Trimester
  - Repro tox: starting 8-10 weeks' gestation

Goals

4

- To present a method for classifying exposure to endocrine disrupting compounds in the NCS
- Context – Environmental samples may or may not be available for analysis & may not be required for optimal exposure assessment for all chemicals
- In some cases sample size will be small and it will be practical to measure biological and environmental samples within a case-control design
- In some cases sample size will be large and it will not be practical to provide measurement values

Process for selecting compounds

5

- List of compounds taken from early NCS materials
- How important from a health perspective and how much exposure there was likely to be
- We also considered whether or not another group would be addressing the compounds
- Concerned with co-exposure to neurotoxins
- We ultimately prioritized the list to some degree

Compounds Considered

6

- Phthalates
- PBDEs
- Bisphenol-A
- Phytoestrogens
- PFCs
- Perchlorate
- Triclosan/Triclocarban
- Other phenols
- Other Flame Retardants
- PCBs
- PAHs

- Co-exposures of concern
- Pesticides
- Organotins
- Cotinine
- Mercury
- Lead

- Compounds not discussed
- TCDD/Fs
- Limited agricultural pesticides

Challenges

7

- We have a very large set of compounds
- Primary source of exposure is through indoor sources and consumer products that may not be well known to consumer and are not tied to ambient levels

Challenges with Biological Samples

8

- Blood
- Limited in early childhood due to small blood volumes
- Limited by parent refusal and sample collection failure

- Urine
- Interference with diapers
- Low percentage of samples collected if there are difficulties using urine bags
- Bags are the preference

Approach

9

- We each created a table listing our level of concern over health effects, relevant routes of exposure by time period, and recommended methods for evaluating exposure
- We went over all the chemicals one by one, challenging ourselves to come up with other ideas and trying to come to a general consensus for each compound

Approach

10

- Some compounds can easily be classified by questionnaire data or biological samples are available and low cost – Easy Compounds
- Other compounds provide additional challenges
  - Justification
  - Exposure Routes by Time Period
  - Samples Needed
  - Exposure Metrics

Phthalates – Justification for Inclusion

11

- Phthalate metabolites have been detected in a wide range of body tissues including urine, blood, semen, amniotic fluid and breast milk
  - Phthalate exposures are ubiquitous and high internationally and across all age ranges
  - At least 10 metabolites are commonly detected; median levels in urine range from 1-500 ug/L (4-4000 nmoles/L)
- Animal studies demonstrate reproductive toxicity and thyroid hormone antagonism
- Recent human health studies demonstrate associations with anogenital distance in male babies, sexually dimorphic behaviors, and neurobehavioral problems

Phthalates – Exposure Routes

12

- Prenatal
  - Phthalates cross the placenta
  - Direct effect on maternal prenatal thyroid hormone
- Postnatal
  - Exposure from breastmilk (0-1y)
  - Exposure from housedust (0-4y)
  - Exposure from consumer products across the lifecourse

Phthalates – Samples Needed

13

- Urine (best option)
  - Short half-life, modest reproducibility across spot urines
  - Prenatal, ideally 1 per trimester
  - Postnatal, 6m, 1 per year thereafter
  - Unable to quantify exposure without urine specimen, difficult in early childhood
- Environmental samples - Brominated phthalate (potentially some additional traditional ones as well)
  - House dust or hand wipes (6-12 m)
  - Possible to extrapolate back to pregnancy?
- Consumer product questionnaire
  - Composition of products changes over time
  - General questions (i.e., use of scented products) may be able to crudely rank for some phthalates, but significant concerns about accuracy of self-reporting

Phthalates – Exposure Metrics

14

- Pregnancy – Concentration in maternal urine, ideally more than one
  - For brominated phthalate need dust
  - Variability in metabolites over time makes single spot urine undesirable
- Early Childhood – Ideally childhood urine, one per year.
  - For brominated phthalate need dust
  - Possibly can extrapolate 6-12 m dust sample back to pregnancy
  - Lack of child urine will make classification impossible
- Later Childhood – Concentration in child's urine
- Non-Physical Estimations :Product-use questionnaire unlikely to reliably quantify exposure
- Piloting needs
  - Comparison of 6-12 m dust with pregnancy dust
  - Ongoing & published studies have quantified urinary phthalate metabolite variability over pregnancy

Polybrominated Diphenyl Ethers (PBDEs) – Justification for Inclusion

15

- PBDEs are bioaccumulative and persistent
  - Levels in US population 10X higher than other countries
  - Detected in >95% of population (Sjodin et al., 2008)
  - Levels in children significantly higher than adults (from breast milk and dust exposure)
- Animal studies demonstrate effects on thyroid homeostasis and on neurodevelopment (Review: Birnbaum and Staskal, 2004)
- Recent human health studies demonstrate associations between:
  - Body burdens and fecundability in women (Harley et al., 2010)
  - Neurodevelopmental outcomes in children ages 1-6 years at environmentally relevant levels (Herbstman et al., 2010)

PBDEs – Exposure Routes

16

- Prenatal
  - PBDEs cross the placenta, exposure from mother
- Postnatal
  - Exposure from breast milk (0-1 yr)
  - Exposure from house dust (0-4 yr)
  - While diet is also a source of exposure, it is impossible to estimate exposure from diet as levels in food are variable and not specific to food types

PBDEs – Samples Needed

17

- Biological samples
  - Top choice: serum
    - Prenatal (3rd trimester)
    - Postnatal (cord blood, 6 m, 2 yr)
  - Second choice: breast milk (higher brominated PBDEs do not partition well into breast milk)
- Physical/Environmental samples
  - House dust (collected at 6 m, 1 yr, and 2 yr)
  - Hand wipes (collected at 6 m, 1 yr, and 2 yr)
- Questionnaires not practical

PBDEs – Recommendations

18

- Collect house dust and hand wipes
  - Some PBDEs have short half-lives in the body and exposure cannot be characterized for these congeners using serum
    - Both are needed to differentiate exposure from breast milk
- Justification for use of hand wipes
  - Better metric for quantifying exposure to dust and can be used to evaluate exposure to other compounds found in dust
  - Easy to collect and store (relatively inexpensive)
  - Significant PBDE residues have been measured in hand wipes collected from adults and children (Stapleton et al., 2008)

PBDE – Exposure Metrics

19

- Pregnancy – Concentration in mother's blood
- Early Childhood – Environmental concentration, modify with breastfed or not, breast milk concentration
- Later Childhood – Concentration in child's blood
- Non-Physical Estimations – There are no non-physical methods for evaluating this compound with the exception of substituting mother's blood concentration for breast milk concentration
- Piloting needed – Available studies looking at blood/ dust correlation

Bisphenol A – Justification for Inclusion

20

- Metabolites detectable in 90% of the population
  - Biomonitoring suggests higher exposures in certain minority groups, children, and women
- NTP-CERHR expert panel noted a varying level of concern for:
  - Neural or behavioral effects resulting from prenatal, infant, or childhood exposure
  - Accelerated puberty resulting from prenatal, infant, or childhood exposure
- Bulk of exposure coming from dietary ingestion

Bisphenol A – Samples Needed

21

- Urine (best option)
  - Short half-life, modest reproducibility in metabolite levels
  - Prenatal, ideally 1 per trimester
  - Postnatal, 6 m, 1 per year thereafter
  - Unable to quantify exposure without urine specimen, difficult in early childhood
- Environmental samples - None required
- Consumer product questionnaire
  - Composition of products changes over time
  - General questions (i.e., use of canned foods, polycarbonate products) may be useful, and significant concern over accuracy of self-reporting
  - Unclear how many polycarbonate products such as sippy cups will still be in use

Biphenol A – Exposure Metrics

22

- Pregnancy – Concentration in maternal urine, ideally multiple
  - Variability in BPA metabolite level over time
- Early Childhood – Ideally childhood urine one per year.
  - Lack of child urine will make classification impossible
- Later Childhood – Concentration in child's urine
- Product-use questionnaire unlikely to reliably quantify exposure
  - Can ask about use of canned food, polycarbonate plastics, sippy cups. Without knowing plastic number hard to tell if contains BPA.
- Piloting needs
  - Ongoing & published studies have/will quantify urinary BPA metabolite variability over pregnancy

Phytoestrogens

23

- Widespread exposure through dietary intake, especially through soy formula in infancy
- Questions regarding use of soy formula in infancy– should take into account amount, timing, and patterns of usage (i.e., supplementing breast milk or exclusive use)
- Biological Samples - urine (short half-life, modest reproducibility in metabolite levels across spot urines)
- Compound can be evaluated well by questionnaire/biological samples!

- Exposure Metrics – questions on use of soy formula

Perfluorinated Chemicals (PFCs) – Justification for Inclusion

24

- Includes perfluorooctanoic acid (PFOA); perfluorooctane sulfonic acid (PFOS); perfluorohexane sulfonic acid (PFHxs); perfluorooctane sulfonamide; perfluorinated telomer alcohols (e.g., 6:2, 8:2, and 10:2 FtOH)
- Detected at high frequencies (>99%) in US serum (Calafat et al., 2007)
- Detected in US house dust (Strynar and Lindstrom, 2008)
- Developmental and thyroid effects observed in laboratory exposures (Lau et al., 2004; Yu et al., 2009)

PFCs – Exposure Routes

25

- Prenatal
  - Likely crosses to fetus via bloodstream (support from rat study by Yu et al., 2009)
- Postnatal
  - Exposure from breast milk (0-1 yr)
  - Exposure from house dust and treated products in home (e.g., furniture, carpets, etc.) (0-4 yr)
  - Diet/food packaging (age 1-adult)

PFCs – Samples Needed

26

- Biological samples
  - Top choice: serum
    - Prenatal (3rd trimester)
    - Postnatal (cord blood, 6 m, 2 yr)
  - Breast milk not recommended as we know nothing about partitioning between blood and breast milk
- Physical/Environmental samples
  - House dust (collected at 6 m, 1 yr, and 2 yr)
  - Hand wipes (collected at 6 m, 1 yr, and 2 yr)
- Questionnaires
  - Not validated although there are ideas available on what could be asked

PFCs – Exposure Metrics

27

- Pregnancy – Concentration in mother's blood
- Early Childhood – Environmental concentration
- Later Childhood – Concentration in child's blood
- Non-Physical Estimations
  - Questionnaires have not been developed for this compound
- Piloting needed
  - None

Perchlorate

28

- Water samples should be collected and analyzed by water distribution system.
- Well water samples should be collected (will be limited)
- Compound that can be evaluated well by Census block
- A biomarker is available for individual classification
- Exposure metric – Census level well water concentrations

Triclosan and Triclocarban – Justification for Inclusion

29

- Detected in US urine (Calafat et al., 2008)
- Detected in house dust (Canosa et al., 2007; Geens et al., 2009)
- Known effects on thyroid (Veldhoen et al., 2006; Crofton et al., 2007; Paul et al., 2010)

Triclosan and Triclocarban – Exposure Routes

30

- Prenatal
  - Likely crosses to fetus via bloodstream
- Postnatal
  - primary exposure from treated products such as toothpaste, hand soaps/gels (age 1-adult)
  - Exposure from breast milk (0-1 yr)
  - Exposure from house dust (0-4 yr)

Triclosan and Triclocarban – Samples Needed

31

- Biological samples
  - Top choice: urine (3rd trimester, 6 m, 2 yr, 4 yr)
  - Second choice: serum (detected, easier to collect urine)
- Environmental samples
  - Not adequately characterized
  - Hand wipes may be a good choice for measuring residues
- Non-physical measures - Add questions to survey/questionnaire regarding use of antibacterial toothpastes and soaps/lotions/gels,

Triclosan and Triclocarban – Exposure Metrics

32

- Pregnancy – antibacterial product use, concentration in mother's urine
- Early Childhood – antibacterial product use, concentration in child's urine
- Later Childhood – antibacterial product use, concentration in child's urine
- Piloting needed
- None

Nonyl/Octyl Phenols – Justification for Inclusion

33

- 4-nonylphenol/nonylphenol ethoxylates – used in plastics, resins/hardeners, cleaners, cosmetics
- 4-tert-octylphenol – used in paints, plastics, floor polish
- 2,6-Di-tert-butylphenol – used as a UV stabilizer and antioxidant in petrochemicals and plastics
- Residential dust samples may be most efficient and cost-effective for assessing exposures
- Unlikely that a questionnaire would be informative about exposures

Nonyl/Octyl Phenols – Exposure Metrics

34

- Pregnancy and Childhood – analysis of dust samples
- Non-Physical Estimations – There are no non-physical methods for evaluating these compounds
- Questionnaires would not be informative
- Piloting needed
  - None

Alternate Current-Use Flame Retardants – Justification for Inclusion

35

- Includes hexabromocyclododecane (HBCD), decabromodiphenyl ethane (DBDPE), triphenyl phosphate (TPP), tetrabromobenzoate (TBB), tetrabromophthalate (TBPH), tris(1,3-dichloroisopropyl) phosphate (TDCPP), tris (2-chloroethyl) phosphate (TCEP)
- All detected at high frequencies in US house dust (Stapleton et al., 2008, 2009)
- DBDPE primary replacement for DecaBDE
- TPP, TBB, and TBPH present in Firemaster 550/600 which is a primary replacement for PentaBDE
- TCEP and TDCPP are prominent replacements for PBDEs detected in furniture products imported from China
- HBCD affects thyroid regulation (Palace et al., 2008); TCEP is a carcinogenic compound and TDCPP is a neurodevelopmental toxicant (Dishaw et al., 2010, work in progress)
- Recent human health studies found negative associations between TDCPP and hormone levels in men (Meeker and Stapleton, 2010)

Other Flame Retardants – Exposure Routes

36

- Prenatal
  - Likely crosses to fetus via bloodstream; not full evaluated
- Postnatal
  - Exposure from breast milk (0-1 yr)
  - Exposure from house dust (0-4 yr)
  - While diet is also a source of exposure, it is impossible to estimate exposure from diet as levels in food are variable and not specific to food types

Other Flame Retardants – Samples Needed

37

- Biological samples
  - Top choice: serum
    - Prenatal (3rd trimester)
    - Postnatal (cord blood, 6 m, 2 yr)
  - Breast milk not recommended as we know nothing about partitioning between blood and breast milk
- Physical/Environmental samples
  - House dust (collected at 6 m, 1 yr, 2 yr)
  - Hand wipes (collected at 6 m, 1 yr, 2 yr)
- Questionnaires not practical

Other Flame Retardants – Recommendations

38

- Collect house dust and hand wipes
  - Questionnaires not practical
  - Some have short half-lives in the body and exposure cannot be characterized using serum
- Justification for use of hand wipes
  - Better metric to quantify exposure to dust
  - Can be used to evaluate all flame retardants found in dust
  - Easy to collect and store (relatively inexpensive)
  - Significant residues of HBCD, TBB, TBPH, TPP, and TDCPP have been measured in hand wipes collected from adults and children (Webster and Stapleton, work in progress)

Other Flame Retardants – Exposure Metrics

39

- Pregnancy – Concentration in mother's blood for some, environmental concentration
- Early Childhood – Environmental concentration
- Later Childhood – Concentration in child's blood for some, environmental concentration
- Non-Physical Estimations – Non-physical measures are not practical, potentially substitute one time period for many
- Piloting needed
  - Some research becoming available

PCBs

40

- Questionnaire – fish consumption, age of home
- Biomarker available
- May want environmental sample in some older housing stock

PCBs – Exposure Metrics

41

- Pregnancy – Concentration in mother's blood
- Early Childhood – Use concentration in child's blood from later time period
- Later Childhood – Concentration in child's blood
- Non-Physical Estimations:
  - Pregnancy – Fish Consumption
  - Childhood – Fish Consumption/ potentially need environmental measurement for participants in older housing stock
- Piloting needed - None

PAHs

42

- Exposure primarily from traffic, cooking sources, and certain foods
- Traffic exposure can be evaluated through GIS
- Exposure to foods and cooking methods can be addressed by questionnaires

Co-Exposures Considered

43

- Organotins – Can be measured in blood but not a standard method, found in the home so can be measured in dust
- Cotinine – Questionnaire – Cigarette use and exposure to second hand smoke, biomarker also available
- Mercury – Questionnaire – Fish consumption, biomarker also available
- Lead – Questionnaire – Age of home, condition of paint, low cost biomarker available
- Indoor Pesticides – Consult with pesticide group

Agricultural Pesticides

44

- There may be additional pesticides of concern in terms of endocrine disruption by distance to fields and use on fields should be able to be collected for each Census block and not on an individual level
- Compounds that can be evaluated well by Census block

Environmental Sampling Conclusions

45

- Critical time window that cannot be captured by biological samples and/or questionnaires is 0-12 months
  - Sample collected in the home during this time frame is strongly recommended
- This sample would serve as the primary means of classifying the following compounds:
  - PBDEs (high priority)
  - Other flame retardants (high priority)
  - PCFs (high priority)
  - Organotins
  - Nonyl/octy phenols

Biological Sample Research Needs

46

- Develop a diaper or an insert that can be used easily by participants and that does not have interference problems
- Critical for determining exposure in first 2 years of life to:
  - Phthalates
  - Bisphenol-A
  - Helpful for Triclosan/Triclocarban

Compounds Considered

47

- Phthalates – urine, dust
- PBDEs – blood, dust
- Bisphenol-A - urine, Q
- Phytoestrogens - Q
- PFCs – blood, dust
- Perchlorate – Regional
- Triclosan/Triclocarban – Q, urine
- Other phenols - Dust
- Other Flame Retardants - Dust
- PCBs - Q
- PAHs – Q, GIS

- <u>Co-exposures of concern</u>
- Pesticides
- Organotins - dust
- Cotinine – Q, biomarker
- Mercury – Q, biomarker
- Lead – Q, biomarker

- <u>Compounds not discussed</u>
- TCDD/Fs
- Limited agricultural pesticides

What Sort of Environmental Sample?

48

- Dust
- Wipe
- Hand Wipe

- Recommend collect and store to leverage for future grant support if funds are limited

Evaluating Environmental Measures

49

- Correlation with biological sample
- % of samples likely to be above LOD
- Sample can be evaluated with multiple extraction methods
- Stability of sample

Dust Methods

50

- HVS3: Pro: Uniform sample collection, powerful suction collects sample quickly
  - Con: Heavy and awkward
- Mighty Mite: Pro: Easy to carry
  - Con: Often overheats, can be time consuming
- Participant Vacuum: Pro: Easy to Collect
  - Con: Not all people have vacuums, no uniformity
- Provided Vacuum: Pro: semi-uniform, avoids staff time
  - Con: Not sure all participants will collect sample, semi-uniform

Dust Collection Evaluation

51

- Need to collect dust samples through multiple methods in conjunction with biological samples and determine which method has the best correlation
- Samples Available:
- 1) EPA analyzing HVS3 and participant vacuum cleaner bags and CDC is analyzing biological samples, waiting for analytical results.
- 2) UC Davis has 25 co-located HVS3 and Mighty mite samples with biological samples from within a couple of months. Analysis not planned.

Household Wipes

52

- Collection from hard flooring is problematic due to potential high loading for phthalates
- David Camann is experimenting with door frame wipes

Employing Hand Wipes for Measuring Exposure

53



Wipe Top of Hand



Wipe Bottom of Hand

-Methods based on those published by Stapleton et al., 2008 for measuring PBDEs in hand wipes
-Uses sterile gauze pads and isopropyl alcohol (relatively inexpensive)
-Can be collected by participants
-Collects most organic residues on hands
-Analysis in extracts by Mass Spectrometry methods

-Can be evaluated for several chemical classes; collect sequential wipes from a sub-population of individuals to assess recovery from first wipe collection

What Compounds to Analyze For?

54

- Ideally we would like to include a wide range of compounds – this adds costs
- One idea: Two Dimensional Gas Chromatography with Time-of-Flight Mass Spectrometry (GCxGC TOF-MS)
- Response factor quantification based on surrogates approaches can be considered for new compounds
- Significantly enhanced chromatographic resolution limits interferences
- Detection limits similar to conventional GC/MS/SIM

Cumulative Exposure

55

- We acknowledge that in a perfect world, we would be able to sum across all the compounds based on the toxicity
- Only limited data is available to do this in an effective way
- Research on phthalates and other anti-androgens indicates that compounds which impact the same pathway or endpoint will act in a dose additive manner (Hotchkiss et. al. 2004, Biol Repro; Howdeshell et. al. 2007, Tox Sci; Howdeshell et. al. 2008, Tox Sci; Rider et. al. 2008 Int J Androl; Rider et. al. 2010 Int J Androl.)
- These studies argue for combining exposure assessments for some compounds (such as those phthalates known to be reproductive toxicants) as a better indicator of risk

Biological/Environmental Studies

56

- Goal: Is dust representative of exposure in early childhood?
- Stapleton Study – 60 kids, 12 – 30 months, dust, handwipe, blood, PBDE and other flame retardants
- Webster Study – Better correlation between blood/handwipes than blood/dust for adults
- Bennett Study – 100 kids 3-6 years, blood, HVS3 and participant vacuum dust, PBDE and PFC
- Hertz-Picciotto Study – 33 bloods @ 1 year w/ 6 month dust – Analysis not planned

Variability in Dust Concentrations

57

- Goal: Can we say dust collected at 6 months is representative of dust collected during pregnancy?
- Bennett Study – 50 HVS3 samples 1 year apart being analyzed for PBDEs, houses with young kids
- Hertz-Picciotto – 25 samples from pregnancy visit and 6 month visit – Analysis not planned

Variability during Pregnancy

58

- Goal: How representative is spot urine?
- Engel Study: Phthalate and phenol metabolites (BPA, TRCS, 2,5-DCP, BP3) measured in 100 women enrolled with 3 urines per woman. Amniotic fluid being processed.
- Hertz-Picciotto Study: 65 woman with 6 or more samples, 40 more with 4 or more. At least one 24 hour sample per woman. Analysis not planned.

Integration with Vanguard Centers

59

- Dust collection and hand wipe methods are developed and could be integrated into Vanguard centers to test for acceptability and potentially compare with biological samples
- Although a “special” diaper is not yet developed, vanguard centers could provide a regular diaper and ask that participants use that diaper to determine if participants remember to use the specified diaper

Conclusions

60

- Potential limitations with biological samples during early childhood coupled with the lack of practical non-physical measures support need for environmental sample/hand wipe in early childhood
- Environmental analysis methods should be developed to get as many compounds as feasible in a cost effective way
- Note that samples may be able to be stored
- Develop a urine collection method that will be acceptable and limit interference

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