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The National Children's Study Of the Effect of Environment on Health

Précis

The Children's Health Act of 2000 authorized NICHD and a consortium of Federal agencies "to conduct a national longitudinal study of environmental influences on children's health and development." Children have special vulnerability to a wide array of exposures in their total environment. The study will investigate the interaction of biologic, genetic, social, and environmental factors to better understand their role(s) in disease etiology and to increase understanding of the origin of health disparities. It will be the most comprehensive study ever undertaken to examine the effects of the environment on children, both helpful and harmful. With a longitudinal study design and a life stage approach, this study will include approximately 100,000 children across the US, identified early in pregnancy and followed through birth and childhood, and into adulthood. The successful completion of a study of this magnitude will require, among other things, well-defined scientific questions, careful integration and communication with community groups and health care providers throughout the country, and a state-of-the-art data collection and management system. The planning process will emphasize strong partnerships with federal and non-federal scientists and with community, parent, advocacy, and industry groups. This study will provide a rich national resource for study and evaluation of a wide array of child health questions and form the basis of child environmental health guidance and policy over the next generation.

Executive Summary

Rationale

- Compared to adults, children have increased vulnerability to environmental exposures (e.g., lead exposure in children and maternal alcohol abuse in the fetus)
- Known environmental chemical exposures to children (pesticides, heavy metals, dioxins and PCB's) have been associated with delayed psychomotor development and poor performance on IQ tests.
- Social and physical environments are important exposures and essential to understand the environmental influences on child health and development
- Conditions with possible environmental etiology include birth defects; developmental disabilities including mental retardation, cerebral palsy, attention deficit/hyperactivity disorder (ADHD), and autism; asthma; and hypospadias and other abnormalities of sexual development
- Children's Health Act of 2000 directed NICHD to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development.

Proposal

- Aims, to:
 - determine the presence, or absence, of effects of chemical, physical and social exposures in children's environments;
 - determine cause and severity of specific conditions of children that are related to environmental exposures;
 - create a national resource for future studies of child health and development
- Hypothesis driven
- Population – Approximately 100,000; from early in pregnancy to age 21, over-sample economically disadvantaged & “at risk” populations, generalizable to US
- Measures – Genetic, chemical, biological, physical, social, community
- Follow-up – pregnancy, infancy, childhood, adolescence
- Organization
 - Multi-agency
 - Public-private partnerships
 - Federal advisory committee
 - Center-based
- Schedule
 - 2000-2003 - Methods development and pilot studies
 - 2004 Pilot -Test core protocol
 - Mid 2005 - Begin full study
- Estimated cost – \$2.3 billion over 30 years

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Short Proposal

[For more information a detailed proposal is available that describes the background and components of the study developed thus far and includes references.]

Introduction and Background

Experiences over the last several decades with effects of lead toxicity in children and maternal alcohol abuse on the fetus illustrate the concern for potential effects of environmental exposures to children. These examples of subtle but serious long-term effects to vulnerable developing systems from chronic environmental exposure are the basis of concern that compel clarification and study of various other potential and serious environmental influences. Compared to adults, children experience increased vulnerability to a number of environmental exposures of organs or systems that are more susceptible to damage and disruption during periods of rapid maturation. Children have immature mechanisms for protection or detoxification, and differences in metabolism and physiology, such as increased respiratory rate, and differences in behavior, such as hand to mouth activity, that place them at increased risk.

Environmental threats

Known environmental chemical exposures to children such as measured levels of pesticides, heavy metals like methylmercury, dioxins and PCB's have been associated with delayed psychomotor development and poor performance on IQ tests. Concerns regarding the effects of air pollution on children's health include the recent increase in asthma prevalence and associations of air pollution with poor fetal growth and with other aspects of development. Concerns regarding drinking water include known contaminants such as pesticides, phthalate plasticizers (anti-androgenic properties that may be teratogenic), and by-products of water disinfection. Widespread use of pesticides places them high on the list of environmental child health concerns, and for each of the major pesticide classes, organophosphates and pyrethroids, animal and laboratory evidence points to possible permanent effects in the developing nervous system.

Exposure to physical forces such as magnetic fields, heat, sound and other energy raise continued concerns about possible health effects. Though the frequency of Sudden Infant Death Syndrome (SIDS) in the U.S. has decreased significantly around the world by modifying the infant sleep environment, it is still the major killer for post neonatal infants in the U.S. The interaction of physical factors and other exposures with infants demands greater study. Despite the lack of studies establishing a relationship between electromagnetic fields and adverse health effects, concern about possible health problems remains pervasive in society and the lack of sufficient information leaves this wide spread concern unanswered. The leading causes of mortality beyond the first year of life

are consequences of human exposure to physical forces in a manner that result in injury. Longitudinal cohort studies are essential to understand how environmental risk factors and contextual factors can be identified and modified to reduce this toll.

The influences of social experiences and the cultural contexts of children's environment are of considerable concern for the study. Interactions with physical and chemical exposures are complex, with social exposures serving as modifiers or intermediaries in some instances and direct determinants in other instances. Thus, the study of the influences of socio-cultural disparities and other aspects of children's social environment is essential to understand the environmental influences on child health and development.

Conditions with potential environmental etiology

Various environmental exposures are suspected to influence or even cause a number of major chronic health or developmental conditions in children. Because these low-level exposures are very common, small changes in functioning for a substantial portion of the population can be very dramatic. Conditions in children with possible environmental exposure etiology include birth defects; developmental disabilities including mental retardation, cerebral palsy, attention deficit/hyperactivity disorder (ADHD), and autism; hypospadias and other abnormalities of sexual development. The cause of approximately 80 percent of developmental disorders of childhood is not known; and in the absence of knowledge about causal factors, environmental exposures should be considered prime suspects for causing such problems or interacting with other factors (e.g. physical, genetic or psychosocial factors) to cause or exacerbate these conditions.

The prevalence of many childhood conditions such as asthma, autism, ADHD and childhood cancer appears to be increasing, and this increase may be related to environmental quality. For example, although the precise pathologic mechanisms for the cause of asthma's recent increase remain poorly understood, a number of environmental exposures have been linked to the onset or acute exacerbations of asthma. Attacks may be triggered in some children by contact with certain products, such as latex, or by ingesting particular substances such as peanuts. A longitudinal study can provide an excellent opportunity to study competing theories regarding the pathogenesis of asthma.

Why a Longitudinal Study

Given the well established vulnerability to the effects of environmental exposures for the fetus, young child and even the developing adolescent and the presence of a broad array of environmental exposures that have not been studied, identifying the presence or absence of specific links between children's health effects and environmental exposures is critical for our children's health, development and ability to learn. When charged with developing strategies to protect children from environmental hazards, the President's Task Force on Environmental Health Risks and Safety Risks to Children concluded that a study to define the actual risks associated with broad environmental exposures is essential. Subsequently the Children's Health Act of 2000 directed NICHD to conduct a

national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development.

Only by combining measures of exposure with observations of outcome over an appropriate time interval through a longitudinal study can inferences about the presence or absence of a causal relationship be made. However, few longitudinal cohort studies have actually been carried out, and the only U.S. study to take a longitudinal approach to examining multiple facets of exposures and specific health outcomes in children was the NIH Collaborative Perinatal Project, which was conducted four decades ago. Recent advances in biomedical, social, behavioral sciences and information technology now enable the design of longitudinal studies that can inform us how to optimize children's potential as they make the transition to adulthood.

Preliminary Studies

To address whether existing or planned studies could answer the concerns regarding environmental exposures of children, an extensive inventory and review of longitudinal studies was commissioned by the National Center for Health Statistics. Of over 37,000 citations identified, 154 studies met screening criteria, and only five met the criteria of sufficient size, pregnancy or early infancy, and US population. Only the Early Childhood Longitudinal Study Birth Cohort (ECLS-B) could possibly be adapted to study of environmental factors and children's health, but to do so would require collecting exposure data not included and increasing the sample by at least six fold. A review of the population-based studies of the National Center of Health Statistics revealed only the NHANES with potential for the evaluation of environmental effects, but its cross sectional design, small sample of children and limited exposure measurements severely limit the ability to answer the above concerns.

A longitudinal cohort study of the size and complexity necessary to assess the relationships between environmental exposures and possible near and long-term effects will constitute a significant national resource. Such an extensive database and repository of environmental and biological measures will be used to study questions beyond the specific stated aims of the study, and constitutes a major additional contribution of the project. Therefore, it is important to collect and retain the samples and measurements in such a manner as to optimize the opportunities for future testing and analytic methods.

Some preliminary studies to support cohort planning are underway. These include projects to improve environmental exposure assessment methods for a large scale population-based study; to investigate methods for measuring endpoints and potential biomarkers of effects developed in animal models that can be applied in human populations; to evaluate methods of DNA collection and storage; to gather information on emerging technologies and human biomarkers; to evaluate strategies for subject recruitment and community involvement; to evaluate the feasibility and cost effectiveness of various sampling strategies; and to systematically evaluate the potential hypotheses for consideration in this study.

Proposed Design and Methods

The following proposal provides a framework for discussion, and future planning. Much additional input, methodology development and pilot testing will be needed, but this outline provides a basis for estimating the scope of the project, the feasibility, the sample sizes and many other aspects of the project.

Aims

Principal aims of the study are to: a) determine the presence, or absence, of long term effects, both harmful and helpful, of specific chemical, physical and social exposures in children's environments; b) to determine whether the cause and severity of specific diseases and conditions of children are related to environmental exposures; and c) to serve as a national resource for future studies of child health and development.

This study is primarily hypotheses-driven, however, no single hypothesis fulfills the primary aims of this study. To answer the question of whether exposure to environmental factors affect the health and/or development of children requires a number of well-defined hypotheses. Hypotheses that convey the scope and breadth of the proposed study include the following (more extensive hypotheses are included in the full proposal):

1. Typical or frequently encountered exposures to widely used pesticides are associated with measurable differences in neuro-developmental outcome compared to children with little or no exposure.
2. Incidence, severity, and outcome of injuries in childhood are a function of modifiable individual, family and community factors.
3. Exposure to environmentally acquired infections early in life is associated with effects on health at later stages in life.
4. Prenatal and/or early childhood exposures to potential immune-modulating factors influence asthma incidence and severity.

Study Population

The primary study cohort will consist of children followed from early in their prenatal period through childhood to adulthood. A nationally representative sample, or as close an approximation as feasible, is ideal to enable the calculation of national estimates and to address the concerns felt by all segments of the population. Whether or not this is possible, the sample should be as generalizable as possible to the U.S. population at large. A sample of approximately 100,000 participating children and their families is proposed. This would permit identification of a 20% change or difference in the rate of a condition that occurs in the general population at a frequency of 5 per 1,000 (infant mortality) or a

50% difference in the rate of a condition that occurs at a frequency of 2 per 1,000 (autism).

To insure that the most appropriate and effective sampling strategies are used for the study, a careful and systematic review and analysis of possible alternatives is being conducted to identify the major candidate strategies for the core/main sample of the study. From all plausible strategies, leading approaches will be identified and carefully evaluated. Leading candidates for the sampling strategy will then be evaluated with a field pilot study.

Some populations known to be at high risk for adverse exposure and outcome are relatively under-represented in traditional samples. Therefore over-sampling of specific populations potentially at risk for adverse exposure and outcome will be necessary, such as residents near highly industrial or polluted areas, specific occupations such as farm workers, families with minimal economic resources, and racial and ethnic minorities.

Data collection

The study will likely (pending analyses of sampling strategies) be conducted through multiple centers dispersed geographically throughout the United States. Each center will be responsible for following a common protocol regarding recruitment, exposure measurement and data collection, follow-up, and outcome measurement and data collection for the population in the respective geographic area. We anticipate that approximately 30-40 sites will be selected to participate. Follow-up data collection for exposure and outcome measurements are proposed at approximately the following intervals: Pregnancy – entry with first prenatal care, beginning of third trimester, delivery; Infant – newborn, 6 months, 1 year; Child - 2 years, 4 – 5 years 7- 8 years; Adolescent - 11-12 years, 16-17 years, 20-21 years. Yearly contact will help maintain follow-up. Some special studies may contact portions of the cohort more frequently.

As hypotheses are more clearly defined and refined, exposure assessment protocols will be developed to capture the major routes and pathways of exposure to the relevant agents. Multiple pathways of exposure will be evaluated to estimate exposure to compounds or agents of interest. Samples may be taken of environmental media such as indoor air, outdoor air, house dust and food. EPA is currently working on a variety of strategies to improve low cost, low subject burden exposure measurement techniques to use in this study. More detailed exposure assessments can be targeted towards individual households, neighborhoods and communities at higher risk as determined by screening. Exposure and outcome measures will be conducted by three general classes:

1) biological samples, 2) subject observation and measurement, and 3) environmental and contextual measures. Biological samples will be taken from participants at times and intervals appropriate to measure absorbed dose of agents of interest concentrating on the critical windows of exposure in relation to the expected risks and conditions. Care will be taken to collect, process and store the samples in proper fashion appropriate for their intended use and to maximize the potential for future analyses not currently planned.

Data will be collected also using narrative reports and objective observations of exposures, such as frequency of use of certain classes of material in the child's and family's environment, travel, both local and beyond, to areas of potential exposure to environmental agents, and other factors of interest. Routine environmental monitoring such as air pollution, water quality and satellite images will be integrated into exposure measurement where available and appropriate.

Age appropriate outcome observations and measures will assess birth defects, growth, neurodevelopmental function, respiratory and immune function, reproductive development, endocrine function, cardiovascular risks, and other measures of health and function. The study will evaluate developmental, behavioral and cognitive levels and disorders using appropriate and state-of-the-art instruments. It will obtain relevant descriptive family, community and physical environment data, such as family composition, socioeconomic resources and support, child-care arrangements and practices, characteristics of the home environment, characteristics and quality of the child's social and physical environment.

Some development and testing of measurement methods specifically for this study will be required. For example, micro-assays and biomarkers for field measurement of exposure will require further development and refinement. The most appropriate samples for present and future genomic assessments and analysis will need to be developed and tested. Subject acceptance and minimizing measurement burden will need to be examined and pilot tested. Therefore, a series of studies, focus groups (where needed) feasibility studies and pilot testing will be undertaken to derive the optimum assessment batteries at respective ages. Internet technology (Web based) will be used extensively for data collection by patients, where appropriate, and for data transfer and analysis between centers and a data management center for the overall study.

Human Subjects – Ethical Issues

The NCS raises a large number of ethical issues related to the treatment of human subjects and the collection, storage, use, and dissemination of sensitive biological data and materials. These issues are amplified given the size and scope of this study. Study planners recognize the importance of calling attention to these issues from the very beginning stages of planning. In addition, we recognize the necessity of providing mechanisms that will be able to appropriately address unforeseen ethical issues that may arise in the future. Above all, this study must minimize the risk to participants and to respect the foundations of the ethical practice of research: respect, beneficence, and justice. Because the study's subjects will be children (for most of the time) and because sensitive genetic information will be collected, heightened scrutiny and evaluation of all proposed research and protection mechanisms must be applied.

Planning and Organization

The organization and process for planning the study embrace the following principles: 1) establishment of “a consortium of representatives from appropriate Federal agencies to plan develop and implement a prospective cohort study”; 2) extensive use of public-private partnerships to insure the best possible scientific input and the widest possible support and cooperation; 3) efficient and assertive leadership to manage a large and complex project; 4) flexible structure and leadership to accommodate change as the study evolves and grows.

A committee of assigned scientists from each of the lead Federal Agencies, with oversight by the Director of NICHD, will oversee the planning and implementation of the NCS. This Interagency Coordinating Committee (ICC) is comprised of dedicated staff from HHS (OS, NICHD, CDC, NIEHS) and the EPA, and will meet as frequently as necessary to assure that the planning process proceeds successfully. The ICC is co-chaired by a senior staff member appointed by the NICHD Director and, on a rotating basis, staff members from the other lead agencies. Over 20 Work Groups comprised of both Federal staff and scientists and non-Federal scientists and representatives of key organizations will focus on specific scientific aspects of planning the study. The findings of these groups will be integrated and reviewed by a chartered advisory committee (FACA) before being finalized by the ICC. The necessary reviews, pilot studies, feasibility studies and detailed planning tasks identified by the Work Groups and the ICC will be carried out (procured as necessary and appropriate) by a Program Office of federal staff at NICHD. Unique aspects of this structure are the inclusion of both Federal and non-Federal scientists in the planning of the study and incorporation of both the scientific planners and the principal investigators of centers collecting the data in the process of analysis and reporting results.

Schedule

The following time line provides for establishing over 20 working groups engaged in the planning, for the organization and participation of many federal agencies and professional and special interest groups, and for conducting a series of pilot studies and feasibility research necessary to develop the protocol and measures of the study:

2001	Form advisory committee and workgroups.
2001-2003	Methods development and pilot studies, finalize specific hypotheses
<i>Periodically:</i>	Meetings, peer reviews, consultations.
Early 2003	Develop core study design. Select initial sites.
2004	Pilot test core protocol
Fall, 2004	Begin full study.
2005	Enroll additional sites.
<i>Periodically</i>	Analyze data as collection continues, publish early results.
~2030	Complete analyses.

Cost and Funding

The planning and pilot phases (FY02; FY03-04) are projected to require \$10 million and \$19 million per year, respectively. For the most intense recruitment and follow-up during pregnancy and infancy, costs increase to a maximum of \$151 million in 2007 decreasing to approximately \$93 million per year from 2010 to completion of follow-up in 2028. Excluding costs for analysis and reporting, estimated total costs for the study are approximately \$2.3 billion, not adjusted for inflation.

Three options have been identified for allocating new funds to this effort. The first and least feasible option is for new funds to be directed by multiple congressional appropriations subcommittees to multiple Federal agencies that will fund various components of the study. Second, a small number (two or three) of the lead agencies could receive portions of the money and coordinate to fund the study. Third, a single lead agency or Institute could receive the bolus of the funds, thereby allowing for centralized coordination and administration.