3. PRELIMINARY STUDIES

As part of the National Children's Study's conceptualization, the President's Task Force on Environmental Health Risks and Safety Risks sought advice concerning exposure measurement and study design from a panel of experts involved in recent or current major longitudinal studies. These included the Collaborative Perinatal Project, The Danish National Cohort Study, the Bogalusa Heart Study, The Avon Longitudinal Study, The Women's Health Initiative, The Framingham Heart Study, The Nurses Health Study, and HMO-based studies. In addition to strong endorsement and encouragement for a national longitudinal study of children's environmental health, the panel recommended the development of specific hypotheses that would frame the study and assure the most critical contemporaneous health concerns of children were not neglected. Additionally, the work group exhorted the planners to be bold and ambitious to ensure the study would be worth the considerable expenditure of time and resources (Iowa Department of Human Services, 2003).

3.1 Review of Existing Longitudinal Studies and Databases

Before the planning and initiation of a new large and expensive study proceeded, an inventory and review of longitudinal studies was commissioned by the National Center for Health Statistics and undertaken by the Lewin Group (2000). The review examined existing resources for assessing the possibility of addressing the Study goals without embarking on an entirely new study and identified needs for longitudinal research by the Centers for Disease Control and Prevention. This search sought to identify possible duplication of efforts by the proposed longitudinal cohort study. To identify virtually all of the significant longitudinal studies, two databases served as primary sources of identification: Medline and the listing of National Institutes of Health (NIH)-funded studies at the Community of Science, a network of scientists and research organizations on the Internet. Searchers used the terms "longitudinal studies," "cohort study," and "risk assessment." From more than 37,000 citations, the search identified 154 studies that met the criteria of longitudinal (studies must collect data at two points in time), longer than one year, prospective, observational (as opposed to interventional), general population (as opposed to disease specific), and meaningful sample size (generally 1,000 and greater) conducted in the United States. The Lewin inventory did not include studies that could be identified only through the behavioral, psychological, or social science literature or studies of occupational health. The studies from the initial search cover an array of health conditions in youth and adults, including, but not limited to, asthma, behavioral health, cancer, and child development.

A systematic review of all available longitudinal cohort studies found no study capable of answering the questions and concerns that led to proposed National Children's Study regarding potential long-term effects in children from environmental exposures. Although the Lewin inventory identified 62 longitudinal studies of youth and their health outcomes, only five met the criteria of a predominantly U.S. sample, sample recruitment during pregnancy or early infancy, and sufficiently large sample size (greater than 10,000). Of these five, only one, the Early Childhood Longitudinal Study (ECLS-B) Birth Cohort (National Center for Education Statistics, 2000) met the above criteria and could possibly be adapted or used as a framework for a large longitudinal cohort study of environmental factors and children's health. The goal of the ECLS-B is to assess the health, growth, and developmental factors critical for school readiness and achievement. It identified a nationally representative sample of approximately 15,000 children at birth and is performing examination batteries at 9, 18, 30, and 48 months of age. Because the ECLS-B recruited participants at birth, the issues involved in recruiting during the prepregnancy or early pregnancy period still needed to be identified. Thus, the ECLS-B excluded the possibility of observing effects of prenatal and infancy exposure and did not collect data for any chemical or biological exposures.

Ongoing population-based studies of the National Center of Health Statistics were also considered as resources to address concerns about environmental effects in children. These included the National Health and Nutrition Examination Survey (NHANES), the National Survey of Family Growth (NSFG), the National Maternal and Infant Health Survey (NMIHS), the National Health Interview Survey (NHIS), and vital statistics. Of those surveys, only NHANES met key criteria of activity that is done on a continuous or relatively frequent interval, and of the ability to collect physical measurements of the child or environment, or biomarkers, in the context of the effort. While NHANES serves extremely important surveillance and monitoring functions, it is not a cohort study and its cross-sectional design does not permit it to identify the kinds of exposure-outcome relations critical to the goals of the NCS. NHANES collects data on approximately 5,000 people per year selected to be a nationally representative sample of the U.S. population of all ages (Centers for Disease Control and Prevention, National Center for Health Statistics, 2007). In the course of this effort, mobile examination centers (MEC) and technical personnel travel around the country collecting the data. Since NHANES is representative of all ages, the numbers of children are relatively few overall, and it would take many years to gather information on the number of children required for the work proposed on the NCS. The importance and uniqueness of the proposed Study is its ability to examine exposures very early in development, including intrauterine exposures. Given its household sampling frame, NHANES would contain too few pregnant women to enable detailed analysis. Most importantly, NHANES is not designed to do multiple assessments in specific individuals over time.

3.2 NCS Planning and Methods-Development Studies

More than 2,500 scientists and other professionals had input on the NCS. Guided by the Interagency Coordinating Committee (ICC) of scientists and staff of the federal funding agencies (HHS, NICHD, NIEHS, CDC, EPA) a federally chartered advisory committee (NCSAC) was established under the Federal Advisory Committee Act. The NCSAC established 22 Working Groups, comprised of federal and non-federal scientists, that focused on specific scientific areas or aspects of the study (see Appendix J for a list of working groups). Most of the Working Groups focused primarily on defining the domain-related hypotheses (see Chapters 4 and 7 and Appendix A for details of hypotheses) and study methods that were subsequently reviewed by the NCSAC and incorporated by the ICC as the Study core hypotheses.

The Study planners used a range of approaches to address the numerous issues and questions they faced, including large conferences, workshops, scientific reviews or "white papers," and actual methods-development studies that were labeled "pilot studies." Five large assemblies were held to exchange information and science related to the Study and to provide venues for the Advisory Committee and Working Groups to conduct activities. Thirty-one extremely useful workshops with subject-matter experts have been conducted thus far to define and to clarify scientific issues and methods that could be applied to the various constructs of interest to the Study. For example, workshops on dietary assessment and on the collection and use of genetic information helped identify measurements and assays applicable to the Study and eliminate inappropriate or unfeasible measures. Along with reports from the respective Working Groups, the workshop proceedings were used for input and as a starting place for specific protocol planning. Reports from the workshops are posted on the Study's Web site: www.nationalchildrensstudy.gov.

For a number of aspects of the Study, more detailed reviews and analyses of the scientific literature were needed to inform decision making, and literature reviews or white papers were also commissioned to provide essential guidance for a number of critical issues. For example, to decide the Study's sampling strategy, a series of papers was commissioned to review topics including alternative sampling strategies; the impact of anticipated recruitment and retention rates on sampling options; the

impact of sampling options on core hypotheses; and cost estimates for sampling options. In addition, a series of methods development or pilot studies was conducted to answer specific questions or to develop specific methods. Such studies varied in methods and objectives. For example, focus groups were conducted, using a variety of sources (i.e., young mothers, adolescents, health providers), regarding attitudes and perceptions related to the NCS. One study evaluated the feasibility of three-dimensional versus two-dimensional ultrasound for measurement of fetal growth, which led to the more economical decision to use two-dimensional ultrasound. Another study, testing the feasibility of employing clinical practice sites for data collection venues in the NCS, identified a number of important issues to be addressed where this strategy is used. Thirty-five white papers and 29 pilot or methods development studies have been conducted thus far, and reports are available on the NCS' Web site. Many of these projects have applicability beyond the NCS and have been published in the scientific literature. Lists of the workshops, white papers, methods-development studies, and publications that have come out of these projects appear in Appendix J.