The National Children’s Study of Environmental Effects on Child Health and Development

The National Children’s Study Interagency Coordinating Committee

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Increasing recognition that children may be more susceptible than adults to environmental exposures and that they experience potentially life-long consequences of such exposures has led to widespread support for a large new cohort study in the United States. In this article, we propose a framework for a new cohort study of children, with follow-up beginning before birth and continuing to age 21 years. We also describe the administrative structure that has been built to develop the proposal further. The structure includes a partnership between federal and nonfederal scientists and relies on a collaborative, interdisciplinary research effort of unprecedented scale in medical research. We discuss briefly how the proposed cohort could be used to examine, among many other things, the effect of chemical contaminants in breast milk on children’s health and development. Key words: child, cohort studies, environment, human milk, pregnancy. Environ Health Perspect 111:642–646 (2003). doi:10.1289/ehp.5781 available via http://dx.doi.org/ [Online 21 November 2002]

Interest in ambitious new research to improve children’s health has been spurred by past successes in identifying adverse effects of environmental exposures on children, coupled with growing awareness of the mechanisms underlying children’s susceptibility and the current exposures and risks they undergo. During certain periods of development, or “critical windows,” exposure to a toxic agent can have much more severe consequences than would a similar exposure in adulthood (Selevan et al. 2000). In addition, infants have immature mechanisms for metabolism (Balisteri 2000) and excretion (Kleiman 1982) of toxicants. Newborns also have a higher surface area and respiratory minute ventilation per unit body weight; therefore, a given external exposure can result in larger intake of an agent compared with that of adults (Snodgrass 1992). Furthermore, children’s behavior can result in a higher exposure and internal dose given the same environment as that of adults (Freeman et al. 2001). Recently, the effect of early-life events on subsequent chronic disease in adults—the “fetal origins hypothesis”—has gained acceptance (Lucas et al. 1999). Advances in analytical chemistry are making it increasingly clear that children are exposed to a host of environmental agents (CDC 2001). Furthermore, characterization of the human genome could lead to medical breakthroughs given appropriate research (Collins and McKusick 2001). The increasing scientific momentum to study children’s health is reflected by the recent inception of the Danish National Birth Cohort (Olsen et al. 2001) and the Norwegian Mother and Child Cohort Study (Magnus 2001), both projected to include more than 100,000 pregnant women and their children.

Previous major studies of the consequences of early-life exposures provide some insights into the importance and potential of such projects. For example, data from the Collaborative Perinatal Project (CPP; Nelson and Ellenberg 1976), a study involving a cohort of more than 50,000 pregnant women and their children that was conducted by the U.S. National Institutes of Health and scientists at 12 universities beginning in 1959 (Broman 1984), made a major contribution to stopping the frequent but unnecessary treatment of febrile seizures and to an improved understanding of the etiology of cerebral palsy (Nelson and Ellenberg 1986) and sudden infant death syndrome (Naeye et al. 1976). Furthermore, some of the earliest data on the risk to children from exposure to lead (de la Burde and Choate 1975) and fetal exposure to alcohol (Jones et al. 1974) came from the CPP. Although the overall contribution of the CPP (reviewed in CPP 2001) is difficult to evaluate and characterize, the CPP and other such studies attest to the value of large cohort studies of children for addressing both specific and general health questions.

In this article, we describe a concept for a large new U.S. cohort study of children. Because the full study design and proposal are still under development, we present here those aspects for which there is already agreement, the anticipated scope and capabilities of the study, and a few specific potential core hypotheses. As a more detailed example of the many applications, we briefly discuss how the proposed study might support research on the potentially adverse effects of chemical contaminants in breast milk.

Development and History of the National Children’s Study

In 1997 the President’s Task Force on Environmental Health Risks and Safety Risks to Children (President’s Task Force 2000) was charged with developing strategies to reduce or eliminate adverse effects on children caused by environmental exposures. The task force recognized that to develop such strategies, a much clearer understanding of risk factors was essential. Consequently, the task force proposed a longitudinal cohort study of the effects of environmental exposure (broadly defined) on the health and development of children.

In January 2000, the Developmental Disorders Work Group of the task force

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convened an expert panel to provide advice regarding the proposal (President’s Task Force 2000). The panel considered the experiences of a number of experts from past or ongoing major longitudinal studies and discussed the feasibility of embarking on such a large national study. Overviews were presented of the CPP (Broman 1984), the Child Health and Development Studies (van den Berg et al. 1988), the Danish National Birth Cohort study (Olsen et al. 2001), the Bogalusa Heart Study (Berenson 2001), the Avon Longitudinal Study of Pregnancy and Childhood (Golding et al. 2001), and the Nurses’ Health Study (Colditz et al. 1997). Besides a strong endorsement of the proposed new study, the panel recommended that a) specific hypotheses should be developed and applied; b) families should be included along with index children; c) planning must address ethical issues of collection, storage, and distribution of information, including biologic specimens, genetic material, and environmental samples; d) collaboration among many federal agencies is essential; e) modern information technology and bioanalytic and environmental monitoring techniques should be incorporated; and f) new funds would have to be appropriated from Congress to carry out the study. The final message to the work group was to think boldly in planning for such a study.

Subsequently, the Children’s Health Act of 2000 ($1004) authorized the National Institute of Child Health and Human Development (NICHD) “to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children’s health and development.” It instructed the director of the NICHD to establish a consortium of representatives from appropriate Federal agencies (including the Centers for Disease Control and Prevention, the Environmental Protection Agency) to: 1) plan, develop, and implement a prospective cohort study from birth to adulthood to evaluate the effects of both chronic and intermittent exposures on child health and human development; and 2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes. This mandate was passed with strong bipartisan support, but without supporting appropriations.

To lead the planning and implementation of the study, staff and funds have been allocated by the NICHD, the National Institute for Environmental Health Sciences (NIEHS), and the Centers for Disease Control and Prevention (CDC), all in the Department of Health and Human Services, and by the Office of Research and Development of the U.S. Environmental Protection Agency (U.S. EPA). Investigators from each of these four lead entities serve on an Interagency Coordinating Committee (ICC) that has further developed the conceptual framework for the study, as well as an administrative structure and process for planning the study. The ICC has named the project the National Children’s Study (NCS).

The Conceptual Framework for the NCS

In addition to the outline of the study given in the Children’s Health Act (2000), the ICC has proposed that the study should evaluate low-level but relatively frequent exposures as opposed to rare or episodic events, that full advantage be taken of recent advances in genetics and measurement of gene expression, and that the study serve as a national resource that accommodates future investigations not yet conceived. Furthermore, specific high-risk populations, such as the economically disadvantaged, agricultural worker families, and others, will be included in special samples to provide sufficient power to examine selected effects in these subgroups.

As a first step in defining the scope and design of the study, priority outcomes for examination in the NCS will be selected. Criteria for selecting the priority outcomes will include the following: a) a frequency high enough that effects of exposures can be detected with reasonable statistical power, b) sufficient public health significance to merit the study (morbidity and disability, mortality, cost, or other concerns, e.g., rising incidence), and c) feasibility of reliable measurement. The preliminary list of priority topics includes undesirable outcomes of pregnancy, specifically birth defects and preterm birth; altered neurobehavioral development, developmental disabilities, and psychiatric outcomes; injury; asthma; and obesity and altered physical development.

For each priority topic, core hypotheses will be selected, and these will provide specificity in the scope and design of the study. Criteria for selecting core hypotheses include the following: a) the distribution of exposure should be such that effects, if any, can be detected with reasonable statistical power; b) the exposure can be reliably measured; c) a plausible theoretical rationale exists for the hypothesis(es); and d) a large, prospective study is necessary to test the hypothesis.

Examples of specific, potential core hypotheses for which additional data are clearly needed are as follows: a) Among women without diabetes before pregnancy, impaired glucose metabolism during pregnancy is proportional to risk of major congenital malformations of the heart, central nervous system, musculoskeletal system, and all birth defects combined (Aberg et al. 2001). b) Chronic low-level pesticide exposure early in life has adverse effects on neurodevelopment and cognition (Eskeseni et al. 1999). c) Infection during pregnancy that is not associated with fetal or neonatal meningitis or encephalitis can affect neurodevelopment and risk of psychiatric illness in offspring (Nelson and Willoughby 2002). d) Exposure to indoor and outdoor air pollution and bioaerosols (including allergens, endotoxin, and mold) is associated with increased risk of asthma (Martinez 2002). e) Impaired glucose metabolism during pregnancy increases the rate of insulin resistance in adolescent offspring (Fagot-Campagna et al. 2000; Seidman et al. 1998).

Although the NCS will be national in scope, various sampling strategies are under consideration. Ideally, results would be generally representative of the U.S. population or some large portion thereof, although statistical representation is unlikely. The use of geographically distributed study centers for recruitment, measurement, and follow-up is likely.

A total sample resulting in approximately 100,000 children, after accounting for attrition, has been proposed with follow-up to 21 years of age, although the final decision regarding study size will depend on the specific core hypotheses. Inclusion of other family members may be desirable, especially to facilitate studies of gene–environment interaction, fertility, and social environment.

For dichotomous outcomes, a study of the magnitude proposed for the NCS is best justified by hypotheses regarding conditions with a risk (by age 21) on the order of 2 per 1,000 (0.2%). Figure 1 shows the smallest detectable relative risk, according to exposure prevalence, with a power of 80% and a two-sided c of 0.05, given cohorts numbering 100,000 and 200,000 (CDC 2001b).

Cerebral palsy, type 1 diabetes, autism spectrum disorder, and schizophrenia all occur in about 0.2% of the population by age 21 years (Table 1). Hypospadias among males occurs with a frequency of about 0.4%, but in a population of males and females the effective frequency is about 0.2%. The risk of severe mental retardation is about 0.4%.

Neural tube defects (spina bifida, anencephaly) and acute lymphocytic leukemia (the most frequent childhood cancer) have risks closer to 0.05%, and only relative risks greater than 2 could be detected with reasonable power in a study of 100,000 (Figure 2). For these conditions, doubling the sample size would still not provide much statistical power unless the exposure was frequent. Of course, risk of any childhood cancer is greater, but the wisdom of grouping all cancers is debatable. Combining neural tube defects, however, is often done, but the risk would still be near 0.1%.

The question of how best to group outcomes arises also in the context of many other conditions potentially of interest (e.g., injuries). Although traumatic brain injury is a seemingly homogeneous entity, for etiologic research, grouping injuries that occurred among teenage drivers in automobile accidents
along with those that occurred among toddlers not in cars makes little sense; thus, appropriately grouped outcomes may be more rare than they appear in Table 1.

Studies of outcomes such as asthma, attention deficit–hyperactivity disorder, and childhood obesity, which are relatively frequent, do not require huge samples in prospective studies. For these important conditions, however, the NCS could offer the opportunity to study risk factors within various (e.g., genetic or ethnic) subgroups, risk factors for different levels of disease severity, or health disparities.

A follow-up of the cohort beyond 21 years of age would allow sufficient power to study many frequent chronic diseases of adulthood, such as specific cancers, heart disease, type 2 diabetes, and stroke, if subject retention remains high. Before adulthood, however, environmental influences on preclinical markers of adult diseases could be examined.

In general, continuous outcomes such as cognitive ability require smaller samples for sufficient power (Bhandari et al. 2002), although if the exposure under study is very low, large samples could still be required to detect subtle effects.

Enrollment of parents planning pregnancy is appealing for several reasons but could pose daunting logistical challenges and yield a study population not representative of the general population. Women will be enrolled as early as possible in pregnancy, and fertility and exposures preconceptionally or during critical windows very early in pregnancy may be examined either in later pregnancies among enrolled mothers or in a sample of couples recruited before pregnancy.

Final aspects of the design will depend on the core hypotheses, financial resources, utility for future investigations, and ethical considerations—including subject burden. Plans to date, however, anticipate collection of a wide range of environmental and biologic samples from the parents, the children, and their environment, as well as assessment of pregnancy outcome, birth defects, neurodevelopment, cognition, and behavior; respiratory, immune, and endocrine function; and reproductive development, body size, cardiovascular risks, and experience with infectious diseases. In addition, the social environment, home environment, schools, and access to health services will be evaluated to determine, to the extent possible, the complete environment of the children. In some instances, measurement methods will need to be developed and tested. For example, inexpensive, field-ready methods to assess environmental chemicals and biologic markers of exposure in human blood and urine will require development and refinement. The most appropriate samples for present and future genomic assessments and analysis will need to be developed and tested. Approaches to community involvement will also need to be developed. For example, subject acceptance of collecting and retaining these data will need to be examined and pilot tested. Therefore, a series of focus groups, feasibility studies, and pilot tests will be undertaken to derive the optimum assessment batteries at respective ages. Internet technology and other state-of-the- art information technology will be used for data collection where appropriate and for data transfer among the data collection centers and the data management center (Marshall and Haley 2000).

**Administrative Structure**

Figure 3 shows the present organizational chart for the NCS, for the planning phase. As noted above, a committee of scientists (the ICC) is responsible for the planning and implementation of the NCS. The ICC consists of appointed representatives from each of the lead federal organizations (NICHD, CDC, NIEHS, and U.S. EPA). As specified in the Children’s Health Act of 2000, the Director of the NICHD is accountable for the study. A program office for the NCS has been established at NICHD.

A unique aspect of this structure is the input of both federal and nonfederal scientists for planning the study via the activities of the

| Condition                  | Risk (%) | Reference                  |
|----------------------------|----------|----------------------------|
| Spina bifida               | 0.04     | Feuchtbaum et al. (1999)   |
| Anencephaly                | 0.05     | Feuchtbaum et al. (1999)   |
| Acute lymphocytic leukemia | 0.06     | National Cancer Institute  |
| Cerebral palsy             | 0.2      |                            |
| Musculoskeletal birth defects | 0.2  | Becerra et al. (1990), Hoffman and Kaplan (2002) |
| Type 1 diabetes            | 0.2      | Onkamo et al. (1999)       |
| Autism spectrum disorder (DSM/IV) | 0.3 | Yeargin-Allsopp et al. (2003) |
| Central nervous system birth defects | 0.3 | Becerra et al. (1990), Hoffman and Kaplan (2002) |
| Schizophrenia              | 0.3      | Bresnahan et al. (2000)    |
| Hypospadias (males)        | 0.4      | Paulozzi (1999), Choi et al. (2001) |
| Mental retardation (severe)| 0.4      | Roeleveld et al. (1997)    |
| Congenital heart defects   | 0.6      | Hoffman and Kaplan (2002)  |
| Asthma                     | 0.6      | Mannino et al. (2002)      |
| Traumatic brain injury     | 10<sup>a</sup> | Guerrero et al. (2000)     |
| Attention deficit–hyperactivity disorder | 10 | Rowland et al. (2002) |

<sup>a</sup>Frequency based on the ratio of cases in relation to those of congenital heart defects, and data on the frequency of congenital heart defects. <sup>b</sup>Proportion exposed to age 14 years; based on the average of three U.S. studies reported in Onkamo et al. (1999).

<sup>c</sup>Prevalence in past 12 months among children 5–14 years old. <sup>d</sup>Prevalence at age 14 years.
metabolite DDE (dichlorodiphenyl dichloroethylene), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and tetrachlorodibenzo-p-dioxin (TCDD) (Hooper and McDonald 2000; Rogan 1996). Because breast milk is 3.7% fat by weight, lipophilic xenobiotics partition into it. Thus, breastfeeding results in a greater maternal–child transfer of persistent organic pollutants than occurs in utero. Whether early-life exposure to any of these persistent organic pollutants has adverse effects within the range of current background exposure is unclear (Table 2). The evidence regarding potential adverse effects cited in Table 2 refers mostly to studies in populations with slightly higher exposure levels than now found in the United States. For some pollutants that are present at extremely low levels but are also potent, assessing exposure in breast milk is advantageous because levels can be detected in smaller volumes than is possible using other types of specimens such as blood.

Although levels of most persistent organic pollutants in humans are decreasing (Schade 2001, 2002), those of PBDEs are increasing (Hooper and McDonald 2000), and new data on current levels are available in populations with slightly higher exposure than is possible using other types of specimens such as blood.

Conclusion
Our nation is in the unique position of being able to give children’s environmental health the priority it deserves. A long-range, large-scale child cohort is needed to take full advantage of scientific and technologic advances and to enable greater prevention of humankind’s current and future plights (National Science and Technology Council 1997). The effort to launch a large new cohort study of U.S. children has considerable momentum. To keep

Table 2. Selected pollutants and other toxic chemicals in breast milk, and corresponding potential adverse effects in offspring.

| Agent       | Potential adverse effect                                                                 |
|-------------|------------------------------------------------------------------------------------------|
| DDE         | Decreased stature (Karmaus et al. 2001, 2002)                                            |
| PCBs        | Altered thyroid economy (Osiew et al. 1999), Adverse effect on neurodevelopment (Walkowiak et al. 2001) |
| PBDEs       | Altered thyroid economy (Zhou et al. 2001)                                               |
| TCDD        | Hydropneumothorax (Couture Hawkes et al. 1991)                                            |
| Mercury     | Hypertension (Sorensen et al. 1999)                                                      |
| Alcohol     | Adverse effects on motor development (Little et al. 1989)                                |
| Nicotine    | Increased risk of sudden infant death syndrome (Klunoff-Cohen et al. 1996)                |
this ambitious project moving forward, further development of a compelling rationale, of the protocol, and of additional pilot data is critical. Whether the proposed NCS will be funded will depend on developments over the next few years.

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