Implementing the National Children's Study: Scientific Progress, Challenges, and Opportunities

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Poster Abstracts

Poster 1

The Influence of Stress on Developmental Outcomes in the National Children's Study

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Stress is defined as a feeling of distress experienced when demand exceeds an individual's ability to control what is happening in his/her life. Stress has consequences for physical health, primarily when it is chronic, not acute. The role of stress will be examined in the National Children's Study using a Multi-Level Interactive Model that examines the role of the individual, family, neighborhood, school, and community. Several white papers on psychiatric, neuropsychological, social/emotional, and motor development, as well as workshops on maternal stress and pregnancy, and on gene/environment interactions in the regulation of behavior serve as input to the protocol in this area for the National Children's Study. Reports of these can be found on the Study Web site.

Stress interacts with health and development in 3 major ways: 1) as an independent predictor of health and development (e.g., neighborhood and community characteristics, media exposure, racism, family resources and process, psychosocial stress); 2) through interactions with other environmental exposures (e.g., modulation of lead effects on development by maternal stress); and 3) through gene-environment interactions (e.g., modification of the risk of schizophrenia in adopted children of schizophrenic mothers by family environment). The major health outcomes of concern are psychiatric/mental health, cognitive, neurobehavioral, and social/emotional health and development. In summary, psychosocial and behavioral factors interact with each other and with other environmental and genetic/biological factors to influence health and development from molecular to systemic levels. The psychosocial outcomes in this study are complex behaviors that will be investigated from a perspective of multiple influences which vary in importance by developmental stage. Mechanisms for these behaviors will be examined from molecular to systemic levels.

Poster 2

Social Determinants of Health in the National Children's Study

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"Observational research and intervention studies show that the foundations of adult health are laid in early childhood and before birth (WHO, 2003)." Childhood socioeconomic circumstances shape adult disease risk (Galobardes et al., 2004; Smith et al., 2000) and children from poor families experience chronic health problems (Newacheck, 1994). Low socioeconomic status is associated with higher stress (Orpana and Lemyre, 2004), higher rates of perinatal complications, reduced access to resources that buffer the negative effects of perinatal complications, increased exposure to lead, less home-based cognitive stimulation (McLoyd, 1998), and elevations in immune responses in adolescents with asthma (Chen et al., 2003). The goal of the National Children's Study is to investigate basic mechanisms of environmental and psychosocial determinants of health, both risk and protective, beginning in pregnancy and continuing into adulthood. A number of workshops have been held on topics related to this issue. These include workshops on the impact of stress in pregnancy, parenting, the media, racism, the rural environment, and time-use issues (reports available on the Study Web site). The National Children's Study will include study visits during pre-conception (up to 20% of the cohort), pregnancy (1st, 2nd, and 3rd trimesters), at birth, 1, 6, and 12 months, and 2, 3 5, 7, 9, 12, 16, and 20 years. Social factors related to children's health will be investigated at multiple levels of organization,

including the community, neighborhood and school level, social networks among friends and family, and individual (e.g., socioeconomic, psychosocial, and environmental) as well as genetic characteristics. The psychosocial/behavioral "exposure" domains being considered for inclusion in the Study include demographics, culture, family structure, family process, neighborhood, religion/spirituality, parental competencies, parenting practices, psychological stress, social support, parental psychopathology, public policies, child care, school, diet, smoking, alcohol consumption, and substance abuse, and physical activity. These will be related to various health and development outcomes, including social/emotional, cognitive, neurobehavioral, and physical health and developmental measures.

Poster 3

Collection and Use of Genetic Information in the National Children's Study

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Completion of the Human Genome Project brings great potential to discover the role of human genomics in disease causation and individual susceptibility; however, an immense gap currently exists between the scientific products of the Human Genome Project and our understanding of how genes interact with the environment to influence the health and development of children. The National Children's Study provides a unique opportunity to investigate the combined effect of genotype and exposure so that these data can be translated into relevant clinical and public health applications. The majority of genetic studies to date have focused on genomic variation and its relation to a particular phenotype; however, genetic information can be used not only to identify risk factors (e.g., determining DNA variation and its relation to disease susceptibility, severity, prognosis; interaction with other risk factors; response to therapeutics), but also to assess exposures (e.g., using mRNA transcripts to estimate exposure levels, and outcomes (e.g., use of molecular biomarkers or proteins to characterize outcomes).

A workshop held September 8, 2004 in Washington, DC brought together experts in the federal government (NIH, EPA, CDC, FDA) to explore opportunities and challenges for *Collection and Use of Genetic Information in the National Children's Study.* The primary objective of the workshop was to consider available methods to ensure that biologic samples are appropriately collected and stored to provide sufficient quality and quantity of genetic information to study health outcomes over time. Issues considered included types of specimens (essential, optional) to be collected from the child and family members, optimal timing of specimen collection, ensuring sufficient quantity of genetic material, and impact of technologic advances and recommendations were made.

The workshop participants concluded the following:

- Essential to collect biologic materials to study both genetic variation and gene expression
- Collection, storage, and analytic approaches need to be reconsidered as studies are developed and new technologies become available
- Planning should focus on collection of high quality biologic specimens for genetic studies and storage of sample aliquots for genomic DNA, RNA, protein; whole genome amplification; and cryopreservation
- Specimens to be collect from the child include
  - Cord blood collection (key)
  - Peripheral blood sampling in early and late childhood (key)
  - Blood spot in infancy (desirable)
- Family members to be sampled include mother, father, and, if possible, siblings enrolled in Study
- Flexibility desired to add other collections in certain situations such as acute, unpredicted exposures (e.g., natural disasters, disease outbreaks)

Poster 4

Measures of Maternal and Fetal Infection and Inflammation in the National Children's Study

Poster prepared by Cynthia Moore, MD, PhD[1] and Ken Schoendorf, MD, MPH[2] for the participants of the National Children's Study Infection and Inflammation Workshops
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Studies have shown an association between maternal and fetal infection and inflammation and a number of adverse perinatal and childhood outcomes such as cerebral palsy, autism, and preterm birth. Two workshops, *Measures of Maternal and Fetal Infection and Inflammation in the National Children's Study* on May 20–21, 2004 and *Assessment of Fetal Exposure to Infection and Inflammation for the National Children's Study* on August 22, 2005, brought together experts to explore opportunities and challenges for measuring these infectious and inflammatory risk factors. The workshop objectives were to determine optimal and feasible measurements of maternal infection and inflammation and to identify potential assessments of fetal infection and inflammation or fetal response to maternal infection and inflammation.

Discussion included information to be obtained from questionnaires, biologic samples, and medical record data, at various times during the study, up to and including birth of the infant. The workshop participants recommended a number of specific measurements to study infectious and inflammatory factors in the National Children's Study with collections before pregnancy, during pregnancy (first, second, third trimesters), and at birth.

Overall, workshop conclusions are summarized as follows:

- Important to use multiple data sources
- Imperative to make serial measurements, particularly of biologic samples, to capture timing and extent of exposure
- Pilots needed include serial maternal temperature assessment and use of filter paper collection method for cytokine and inflammatory marker assessment
- Interest in specific infectious agents and inflammatory markers will likely evolve as planning progresses, therefore, biologic samples should be collected to maximize analytic flexibility.

Poster 5

Assessment of Growth and Body Composition: Findings From a National Children's Study Workshop

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The objectives of the Growth and Body Composition Workshop were (1) to assess methods and develop rationales for measuring growth and body composition through the lifecycle; (2) to explore methods for bridging between prenatal and postnatal measurements; (3) to determine the appropriateness of various measures for the National Children's Study and where pilot data may be needed; and (4) to develop a comprehensive list of approved measurements and suggestions for optimal timing, with the understanding that the constraints of the Study protocol would guide the actual selection of when the measurements could be taken.

Measurements suggested for pregnancy included anthropometric measurements, body composition measurement by dual-energy x-ray absorptiometry (DXA) before pregnancy for the preconceptional sample and at 6 weeks postpartum for all women, measures of body water by bioelectrical impedance

analysis (BIA), and several metabolic biomarkers. Because it is now possible to measure fetal growth by ultrasound, panelists recommended 2-dimensional (2D) ultrasound for bony and organ measurements and that 3-dimensional (3D) scans be taken and saved for later analysis for organ volumes and detection of anomalies. The 2D ultrasound fetal measurements were selected to transition to the infant and toddler measurements, with anthropometry being the primary method because of its non-invasive nature.

It was strongly recommended that infants and toddlers be measured by DXA for body composition (lean and fat mass, bone mineral density, regional fat distribution) at some point in the first 3 years of life. For children and adolescents, ages 4 years and older, again anthropometry, including lengths, circumferences, and skinfold thicknesses, was recommended, with implementation as frequently as possible. However, it was universally concluded that measures of body composition by DXA are far superior in both precision and validity to anthropometric techniques, and whole-body DXA scans should be scheduled at several times during childhood and adolescence. Like 3D ultrasound, DXA scans can be saved and reevaluated as new validation studies are done and new equations for estimating body compartments are developed. Assessment of pubertal development by sexual staging, accompanied by other soft signs and biomarkers when possible, should begin as early as age 8 and continue at frequent intervals throughout adolescence.

The main conclusion from the workshop was that, aside from anthropometry, the most important measurement to obtain in the National Children's Study for assessment of body composition in infants and children is DXA.

Poster 6

Ascertaining Birth Defects: Findings From a National Children's Study Workshop

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The objectives of the workshop were: (1) to outline feasible protocols for ascertaining birth defects in a systematic and reliable manner in the Study; and (2) to identify possible pilot studies. This workshop included presentations and breakout sessions on ascertaining birth defects prenatally, and among stillbirths, infants and children, with special consideration given to heart defects.

Examinations suggested during pregnancy include: 1) 2-dimensional (2D) ultrasound at 11–14, 18–23, and 30 ± 2 weeks of gestation; 2) 3-dimensional (3D) ultrasound at 18–23 weeks; 3) an MRI if anomaly suspected; and 4) maternal blood samples pre-conception, at 11–14 weeks, and at 15–20 weeks. 3D ultrasound and MRI will require special training and procedures to ensure quality control. One pilot could be to conduct MRI in a small subgroup of pregnancies at 30 ± 2 weeks of gestation to determine the yield above that of ultrasound alone.

Examinations suggested among fetal deaths include: 1) external exam, including anthropometry; 2) internal exam; 3) imaging; 4) digital photography; and 5) chromosome analysis. The performance of these examinations will depend on the center, gestational age, and condition of the fetus. Protocols may include: 1) standard post-mortem (PM) examination; 2) PM as part of a comprehensive and standard protocol to determine conditions associated with fetal losses and child death; and 3) standard protocol for placental examinations of all pregnancies. Pilot studies may include: 1) feasibility study of PM examinations at 12–20 weeks gestation; 2) feasibility study of MRI to ascertain structural defects in cases of autopsy refusal; 3) utility of 3D photography for non-macerated fetuses; and 4) estimation of prevalence of confined placental mosaicism in normal or growth-restricted fetuses, and in fetuses with congenital anomalies.

To identify children with heart defects, examinations suggested include: 1) family and patient history at every visit; 2) fetal echo at 18–22 weeks; 3) 2D echo at birth and 14 years; 4) pulse oxymetry at 24–36 hours; and 5) ECG at 6 years. Issues that should be addressed before implementing these examinations

include: 1) determination of the accuracy of the examination at the proposed age; 2) feasibility of implementing standardized tests and interpretations; and 3) availability of procedure equipment. To ascertain other birth defects, examinations suggested during infancy and childhood include: 1) a dysmorphologic exam at 1–3 days of age and every 5–7 years; 2) a standardized medical history prenatally and at 1–3 days; and 3) standardized 2D photos of the face at 1 and 3 years. Implementation of a structured and standardized dysmorphologic exam will require development of a protocol and training of Study personnel in a centralized setting.

The workshop concluded that the suggested methods of birth defect detection should be considered to enhance the completeness of case ascertainment and the quality of obtained diagnostic information in the Study.

Poster 7

Assessment of Neurodevelopmental Outcomes in the National Children's Study

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The National Children's Study will evaluate a wide range of neurodevelopmental outcomes and alterations due to environmental exposures. Because alterations in neurobehavioral development can be expressed through a number of different structural and functional endpoints, assessments of multiple endpoints are necessary to characterize the effects of environmental agents. In addition, the role of developmental insults in the etiology of psychiatric disorders that are manifested in adolescence and young adulthood is of concern. A number of projects have been conducted in preparation for development of the protocol on measurement of neurobehavioral outcomes. These include a series of white papers on psychosocial, motor, and social-emotional development and psychiatric assessments. A paper on lessons learned from the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention addressed principles and practices of neurodevelopmental assessment (Dietrich et al., 2005). Two workshops were held: the Gene-Environment Interactions and the Regulation of Behavior Workshop, and the Neurobehavioral Development and Environmental Exposures Workshop: Measures for the National Children's Study. Reports for these efforts are available on the Study Web site. Finally, methods development studies are being conducted to evaluate analogous neurobehavioral measures in humans and animals; these animal models can then be used to further study environmental exposure-outcome links found in the National Children's Study. This poster summarizes several of these activities and provides an overview of the recommendations made by experts from a broad range of disciplines. Results of these efforts are now being used to inform development of the Study Protocol for the National Children's Study.

Poster 8

Lessons Learned for the Study of Childhood Asthma for the National Children's Study

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Asthma is one of five priority outcome areas selected for focused evaluation in the National Children's Study. The environmental causes of both incident asthma and exacerbations of asthma in children are of concern. Two efforts conducted to support the study of childhood asthma in the National Children's Study are summarized in this poster. As part of a mini-monograph, a paper titled Lessons Learned for the Study of Childhood Asthma from the Centers for Children's Environmental Health and Disease Prevention Research was recently published (Eggleston et al., 2005). Seven of the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention Research (Children's Centers) have conducted studies related to asthma in both urban and rural populations. These studies demonstrate that it is necessary and feasible to conduct repeated evaluations of environmental exposures in the home to address environmental factors relevant to asthma. Definition of asthma and assessment of disease severity is complex and requires a combination of questionnaires, pulmonary function tests, and biologic samples for markers of immune response and disease activity. Environmental exposures included demographic, social, medical, and environmental exposure data. Most studies included inspection, air and dust sampling, and biologic sampling for ETS, pesticides, and IgE sensitization that could be compared to allergen exposures. Definition of asthma in preschool-age children is particularly problematic in young children, who may exhibit asthma symptoms without developing chronic asthma. Medication confounds the assessment of asthma symptoms and classification of disease severity. Recruitment and data collection in health care settings requires dedicated study staff. A workshop on Methods for the Assessment of Asthma-Related Health Outcomes, held May 27–28, 2004, in Orlando, Florida, addressed several issues relating to data collection, recommending parental-specific questionnaires (maternal, paternal, and postpartum) and child questionnaires at multiple time points (ages) with questions sensitive enough to identify undiagnosed asthma, as well as children's symptoms and diagnoses, reduced physical activity due to respiratory symptoms, prescribed and OTC medicines, and urgent care. It was agreed that baby calendars may be a useful tool to assist memory, but subject diaries should not be considered for use in the National Children's Study. High-priority clinical outcome measures and biomarkers were identified with the appropriate ages for data collection. Identification of asthma and the environmental factors important in induction and exacerbation will require a multi-faceted repeated measures approach in the National Children's Study.

Poster 9

Integration of National Children's Study Hypotheses with Proposed Exposure Measures

Technology-Environmental Measures Group for the National Children's Study
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The Technology-Environmental Measure Group composed of federal scientists with support from National Children's Study contractors, was assembled to identify/propose sampling approaches, measurement methods, and laboratory analytical methods that could be used in the National Children's Study. The current Study hypotheses were used to identify priority agents/chemicals that are primary exposures, potential confounders, and effect modifiers; and link these to specific outcomes of interest to the Study.

The rationale and considerations used for selection of methods and approaches included:

- Select of agents based on Study hypotheses and the national scope of the National Children's Study
- Identify multi-analyte methods that provide data on additional agents
- Use combinations of environmental and biological measures to balance resource requirements
- Link measurements at different geographical scales (regional, community, household, and person-level)
- Obtain adequate measurement sensitivity
- Adopt accepted approaches from similar large-scale studies or adopt established approaches
- Consider sampling and analytical cost as well as participant burden
- Consider sample storage stability and potential for future evaluation as technology evolves
- Identify QA/QC implications
- Consider ease of use in home settings.

The group catalogued their work in an Excel workbook that identified collection methods, equipment needs, analytical methods, and cost for target compounds/agent in water, soil, air, dust, and biological media. A companion document to the Excel workbook documents the evaluation process and recommendations from the Group. The work helps the National Children's Study planning for cost forecasting, identifying types of laboratories needed, and helps identify logistical consideration for implementing the Study.

Poster 10

Quality Management Plan for the National Children's Study

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The U.S. Environmental Protection Agency (EPA) has taken the lead, in consort with NIH, in developing the Quality Management Plan (QMP) for the National Children's Study; the QMP will delineate a systematic planning process for the implementation of the Study. The QMP will state the goals and objectives of the National Children's Study, the management structure, project schedules, resources, milestones, and requirements. The QMP will identify the type of data and information the Study requires,

how and where this information will be obtained, the Study's design, boundaries, and constraints. The QMP will describe the multidisciplinary effort for the Study and identify all QA documents needed for its implementation. The QMP will identify the organizations and persons responsible for the development, implementation, oversight, and monitoring of the Study quality assurance requirements. The Quality Management Plan for the National Children's Study, which will serve as the "umbrella" quality assurance document under which individual project or institutional specific Quality Management Plans, Quality Assurance Project Plans (QAPP), and Standard Operating Procedures (SOP) will be developed and implemented. The National Children's Study QMP will address how specific quality assurance (QA) and quality control (QC) activities will be coordinated, integrated, and monitored over the course of the 21+ year study. The QMP will cite and explain all individual QA documentation that is expected to be developed over the course of the Study, the timeline for its development, who is responsible for what, who reports to whom, and what procedures will be in place to assure the successful implementation of the QAM and it subsequent component QMPs, QAPPs, and SOPs. The specific roles, authorities, and responsibilities of the various Agencies and Offices involved with the National Children's Study will be clearly delineated. This QMP will be based on EPA's Requirements for Quality Management Plans (QA/R-2), which can be found on the Web at http://www.epa.gov/quality/qs-docs/r2-final.pdf. The QMP will document the National Children's Study Management and Organization, addressing Study quality systems overall policy, scope, applicability, and management responsibilities. The Quality System Components will be discussed on how the Study will manages its quality system and define the primary responsibilities for managing and implementing each component of the system. Personnel Qualification and Training will be reviewed to document the procedures for assuring that all personnel performing work for the Study have the necessary skills to effectively accomplish their work. Procedures for Procurement of Items and Services that directly affect the quality of Study activities will be documented. Appropriate controls for quality-related Documents and Records determined to be important to the mission of the National Children's Study will be discussed. The QMP will document how the Study will ensure that Computer Hardware and Software will satisfy its requirements. The QMP will document the Planning of individual data collection activities within the Study to ensure that data or information collected are of the needed and expected quality for their desired use. And finally the QMP will describe or reference the process(es), including the roles, responsibilities, and authorities of management and staff for Assessment and Response. The QMP will Document how the National Children's Study will determine the suitability and effectiveness of the implemented quality system.

Poster 11

Identification of Existing Exposure Measurement Methods for Individual-Level Environmental Measures

Exposure to Chemical Agents Working Group; Early Origins of Adult Health Working Group; Nutrition, Growth, and Pubertal Development Working Group; National Children's Study Program Office; and the Interagency Coordinating Committee

The assessment of environmental exposures is likely to be done at multiple levels of organization in the National Children's Study. This poster summarizes several activities that focused on individual-level measures of environmental exposures. These activities were carried out or commissioned by Working Groups of the Federal Advisory Committee along with the Program Office and the Interagency Coordinating Committee.

The Exposure to Chemical Agents Working Group prepared a white paper on "Measurement and Analysis of Exposures to Environmental Pollutants and Biological Agents during the National Children's Study," much of which was published as a mini-monograph in *Environmental Health Perspectives* (August 2005). This work provides a resource for addressing environmental exposures of children, and includes examples of chemicals, chemical classes, and biological agents that may be important for exposure assessment associated with specific Study hypotheses. No single assessment approach accurately defines exposures for epidemiological studies. Potential assessment methods include: environmental, personal and biological samples, questionnaires, time-activity diaries, and ecologic classifications.

Information on environmental and personal exposure and bio-monitoring sampling and analysis is summarized for each critical life stage of a child.

The objective of a workshop on "Time-Use Data for the National Children's Study" was to identify the potential applications/uses for time use data information and the strengths and limitations of different approaches to collecting these data within the National Children's Study. The workshop considered various domains that linked time-use (time-activity) data for assessing chemical exposures and social environment (e.g., media exposure) with diet and physical activity, and with injury.

The workshop on "Measuring Physical Activity in the National Children's Study" was aimed at identifying measures of physical activity that would be feasible and adaptable over the lifespan of the Study. The workshop considered what types of instruments should be used at each life-stage, and the types of information each instrument would need to capture. Considerations for feasibility included comparability of measures across ages; differences in measurements by ethnicity, culture, and SES; and the need to anticipate technological advances.

In order to determine the current state of knowledge on dietary intake and exposures, a workshop on "Dietary Assessment in a Prospective Epidemiologic Study of Pregnant Women and Their Offspring" reviewed methodology, validity, and feasibility of various assessment methods. The workshop considered measures by age group which generally corresponded to visits in the Study Plan. Subsequently, the National Children's Study Program Office and ICC members met with dietary experts from other federal agencies to consider how to include measures or estimates of dietary exposures to chemicals based on dietary intake information and other measurements.

The reports from these workshops, white paper, and publications are available on the Study Web site (www.nationalchildrensstudy.gov), and provide valuable information for assessing individual-level measures of environmental exposures that will provide input into protocol development for the National Children's Study.

Poster 12

Identification of Existing Exposure Measures and Databases

Warren Galke, PhD, MSPH[1], John Billy, PhD[2], Rebecca Ramsing, MPH[2], Holly Carmichael, BA[2], Bradley Skarpness, PhD[3], Robert Black, MPH[3], Maureen Wooten, MS[4], Jennifer Zewatsky, MEn[4], Social Environment Working Group
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The broad definition of environment specified in the Children's Health Act of 2000 has imposed on the designers of the National Children's Study a mandate to identify measures of exposure that appropriately cover that expansive definition. This poster presents three activities that served to help identify specific measures: a white paper entitled, "Review of Extant Databases for the National Children's Study," a workshop on "Addressing Rural Children in the National Children's Study," and a white paper entitled, "Literature Search on Measurement of Housing and Neighborhood Quality Related to Child Health and Development." The purpose of the first white paper was to identify existing sources of information that could be merged with data collected in the National Children's Study allowing the Study to capture a broad spectrum of "environmental exposures" on both an individual study participant basis and representative of a community level exposure. A team of experts was called upon to identify potential sources of such information and then prepare an abstracting exercise that could be fed into a database for subsequent consideration. A Microsoft Access database was developed that contains information on the sources of the datasets, characteristics of the datasets, and descriptors that can be used to identify available information matching various exposure domains. The workshop on rural children in the National Children's Study was designed to identify key features of rural life that need to be considered by the Study designers so that rural children, which represent about 20% of the U.S. population, are appropriately considered. Key unique aspects of the rural environment were discussed including how one

"measures" rurality. The final activity presented on the poster pertains to a white paper discussing the housing and neighborhood physical environments and their potential relationship to children's health and development. This white paper described recent literature from both the medical/public health research communities and the social science research community. Key domains of the housing and neighborhood environments that should be considered for inclusion in the National Children's Study were identified. Also identified were ways of assessing those domains.

Poster 13

Development of Statistical Sampling Strategies and Optimal Design Considerations for National Children's Study Exposure Assessments

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(Conducted under contract from the National Children's Study to Battelle Memorial Institute)

For longitudinal exposure studies like the National Children's Study, one of the important considerations when planning and designing the Study is the need to introduce resource efficiency in the data collection effort while maintaining data quality. To satisfy the scientific objectives of the Study, such as collecting sufficient data to adequately assess study hypotheses, data quality is a primary concern; however, to satisfy the resource limitations of the study and maintain the feasibility of the Study, efficient data collection is necessary and may often be in opposition to the need to collect detailed (and expensive) Study subject information. This research evaluated the use of validation samples for introducing efficiency in the National Children's Study data collection effort. We measured loss of statistical efficiency by computing a design effect that is the ratio of the variance estimate for the relationship between a health outcome of interest (Y) and the true measure of exposure (X) for a validation sampling approach versus an approach measuring Y and X on the full cohort. We conclude that the use of validation sampling can play an important role in allowing the National Children's Study to collect information that will allow adequate assessment of Study hypotheses while maintaining cost efficiency and study feasibility.

Poster 14

Exposure Assessment Methods Development Pilots for the National Children's Study

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Accurate exposure classification tools are needed to link exposure with health effects. The U.S. Environmental Protection Agency (EPA) began methods development pilot studies in 2000 to address general questions about exposures and outcome measures. Selected pilot studies are highlighted in this poster.

The "Literature Review for Integrated Long-Term Sampling Methods" was conducted because single point samples do not adequately describe exposure events; hence, knowledge of exposure over time is needed. The focus of the review was on methods/instruments for exposure classification or long-term monitoring of chemicals in air, water, soil, and dust. Chemical classes included volatile organic compounds, semivolatile organic compounds, pesticides, and metals. The review provides information on matrix, method type, method performance, chemicals, detection limits, burden, and estimates of analytical costs.

A pilot study, titled “Demonstration of Low-Cost, Low-Burden, Exposure Monitoring Strategies for Use in the National Children’s Study,” was conducted to develop and demonstrate relevant exposure measurement strategies that can be used in a longitudinal epidemiological study including remote data collection by study participants. The approach included evaluation of readily available and commonly used methods, instruments, and techniques over a 12 month period. The study demonstrated that participants could effectively collect many types of environmental and biological samples but had difficulty with more complex sampling methods.

Another pilot study addressed “Methods Advancement for Milk Analysis.” The objective of this study was to develop and evaluate methods for collection, preservation, storage, and analysis of human breast milk samples. In addition, blood, saliva, and urine samples were assessed as potential surrogate media. The approach included using commonly available breast pumps and standard collection containers and preservatives. Method verification and development studies with fresh and frozen human milk samples were conducted for a variety of chemical contaminants. Chemical measures in milk were compared with urine, saliva, and serum. Preliminary analysis of study results determined the appropriate sample collection and preservation techniques. Participant recruitment was best accomplished through office managers and nurses in doctor’s offices.

A third pilot study focused on “Evaluation of Disposable Diapers for Measurement of Pesticide Metabolites and Creatinine in Urine.” The objective was to evaluate methods of using disposable diapers for collection of infant/toddler urine samples for analysis of metabolites and creatinine. A laboratory study evaluated an extraction and analysis method for measuring metabolites of organophosphate and pyrethroid pesticides. The results demonstrated that disposable diapers can be used to collect urine samples for pesticide analysis with acceptable analytical performance. Diapers could be stored for short time periods and shipped at ambient temperatures without sample degradation.

These studies provide the National Children’s Study with additional information on exposure methods that can be more accurately and efficiently used to evaluate environmental exposures of children at different ages and stages of development.

Poster 15

Information from Field Studies for Exposure Assessment in the National Children’s Study

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Poster prepared by Richard Callan, MPH, ASPH-EPA Fellow
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The National Children’s Study has commissioned a number of publications and field studies to support development of the exposure assessment portion of the Study protocol, some of which are presented on this poster. These include papers on lessons learned from the NIEHS/EPA Centers for Children’s Environmental Health and Disease Prevention Research on how to assess exposure to pesticides and air pollution (Fenske et al., 2005; Gilliland et al., 2005). Conclusions of these papers include: (1) It is likely that a combination of biomarkers, environmental measurements, and questionnaires will be needed to consider specific hypotheses involving pesticides; and (2) Due to the large size, diverse outcomes, and exposures of interest in the National Children’s Study, exposure assessment efforts on air pollutants should rely on modeling to provide estimates for the entire cohort, supported by questionnaire data and

individual measurements. Another project presented on this poster is a field study in support of the National Children's Study conducted in 2002 by researchers at the National Exposure Research Laboratory of the U.S. Environmental Protection Agency, which measured the health of a population of farm worker children in California and their exposure to pesticides. Researchers found significant levels of diazinon, chlorpyrifos, cis- and trans-permethrin in house dust, socks, and other clothing worn by children in the study. A third project, the Tampa Asthmatic Children's Study, conducted in 2002 in Florida with nine children, was aimed at developing and evaluating simple, cost-effective methods for assessing environmental exposures relevant to pre-school children with asthma. Researchers developed a lunchbox-sized near-personal exposure monitor, evaluated DNSH-coated sorbent methodology for measuring acrolein, and GPS monitors to locate participants relative to sources. The most recent project to be developed, the North Carolina Herald Study, will begin in early 2006 and will provide an opportunity to field test the National Children's Study protocol. The North Carolina Herald Cohort can serve as a platform for validation studies to estimate and, ideally, lower the subject burden for Study participants. Data from this pilot study can also be used to improve on and/or replace the methods and approaches proposed for the National Children's Study. These publications and field studies will provide an important foundation for exposure assessment and methods to be used in the National Children's Study.

Poster 16

Community Engagement and Methods for Conducting Longitudinal Birth Cohort Studies: Lessons Learned from the NIEHS/EPA Children's Centers

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Poster prepared by Richard Callan, MPH, ASPH-EPA Fellow
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Many complex issues impact children's health, including the communities in which they live. Significant community engagement will be highly important to ensure the success of the National Children's Study for many reasons, including measurement of the role of community in the health of its children, recruitment and retention, ensuring active and meaningful participation, and maintaining an ongoing, trusting relationship between National Children's Study environmental health researchers, local health care professionals, and local community partners. Important related issues include ethics, outcome and exposure assessments, specimen management systems, and communication of results. The NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention Research have had considerable experience in these areas, and two papers from a mini-monograph on "Lessons Learned" (*Environmental Health Perspectives*, October 2005) commissioned by the National Children's Study from the Children's Centers focus on some of these issues—one on community-based participatory research—CBPR (Israel et al., 2005), and the other on methodologic and logistic issues in conducting longitudinal birth cohort studies (Eskenazi et al., 2005). Highlights of these papers are presented in this poster. Lessons learned and recommendations include the following: (1) Considerable commitment and time are needed for all partners to ensure active and meaningful participation and to establish and maintain trust;
(2) Acknowledging and addressing power and equity issues is critical; (3) Hiring and training staff from the local community is essential; (4) Recognizing, respecting, and embracing different cultures of the community partners and partner organizations is imperative for successful research efforts; (5) Soliciting and answering questions is important to the informed consent process, and obtaining consent for low-literacy and immigrant populations may require additional steps; (6) Biological and environmental specimens should be carefully collected, processed, and banked in multiple aliquots. Specimen collection may need to vary from site to site to accommodate cultural concerns and logistical differences; (7) A communication plan needs to be developed with community partners, and Study results must be communicated to participants, lay, and scientific communities in a timely and sensitive manner. Drawing on the experience of the NIEHS/EPA Children's Centers with community-academic partnerships will be of

vital importance for the design of the National Children's Study protocol and implementation of the Study as it moves forward.

Poster 17

Use of Focus Groups to Identify Recruitment and Retention Issues for the National Children's Study

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The goals for this research were to explore the most effective recruitment and retention strategies for community-based child environmental health research using focus groups to gather qualitative information on the topics: getting you interested, time and data collection activities, keeping you interested, and barriers to participation.

A series of 18 focus groups were conducted in February 2003, including groups of expectant parents, parents of disabled children, parents of non-disabled children, health care providers, and community organizations. A follow up set of 14 focus groups in late 2003 explored barriers to participation among various racial and ethnic groups, teen moms, and couples attempting pregnancy. The second phase groups also discussed issues related to biologic specimen collection that needed more attention based on Phase I results.

Some common themes for getting people interested were to hear about the Study from their doctor or doctor's office and wanting information on the purpose, risks, and benefits of participating. Participants wanted to combine Study visits with regular doctor visits where ever possible and preferred to have options for methods of data collection. Some biologic samples were not acceptable, including resistance to parting with baby teeth, while in general people were willing to provide samples if the purpose was explained to them. Most participants preferred monetary incentives and wanted timely feedback on the information provided to the Study. Barriers identified included perceptions of mistrust of researchers and federal government; fears about the Study targeting minorities or conducting "secret" research as well as concerns about using biospecimens for drug testing. Barriers could be overcome or ameliorated by guarantees of confidentiality; assurances that only Study staff would see results; no release of data to insurance or law enforcement agencies; endorsement by organizations respected in the community (national and/or local); and stressing that the Study was not singling out or excluding any particular groups.

Overall, these focus group provided insights into potential participants' decision making processes. These results will help plan and design protocols for the National Children's Study to maximize participation while minimizing selection bias and loss to follow-up.

Full reports are available at: http://nationalchildrensstudy.gov/research/methods_studies

Poster 18

Developing Biomarkers for the National Children's Study

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This poster represents a snapshot of a series of projects conducted to develop novel biomarkers that can be incorporated in the National Children's Study. Particular attention was paid to maximizing the potential for human-animal extrapolation by identifying and validating common biomarkers from observational human studies and experimental animal studies. Using this approach, findings that are observed in human populations can be tested in laboratory studies and findings from animal studies can provide clues to measurements that should be made in human studies. With a strong focus on non-invasive samples, such as nails, we attempted to determine if other samples could replace the more traditional blood samples for genetic studies to improve the acceptability of specimen collection for children, infants, and pregnant women.

Projects ranged from developing a computer database to help synthesize the complex biomarkers literature (see http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=85844), to developing methods for assessing compounds in breast milk and using various biologic samples from the same individuals to evaluate variation in gene expression.

We found that whole blood and hair follicles yield sufficient quantity and quality of RNA to conduct microarray analysis, suggesting that hair samples may be used as a surrogate tissue for gene expression profiling studies. Human sperm contain a common set of RNAs reflective of spermatogenesis and male fertility, with variation in gene expression suggesting the utility of sperm RNA as a biomarker of reproductive exposures. Uroepithelial cells are of insufficient quality (and in some cases quantity) to be a useful source of RNA for gene expression profiling studies. Studies on fingernails in infants suggest that they may be useful for exposures occurring *in utero* that are otherwise difficult to measure.

Evaluating the utility of non-invasive sample matrices is important for the long-term success of the National Children's Study, especially for methods in developing fields of science such as gene expression. Understanding data needs relevant to risk assessment implementation, such as comparable animal and human biological markers, as well as their validity relevant to exposures and outcomes.

Poster 19

Measuring and Coding Exposures to Medicines and Herbal Products: Implications for the National Children's Study

Medicine and Pharmaceuticals Working Group
Poster prepared by Rebecca C. Brown, MPH, MEM
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The Medicine and Pharmaceuticals Working Group of the National Children's Study Federal Advisory Committee held two related workshops to discuss the collection of data on the use of prescription and over-the-counter (OTC) pharmaceuticals, dietary supplements, and herbals during preconception, pregnancy, breastfeeding, and childhood.

The Medicines Exposures: Collection, Coding, and Classification Workshop (December 16, 2002) was focused on providing the National Children's Study with an updated understanding of methods for assessing exposure and the current methods available for classifying and coding these products. The aim

of the Use of Herbal Products in Pregnancy, Breastfeeding, and Childhood Workshop (December 16, 2003) was to determine whether the use of these products could be incorporated into the Study. Several recommendations were made by participants at the two workshops. With regard to exposure measurement, it was agreed that herbals must be included in exposure assessment along with medications. When querying participants, it was recommended that the interviewer should be someone other than the patient's healthcare provider. A variety of tools should be used to enhance recall, e.g., visual aids, diaries. Route, dose, duration, frequency, and timing of use of these products should be collected. Product samples, manufacturer information, and ingredient lists should be collected from Study participants, when available. Biologic samples should be collected from Study participants, allowing for possible biomarker identification. Information on product use should be collected from Study subjects at regular intervals and when triggered by hospitalizations or other illness. Focus groups should examine the use of two groups of herbal products: vasoactive herbals used during pregnancy, and phytoestrogens used during pregnancy and breastfeeding. With regard to coding of medicines and herbals, several commercial systems are available for coding and should be compared to determine which are most amenable for use in the Study. Nomenclature system criteria should include: relational data; ease of inquiry; inclusion of prescribed, over-the-counter, and herbal products; clarity of codes and their specificity; ease and frequency of updating; ability to capture excipients or preservatives; and ability to capture specific data (e.g., manufacturer identification). The development of an entirely new nomenclature for medications was not recommended for the Study, but further investigation of an appropriate nomenclature system for herbals should be conducted.

Poster 20

International Childhood Cancer Cohort Consortium

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The *International Childhood Cancer Cohort Consortium (ICCCC)* workshop was held on September 28–29, 2005 in Rockville, MD, USA. The purpose of this workshop was to discuss the development of an international alliance of longitudinal studies of children to enable investigations of the role of various environmental exposures in the etiology of childhood cancer. This meeting was a result of the workshop *Cancer and the National Children's Study: Opportunities and Challenges* on May 20, 2004 in Bethesda, MD that determined that since childhood cancers are extremely rare, even large individual cohort studies such as the National Children's Study have limited power to evaluate the possible relationship of common exposures with common types of childhood cancer. A consortium formed to enable pooling of data would provide an opportunity to examine postulated risk factor associations.

Establishment of an ICCCC would also complement current efforts underway by the *International Interest Group* of the National Children's Study and the World Health Organization (WHO) to encourage other countries to implement longitudinal studies for environmental exposures to children. The proposed effort to enable investigations of hypotheses for childhood cancer etiology would enhance and parallel development of harmonized hypotheses and protocols for longitudinal studies of children internationally.

This two-day workshop brought together international researchers involved in large-scale cohort studies of the effects of the environment on children's health, as well as experts in epidemiology, pediatric oncology, and other interested parties. Information was presented incidence rates of childhood cancers, hypotheses of the etiology of childhood cancer, statistical power calculations, methodological considerations, and initiation and success stories other cancer consortia.

A Steering Committee for the consortium was established and tasked with the development of policies, procedures, and ethical requirements; hypothesis selection and protocol development; portal and

database development; and outreach to other ongoing or proposed cohorts. In addition, the consortium will publish the meeting summary in a peer-reviewed journal, and will plan for the next meeting of the consortium in 2006.

Poster 21

Long Term Cohort Studies on Children's Health and the Environment in Developing Countries

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Evidence is mounting regarding associations between the environment and children's health and children's greater susceptibility to environmental risk factors, particularly *in utero* and the first two years of life. Outcomes of environmental exposures early in life are often subtle but may have major consequences later in life, impacting on health, development, productivity, and quality of life. In developing countries, children are doubly burdened as the effects of the industrial transition are superimposed on the traditional problems of diseases linked to unsafe water and food, indoor air pollution, vector proliferation, and degraded environments.

Long Term Cohort Studies (LTCS) of environmental influences on children's health help identify and assess harmful and helpful effects of a broad range of environmental factors. LTCS demonstrated that certain pollutants, e.g., lead, mercury, polychlorinated biphenyls (PCBs), and pesticides, are especially dangerous due to their ubiquity and effects on developing nervous systems. Planned or existing LTCS in North and South America, Europe, and Asia, offer unique opportunities for collaboration. Successful implementation of such complex and costly studies in developing countries will require innovative approaches and close international cooperation. The WHO, in collaboration with the National Children's Study International Interest Group, the U.S. Centers for Disease Control and Prevention, and the U.S. Environmental Protection Agency, is piloting the development of an international collaborative network of LTCS through a that will including investigators from developed and developing countries. The activities include: 1) establishing a working group to coordinate initial planning; 2) identifying partners and donors; 3) identifying environmental components for inclusion in new/existing LTCS; and 4) developing shared core protocols.

Although LTCS in developing countries represent a challenge, they offer substantial benefits, as evidenced by success in Thailand, South Africa, Guatemala, and other countries. Establishing LTCS in other developing countries will bring collateral benefits, e.g., strengthening health care and surveillance services, transfer of technology, improving case data collection, and building and coordinating research capacity.

Poster 22

The National Children's Study Information Management System (IMS)

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Project Objective: The National Children's Study is a complex longitudinal research endeavor that plans to collect and analyze volumes of physical, chemical, biological, clinical, and psychosocial data collected in diverse locations over a twenty year span. Such an extensive study requires a comprehensive and adaptable Information Management System (IMS) that can assist in achieving its goals and objectives

throughout its life. The IMS will support the operation of the Study's protocol and the Study's administrative needs by sustaining the implementation, tracking, and management of Study activities.

Methods: The National Children's Study IMS Team initially worked to understand the Study's processes and define preliminary requirements. The Team reviewed existing documentation on the Study and research procedures, and interviewed subject matter experts. Through understanding the Study's flow and potential procedures, the Team has defined a preliminary physical architecture design. While a landmark study, the National Children's Study still retains key concepts that are fundamental in epidemiologic research, such as participant recruitment, data and specimen collection, and data management. Currently, the Team is working to validate the requirements and evaluate existing technical solutions that may satisfy the fundamental needs. This evaluation process includes analyzing the schedule, scope, and risk and piloting some of the key technical concepts. The Team recognizes that the requirements will continue to be refined with protocol decisions and development of procedure manuals. As such, an iterative approach has been established to deliver functional capabilities while continuously evaluating evolving needs. The Team continues to track progress for proof of concept and performance evaluation; ensure stakeholder representation for buy-in and understanding of goals; and facilitate decision-making within an organized process.

Results: Due to the multiple locations of the National Children's Study, the IMS will be *Accessible,* i.e., available and useable, even when connectivity to the Coordinating Center is lost. The IMS will be *Comprehensive* to support the wide range of data collected by the National Children's Study and support the multiple data collection methods, functions, and technologies. The IMS will be *Flexible* to support the longitudinal nature of the Study and to accommodate changes in requirements due to new Study hypotheses, updated protocols, and new scientific instruments and technologies. Additionally, the IMS will be extremely *Secure*. It will be *User-Friendly* and *User-Focused* so that those with access are able to accomplish their goals for the Study. Finally, although the IMS will directly collect significant amounts of data utilizing advanced techniques, it will also be *Integrated* with existing information sources to produce a robust and comprehensive database for analysis.

Conclusion: When the National Children's Study begins recruitment in July of 2007, the IMS will support the Study's initial goals, objectives, and activities. However, the development of the IMS does not cease once the Study begins. This ground-breaking study will encounter a number of technological improvements and scientific breakthroughs over its lifetime and the IMS has been designed to continuously evolve throughout the life of the Study.

Poster 23

Development of a Strategy for Preconception Recruitment: From Concept to Study Plan

Fertility and Early Pregnancy Working Group and Study Plan Team of the National Children's Study
Poster prepared by Sherry Selevan, PhD, retired
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The importance of preconception recruitment was highlighted in a number of hypotheses for the National Children's Study. A key reason is the importance of identifying exposures during the peri-conception period, due to the critical windows in development that occur during this time period. This poster outlines the process of capturing experts' findings on issues related to preconception recruitment. Their findings were turned into a general strategy, using data on birth rates and contraceptive failures (FDA, 2003). Finally, this strategy was developed in the context of overall recruitment for the Study Plan (Request for Proposals for the National Children's Study, November 16, 2004). The Study protocol will be developed from the Study Plan in the near future, with the collaboration of the Vanguard Centers, Coordinating Center, and the federal partners, and input/review by the National Children's Study Federal Advisory Committee (NCSAC).

Poster 24

Pilot Study: Feasibility of Primary Care Sites Performing Subject Observation and Data Collection for the National Children's Study

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Purpose: To determine if interested primary care practices within practice-based research networks (PBRNs) are capable of satisfactorily participating in patient assessment, data collection, and specimen collection/handling activities similar to what would be expected of them in the National Children's Study.

Setting: Fifty-four primary care practices across the U.S. that are members of a PBRN.

Methods: Between September 27 and November 30, 2004, two to five trained interviewers for each of the six participating PBRNs visited practices during routine business hours to administer and collect the following information from patient and practice staff participants:

- medical and dietary history
- physical exam and a urine specimen
- standardized developmental and health literacy assessments
- survey about the patient's experience in the pilot
- survey of involved staff about the experience and impact of the pilot.

The study recruited a total of 425 patients through 54 practices, including 137 pregnant women, 160 1-year-olds, and 128 5-year-olds. All data were evaluated for completeness and accuracy, structural and statistical significance, and to what degree and how data collection activities burdened the participating practices.

Results: Practices collected complete and accurate data on the health and dietary histories, with an average completion rate of 87% and kappa scores between .56 and .75. The practices had a 98% completion rate for all standardized assessments, although practices experienced some difficulty allocating an appropriate space for the developmental assessments in children. Practices attained an average completion rate of 99% on the physical exams, and 95% on the collection of vital signs. Practices experienced difficulty with the collection of urine samples, achieving only a 74% completion rate.

Conclusions: The results of the pilot study indicate that practices are capable of collecting data similar to the types of data that will be collected in the National Children's Study. While the results suggest that certain data collection activities are more appropriate for the primary care practice setting than others, both study participants and clinic staff viewed the study activities as appropriate and feasible in the primary care setting.

Poster 25

Reliability and Validity of Injury Reporting for the National Children's Study

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Injuries are the leading cause of death in children greater than 1 year of age in the U.S., and are a major cause of morbidity in children. The objective of this study was to estimate the ability of parents to recall the injuries of their children. Participants were from the Group Health Cooperative, a non-profit health maintenance organization in Washington State. Participants were randomly sampled from all enrolled children aged less than 6 years. Parents of approximately 2,000 children with medically attended injuries during the preceding year, and parents of approximately 1,000 children without an injury visit comprised the study population. Injury event data were collected from the computerized health information system, and the respective parent was interviewed by telephone and asked about the child's medical visits for injuries in the last year. The main outcome measure was the ratio of recalled injuries to injuries actually recorded in the computerized data.

The recall ratio decreased with time from the first visit for an injury. Recall was best for major injuries; intermediate for minor injuries treated in a hospital, emergency department, or urgent care center; and worst for minor injuries treated in a clinic. To collect 90% of major injury events by parent report would require recall intervals no greater than 6 months, while 90% of minor injury events would require recall intervals no greater than 3 months. For reporting at 90% reliability in the National Children's Study, collection of medical event data will require either capture of data directly from health care providers, or recall periods as short as 3 months or less, depending on the severity of the injury and source of care.