

# Exposure Projects to Support the National Children's Study

James Quackenboss<sup>1</sup>, Gary Robertson<sup>1</sup>, Nigel Fields<sup>2</sup>, Roy Fortmann<sup>3</sup>, and Haluk Ozkaynak<sup>3</sup>

U.S. Environmental Protection Agency, Office of Research and Development • 1 National Research Exposure Laboratory (NERL), Las Vegas, NV  
2 National Center for Environmental Assessment (NCEA), Washington, D.C. • 3 National Center for Environmental Assessment (NCEA), Research Triangle Park, NC

research and development

## Science Question

The NCS plans to recruit and follow 100,000 children from before birth to adulthood, to evaluate effects of exposures on children's health and development. Key exposure questions to be addressed in preparation for this study include:

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

In addition, the methods and approaches developed in these studies will also assist the EPA in meeting goals under the Food Quality Protection Act and other programs concerned with the effect of environmental contaminants on human health.

## Research Goals

Several exposure assessment projects were initiated by ORD scientists early in the development of the NCS; two examples of these projects are provided in this poster. In addition, ORD scientists have worked with EPA/NIEHS Children's Environmental Health Center scientists to develop publications highlighting their experiences in conducting studies in birth cohorts and school age children.

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

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

**Synthesis of Applied Exposure Methods and Lessons Learned for the NCS.** The EPA/NIEHS Children's Environmental Health Centers began in 1998 and have specialized in pediatric exposure, epidemiology and intervention research. The exposure papers summarize their shared experiences in sampling, analyzing and translating air pollutant and pesticide exposures in the urban and rural environments. The scientists consider the value of biological and environmental measures, hierarchical designs, interpersonal variability, and analytical challenges for future studies.



## Approach and Results

### Pilot study: Development of Exposure Assessment Study Designs for the National Children's Study

- Conduct a literature survey on exposure related information and statistical design methodologies suitable for NCS
- Examine optimal design strategies that include, selecting subsets of the study for complete exposure evaluation, allocation of replicate measurements and latent variable models to account for exposure measurement error
- Using mathematical models, simulate realistic exposure patterns and health outcomes to identify study design strategies with adequate power, which address: bias, measurement error, attrition

### Possible Sampling Strategy

We anticipate that the NCS will collect information related to major health outcomes of interest and limited exposure (e.g., questionnaires, screening level environmental measurements) information on all study subjects over time. However, many of the core NCS hypotheses will require much more detailed assessment, which could be addressed using a smaller subsample of children to fully characterize aggregate exposures and associated risk factors and on a smaller and other design elements discussed earlier. The following are some important design elements:

- The aggregate exposure study must be conducted on a representative sample of NCS respondents, so that the results can be generalized back to the NCS cohort population
- This study must provide coverage across all stages of vulnerability, including pre-conception exposures among women planning pregnancy, exposures during pregnancy, and exposures during infancy through early adulthood
- The aggregate exposure study must be planned so that sources and pathways of exposure can be characterized within each stage of vulnerability with known precision and accuracy

Given these considerations, one possible sampling plan for the aggregate exposure study is to:

- One percent of respondents (i.e., 1000) could be selected at random upon enrollment for initial inclusion in the aggregate exposure study among women planning pregnancy or in early stages of pregnancy
- Of these 1,000 women who participate in the aggregate exposure study during this first stage, 40 percent (or 400) women would be selected at random to participate in the aggregate exposure study during the first two stages of vulnerability
- 16 percent (or 160 women out of the 400) would be encouraged to participate in the aggregate exposure study for the first three stages of vulnerability
- At each subsequent stage of vulnerability covered by the NCS, the aggregate exposure study would be replenished to achieve a total sample size of 1,000 study subjects - by enrolling 600 study subjects for the aggregate exposure study from a pool of available NCS study participants who previously had not participated in the aggregate exposure study
- Of the 600 study subjects who are chosen for participation in each subsequent phase, 240 would participate in two consecutive phases, of which 160 would participate in three consecutive phases.

### ECAWG White Paper (WP) on Exposure Measurement and Evaluation Considerations

- WP is intended to serve as a resource document to NCS Program Office and NCSAC in designing the exposure assessment component of the NCS
- WP contains an evaluation of different types of exposure measures related to each of the NCS core hypothesis
- ECAWG members research, summarize and interpret environmental and personal exposure and biomonitoring sampling and analysis information for each critical life stage of a child.
- Potential exposure measurements, questionnaires and biological matrices which may be collected by the NCS are summarized in a series of tables by media, route and chemical class

### Demonstration of Low Cost, Low Burden, Exposure Monitoring Strategies for Use in the NCS

Broad study objectives included:

- assessing the feasibility of recruiting and retaining study participants (children and their caretakers) in a set of longitudinal exposure studies,
- demonstrating relevant, low-cost, low-burden remote data collection strategies for use in a longitudinal epidemiological study such as NCS, and
- demonstrating the feasibility of remote data collection by study participants using available, easy to use, state-of-the-art methods, instruments, and techniques for assessing human exposures to environmental contaminants.

Readily-available and commonly used methods, instruments, and techniques were tested over a 12-month data collection period. Selected exposure data (environmental samples, biological samples, and survey data) were collected periodically from participants who were enrolled from an existing web-based panel. The feasibility of remote (home) data collection using a web-based panel was evaluated in the pilot studies.

### Answers to Key Questions

**Can study participants be successfully recruited through a pre-existing web-enabled panel?** Yes. The web can be used successfully to recruit participants. A very detailed recruiting e-mail/survey was critical in ensuring that potential participants understood what was expected of them and why. Data from the debriefing surveys indicate that participants felt informed and knowledgeable about the study requirements prior to hard copy informed consent.

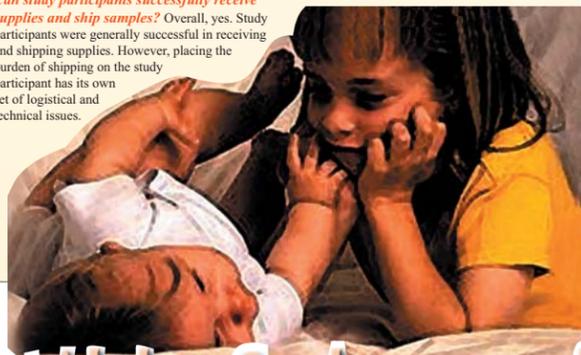
**Are the incentives used in the study appropriate for level of burden?** Possibly. We were able to ask this question of the 0-1 participants in the debriefing survey. Samples collected by this cohort included breast milk, duplicate diet and urine samples. Those data show mixed results, some said the incentive amounts for the 12-month study were appropriate, others said they were not.

**Is the web a feasible way of collecting questionnaire, activity and food diary data?** Yes. The consistently high completion rates for web surveys, and activity and food diaries demonstrate that when survey burden is kept to a minimum, participants will comply.

**Can study participants coordinate the temporality requirements of collecting data shortly after biological and environmental samples have been collected?** Yes. Study participants were instructed to complete questionnaires shortly after collecting the samples. Compliance rates were well over 90% across all sample types. In a few instances questionnaires appeared to have been completed before the sample was collected.

**Can study participants follow instructions and successfully assemble and/or use equipment for collecting samples of food and water, volatile organic compounds, urine, hair, breast milk and others?** Mostly, but some samples were easier to collect than others. Overall, we had relatively high collection rates for the biological and environmental samples that were collected. Some samples, such as hair, dust, and water were relatively easy to collect. Others, such as the VOC and saliva samples were difficult to collect correctly. Sample condition and acceptability was a problem with some sample types.

**Can study participants successfully receive supplies and ship samples?** Overall, yes. Study participants were generally successful in receiving and shipping supplies. However, placing the burden of shipping on the study participant has its own set of logistical and technical issues.



## Synthesis of Applied Exposure Methods and Lessons Learned for the NCS

### Pesticides

Epidemiologic investigations have often relied on questionnaire information for exposure classification, but this approach alone is unlikely to capture the complexity of children's pesticide exposure. In contrast to the Agricultural Health Study, for example, which draws upon the records of pesticide applicators, and has derived a complex exposure algorithm from 40 years of occupational exposure studies (Dosemici et al. 2002), the everyday use of pesticides in homes, schools, and other child environments is not easily codified, and dietary pesticide exposures can only be inferred from questionnaire data. It seems, therefore, that some level of environmental and/or biological monitoring will be required for all study participants. The type of sampling needed will depend primarily on the purpose of the study, be it exposure characterization, long-term health outcomes, or short-term toxic response in children. Lessons learned regarding pesticide exposure can be summarized as follows:

- Biological monitoring appears to be the best available method for assessment of children's exposure to pesticides. However, all pesticide biomarkers have limitations. It is likely that a combination of biomarkers, environmental measurements, and questionnaires will be needed after careful consideration of the specific hypotheses posed by investigators, and the limitations of each exposure metric.
- Environmental measurements, such as surface and toy wipes, and indoor air or housedust samples can characterize residential pesticide contamination, but their validity for exposure classification has not been established. Their value in epidemiologic studies deserves further investigation.
- Emphasis on personal rather than environmental sampling in conjunction with urine or blood sampling is likely to be most effective at classifying exposure.
- A focus on maternal exposures during pregnancy is particularly important for making associations with infant health, given the critical developmental stages during this period.
- Questionnaires will need to be validated with carefully designed studies that involve personal sampling or biological monitoring.
- Interpretation of urinary metabolites is not straightforward, but because of ease of collection, these samples may provide the best available approach to capturing exposure variability of non-persistent pesticides in young children; additional validation studies are needed.
- Repeated exposure measures will be needed to overcome high intra-individual variability of biological samples for most pesticides in use today.
- Post-natal exposure can also contribute to health effects in early childhood. For infants and young children it appears possible to collect urine sample for extended periods of time.

It is clear from this review that the critical tools needed for accurate characterization of children's pesticide exposure are not yet in place. Most of the work discussed here has been conducted in the past 6-8 years, and many of the exposure methods have been exploratory in nature. Substantial resources will be needed for validation of existing methods, support of novel methods, and enhancement of analytical capabilities. It may be possible to initiate epidemiologic investigations and validation studies simultaneously, if biomarker samples can be properly archived. Whatever sampling strategies are employed for epidemiologic investigations, they will need to be selected to support specific hypotheses, and focus on specific pesticides. Studies with substantial exposure assessment activities will be costly, but should ultimately pay benefits in terms of the quality of scientific information produced.

### Air pollution

The National Children's Study is considering a wide spectrum of airborne pollutants that are hypothesized to potentially influence pregnancy outcomes, neurodevelopment, asthma, atopy, immune development, obesity and pubertal development. This paper summarizes six applicable exposure assessment lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research (Children's Centers) that may be of interest to the National Children's Study:

- Selecting individual study subjects with a wide range of pollution exposure profiles maximizes spatial-scale exposure contrasts for key pollutants of study interest;
- In studies with large samples sizes, long duration, and diverse outcomes and exposures, exposure assessment efforts should rely on modeling to provide estimates for the entire cohort, supported by subject-derived questionnaire data;
- Assessment of some exposures of interest requires individual measurements of exposures using snapshots of personal and microenvironmental exposures over short periods and/or in selected microenvironments;
- Understanding issues of spatial/temporal correlations of air pollutants, the surrogacy of specific pollutants for components of the complex mixture, and the exposure misclassification inherent in exposure estimates is critical in analysis and interpretation;
- "Usual" temporal, spatial, and physical patterns of activity can be used as modifiers of the exposure/outcome relationships



## Impact and Outcomes

### Development of Exposure Assessment Study Design Options for the NCS:

**Guidance** and examples will enable NCS researchers to develop statistically valid designs for validation sub-studies to assess exposure measurement error within the NCS and to incorporate these results into testing of study hypotheses. **Demonstration of Low Cost, Low Burden, Exposure Monitoring Strategies for Use in the NCS:** The results from these studies provide NCS researchers with low-cost alternatives to having technicians administer questionnaires and collect samples. Suggestions are provided for improving participant success in these procedures. **Synthesis of Applied Exposure Methods and Lessons Learned for the NCS:** The insightful lessons of these papers will be used to guide the methods and study plan (protocol) of the NCS and potentially other long-term cohort studies where environmental conditions or stresses are of concern.

## References

Rench, J., Raymer, J., Thalii, L., Spruill, M., Salmons, C., Michael, L., Pecha, M., Dean, E., Akland, G. Demonstration of Low Cost, Low Burden Exposure Monitoring Strategies for Use in Longitudinal Cohort Studies - Volume I: Final Report and Volume II: Appendices, EPA/600/R-04/109, September 2004.

Strauss W, Lehman J, Morara M, Ryan L. Development of Exposure Assessment Study Design for the National Children's Study. EPA, September 30, 2003. Exposures to Chemical Agents Workgroup of the National Children's Study. A White Paper on: Measurement and Analysis of Exposures to Environmental Pollutants and Biological Agents during the National Children's Study. EPA, November 30, 2004.

Fenske, R., Bradman, A., Whyatt, R., Wolff, M., Barr, D. Lessons Learned for the Assessment of Children's Pesticide Exposure: Critical Sampling and Analytical Issues for Future Studies. Submitted to Environmental Health Perspectives 12/2004.

Gilliland, F., Avol, E., Kinney, P., Jerrett, M., Dvonch, T., Lurmann, F., Buckley, T., Breyse, P., Keeler, J., McConnell, R. Air Pollution Exposure Assessment for Epidemiologic Studies of Pregnant Women and Children: Lessons Learned from the Centers for Children's Environmental Health and Disease Prevention Research. Submitted to Environmental Health Perspectives 12/2004.

# Susceptible Subpopulations

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