

The Longitudinal Cohort Study (LCS)

Status Report, July 10, 2000



The President's Task Force
on Environmental Health Risks
and Safety Risks to Children

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EXECUTIVE SUMMARY

Longitudinal Cohort Study (LCS)

Compared to adults, children are at increased risk from environmental influences because of vulnerable developing systems and enhanced exposure. Observed effects from low level contaminants, such as lead, or from other influences, such as poverty, raise concerns about a number of environmental factors and their effects on the health and well-being of children. New methods and technologies permit the measurement of low level and chronic exposures and influences, and recent advances in genomics permit the study of possible gene-environment interactions.

Task Force: The Developmental Disabilities Work Group of the President's Task Force on Environmental Health Risks and Safety Risks to Children recommended a longitudinal cohort study (LCS) of environmental impacts on children. The proposed study would be of sufficient size and design to identify subtle, but important, effects of low level environmental exposures, as well as other biological, social and cultural factors that may impact children's health. In addition, the study would become a valuable resource for future investigations.

Consultation (January, 2000): A consultation of experts with experience in major current and past longitudinal studies endorsed the concept of the LCS and recommended development of specific hypotheses, a diversified study population, inclusion of families and communities, use of latest bio-analytic, environmental monitoring and information technology, collaboration among all appropriate federal agencies, the importance of public-private partnerships, strong central coordination, careful consideration of ethical issues and sufficient allocation of new funds.

Hypotheses: General hypotheses addressed by this study: 1) Low or "typical" levels of environmental exposures are associated with health risks or adverse development, 2) Environmental exposure preconceptionally, prenatally and after birth influence subsequent health and development even into adulthood, and 3) environmental exposures may affect host characteristics and genetic expression. Specific hypotheses will be developed further with careful study and in partnership with stakeholders.

Organization: Oversight and resource allocation rests with the Federal Oversight Committee, made up of the heads of lead agencies and other appropriate members. The Coordinating Committee organizes and directs operations while the planning groups consist of other Federal agencies and non-federal partners. Specific work groups, derived from planning and advisory group(s), will address specific issues as needed for the various components of the study. Input and review will be obtained throughout the process from Federal and non-federal organizations (e.g., state and local organizations, professional and community groups, and academia).

Plan/time line: Major milestones: Preliminary studies begin: Immediately.
Additional consultations, start workgroup meetings: FY01
Pilot studies: FY02-FY03
Full study begins: FY04-FY05

BACKGROUND

Why do we need a longitudinal study?

- Children's health is related to their environment. This study can identify factors important for improving children's health and well being.
- Prospective data collection gives more accurate exposure data at critical stages of development to link with health effects occurring later in life.
- Multiple health endpoints and multiple exposures can be studied. This is more relevant to future prevention efforts because results will reflect real-world conditions.
- Many health endpoints cannot be studied by taking a snapshot at one point in time. They require ongoing, repeated opportunities for observation and measurement. The scope of this research is not possible in more traditional research settings.
- Changes in exposures over time can be tracked and risk assessed for intermittent, cumulative and chronic exposures.
- The study becomes a national science resource, allowing for the testing of new hypotheses with already collected data as the science progresses.

What kind of study is being proposed?

- A longitudinal cohort study of the environmental health risks to American children (at least 100,000 children) in a multi-center study.
- Recruitment will begin as early in pregnancy as possible.
- Data will be gathered on environment and outcomes until adulthood.

Why do the study now?

- There is increased concern that even low level exposure to common environmental agents may have important long-term effects on development.
- Science and technological advances have brought new opportunities and insights including dramatic increases in understanding of genetics and its influence on human development.
- We now have a better understanding of where and when to look for the environmental exposures associated with adverse health and development.
- We understand more about the range of conditions with a genetic basis. Many of these are the product of, and can be modified by, complex interactions with the environment.

SCIENTIFIC AND PUBLIC HEALTH BENEFITS

- Aid in identifying important factors to improve children's health and well-being
- Prospective collection of data yields more accurate exposure measures and determination of ages most sensitive to those exposures
- Archived biological and environmental samples available for measurements as new technologies arise
- Will allow investigation of genetic factors (maternal, paternal, and children's) and health status
- Influence on public health decisions in the areas of prevention, intervention, and treatment
- Provide a valuable resource for addressing future questions

Feasibility of a Longitudinal Cohort Study of Environmental Impacts on Children and Families

Summary

Consultation: January 12, 2000

Recommendations:

- Study issues:
 - Include children and families
 - Consider ethical issues from day 1
 - Evaluate behavioral, social and cultural aspects
- Hypotheses:
 - Address questions requiring a large study
 - Should be of public health importance
- Development of study design:
 - Consider representativeness / diversity
 - Include long-term follow-up
 - Management by a strong, small, central coordinating group
 - Incorporate emerging technologies
 - Plan for archiving / long-term maintenance of data & samples
- Partnership issues:
 - Cooperation among Federal agencies crucial
 - Involve both community and professional groups
 - Consider ownership and use of data
 - Explore public-private partnerships
- **New money needed - should not be taken from current research funds**
- **Overall, strong support for the idea**
- ***THINK BOLDLY!!***

CURRENT STATUS

SUMMARY OF PRELIMINARY PROJECTS AND FUNDING Coordinating Committee Members (NCEH/CDC, EPA, NICHD/NIH)

Exposure: Sample Collection, Analysis and Archiving

Developing laboratory capability in ultramicroanalytic techniques (CDC)
Budget: \$70 K per year (proposed)

Exposure-Related Research for the LCS (EPA)
Budget: FY00 \$610 K, FY01 \$350 K (proposed: FY02 \$300 K)

Defining timing of first trimester biological monitoring for environmental chemicals that may negatively impact birth outcome (CDC) Budget: \$300 K per year (proposed)

Participant Recruitment and Retention, Community Involvement

Development of approaches for participant enrollment and follow-up (CDC)
Budget: \$400 K per year (proposed)

Testing Methods of Recruitment, Retention of Participants and Community Involvement (EPA)
Budget: FY00 \$40 K, FY01 \$110 K (proposed: FY02 \$110 K)

Accessing previously recorded community-based information (medical, education, social service records) (CDC) Budget: \$300 K per year (proposed)

Methods Development (Outcome Measures, New Technologies +)

Identification of Emerging and Innovative Technologies for Use in the LCS. (EPA)
Phase I: Evaluation of the state of the science. Budget: FY00 \$55 K

Reliable and Stable Measurement of Learning Disabilities. (NICHD) Budget: \$163 K/year

Development of Measures of Gene Expression (NICHD)
Budgets: Diabetes FY00-FY01 \$717 K/year; Obesity FY00-FY03 \$700 K/year

More details are found in Appendix (pages 13-16)

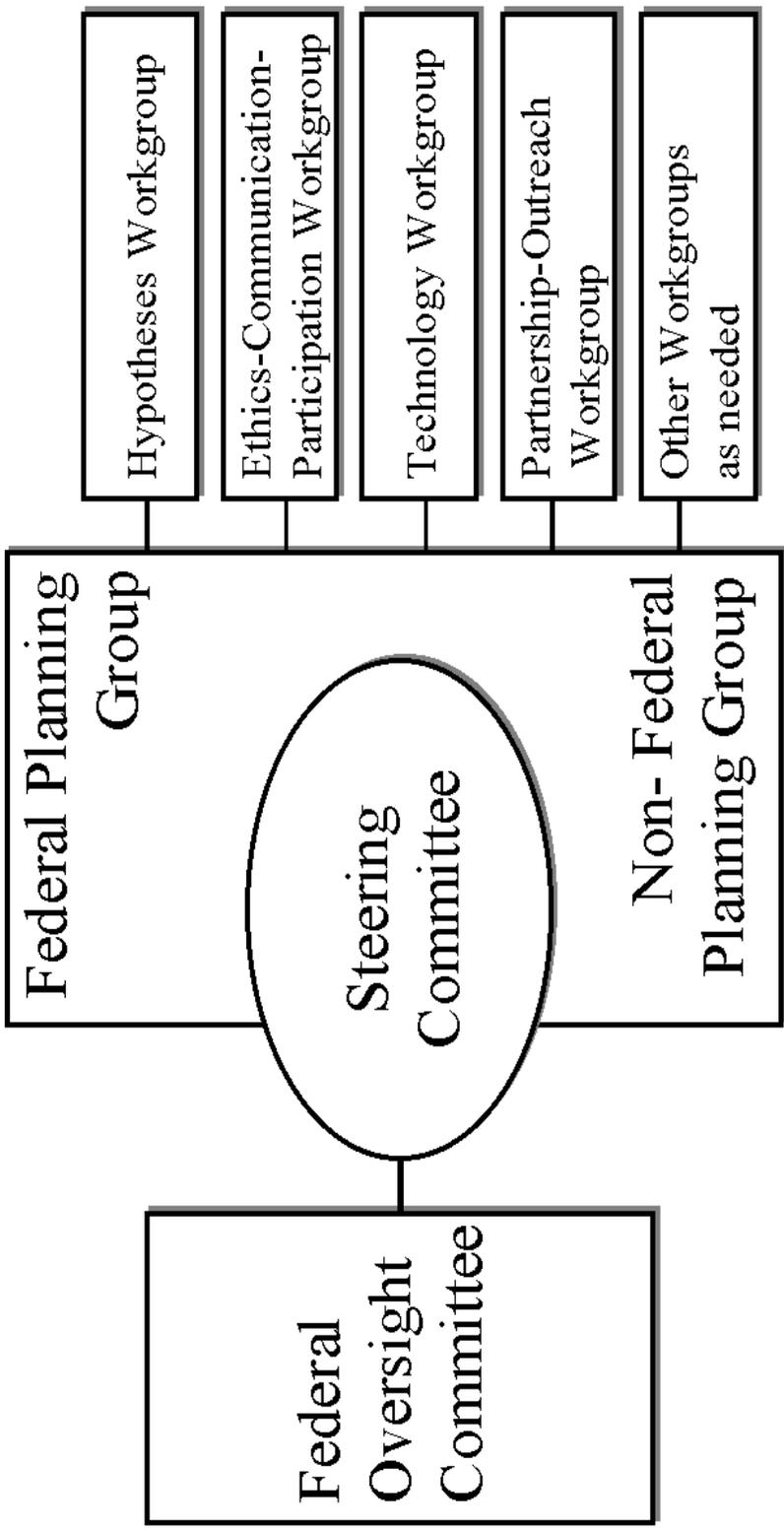
TOTALS:

<i>Organization</i>	<i>FY00</i>	<i>FY01</i>	<i>FY02</i>
NCEH/CDC		\$1M 1FTE	\$1M 2 FTEs *
EPA	\$1.02 M	\$1 M	\$1 M *
NICHD	\$1.58M** 1 FTE	\$1.58M** 1 FTE	\$700K** 1 FTE

*proposed

**relevant ongoing projects

Longitudinal Cohort Study (LCS) Organizational Structure for Planning Phase



Structure for Planning Activities for The Longitudinal Cohort Study (LCS)

- **The Federal Oversight Group** provides overall policy and direction for the Longitudinal Cohort Study. Responsibilities include consultation to all LCS components: the Coordinating Committee, Federal Planning Group and the Workgroups, and interact with government and non-government organizations (NGOs) to secure funding. The Federal Oversight Committee will include the Co-Chairs of the Senior Staff Planning Committee, the Secretariat to the Task Force and the Co-Chairs of the Task Force committees and workgroups. This group will meet at least once a year.
- **The Coordinating Committee** is responsible for coordination, implementation and operations, with administrative support. The Coordinating Committee will be composed of members from each of the designated lead agencies for the planning process (NIH/NICHD, CDC/NCEH, EPA/ORD). Additional members will be added based on specific expertise as identified by the Coordinating Committee and approved by the co-chairs of Developmental Disorders Workgroup. For effective operation, the Coordinating Committee shall remain small; it is not anticipated to exceed 12 members at any one time. Coordinating Committee meetings will be held in person or via conference calls at least twice per month. The Coordinating Committee will propose priorities, construct a time line, and establish Workgroups (consultations) that will provide guidance for the various activities of the planning effort. The Coordinating Committee is part of the Federal Planning Group and will work closely with the Secretariat to the Task Force.
- **The Federal Planning Group (FPG)** is composed of key scientific representatives from Federal agencies with programmatic and scientific interest in the LCS. It will provide scientific and programmatic input and advice for the various tasks that are part of the planning effort. Through this group the interested agencies will have opportunity for participation and substantial input into the design and implementation of the Study. Each of the relevant and interested agencies will be invited to designate a representative and alternate for the Federal Planning Group. The FPG will meet at least once per year.
- **Non-Federal Planning Group (NPG)** is composed of representatives from non-federal organizations with special interests related to the LCS (such as the March of Dimes and the American Academy of Pediatrics) and of invited scientists with expertise relevant to the LCS. Parallel to the FPG, the NPG will have opportunity for participation and substantial input into the design and implementation of the Study and will interact with the Federal Planning Group in establishing and staffing the various work groups. Like the FPG, the NPG will meet at least once a year and, over time, may integrate or even merge with the FPG.
- **The Workgroups** will be housed in the Federal Planning Group, but will consist of federal and non-federal experts. Workgroups will conduct consultations and other efforts to develop recommendations for the conduct of the various aspects of the study. At least one

co-chair of each workgroup will be a member of the Federal Planning Group. The initial Workgroups are:

Study Design Workgroup: This workgroup will develop the study design and implementation. Its first activity will be to evaluate potential hypotheses for inclusion in the study.

Ethics-Participation Workgroup: This workgroup will begin by identifying ethical issues related to recruitment and long-term participation, confidentiality and data access. In initial stages, these topics will be combined since they are focused on the study participants and their communities. As efforts continue, it may be more appropriate to create separate workgroups on these issues.

Technology Workgroup: This workgroup will assess the potential use of new and emerging technologies in the collection, analysis, and archiving of data and samples (biological or environmental).

Partnership-Outreach-Communication Workgroup: This workgroup will focus on building partnerships and communicating with participants and the scientific, public health, and other interested communities.

Other Workgroups will be formed as needed. The Workgroups will meet as often as is necessary to completed the designated tasks. These groups will be assembled around specific tasks and will disband when the work is completed.

As the project develops, external groups will be formed to advise and review the work described.

TIME LINE for the Longitudinal Cohort Study (LCS)

Date	Activity
Spring, 1998	Idea of an interagency LCS first discussed
Spring, 1999	LCS proposed to Task Force; Task Force approved exploratory activities
January 12, 2000	Consultation: Ascertaining the Feasibility of Conducting a Longitudinal Cohort Study of Environmental Effects on Parents and Children
January 13, 2000	Meeting of interagency Longitudinal Cohort Study Planning Group to discuss next steps
Spring, 2000	Began implementation of “next steps” through activities to identify potential hypotheses, developed an organizational structure, and formed a Coordinating Committee which meets regularly. Identified activities within each agency pertinent to the development of the LCS.

PROPOSED

Summer-Fall, 2000	Start preliminary studies
November, 2000	Convene Federal Planning Group to discuss study hypotheses/design, ethical issues related to the study, recruitment and retention of participants, community involvement, and use of emerging technologies.
Early 2001	Convene meeting of “at large” researchers and public health specialists to discuss the same issues discussed in November, 2000, using the summary of that meeting as a starting point.
Periodically:	Have public meetings, peer reviews, special consultations as topics of special interest arise.
Early 2001	Create workgroups to address areas of importance identified at the two meetings. Meetings will continue as needed.
Spring, 2001	Finalize specific hypotheses, initiate work on details of study design, continue pilot studies.
Fall, 2001	Define structure for study.
Early 2002	Develop RFP for identifying collaborating organizations.

Early 2003	Select initial sites. Award contracts. Start collaborative effort to generate core study design.
Fall, 2003	Finalize core study design, prepare for pilot testing of protocol.
Fall, 2004	Begin full study. Enroll families over approximately a 3 year period. Examine participants at predetermined ages.
2005	RFP to identify additional sites. Award contracts.
Periodically	Hold meetings/reviews of collaborating centers, to assure uniformity of protocols, QA/QC concerns. Analyze data as collection continues, publish early results.
2027-8	Continue follow-up until children are approximately 21 years of age.
2030	Complete analyses.

CRITICAL NEEDS

- Coordinating Infrastructure
Support - infrastructure (space, assistants, budget, MOU)
Identify an administrative home
- Set up appropriate financial mechanism(s): *IAG, contracts*
- New funds for long term commitment

<u><i>Activities</i></u>	<u><i>Year</i></u>	<u><i>Resources</i></u>
Initial sites (pilots)	FY03-FY04	\$10 M/year
Core Study	FY05+	~\$50 M/year (on average)
Special studies		To be determined

APPENDIX

The following is a list of some of the efforts underway or currently in planning to support the development of the longitudinal cohort study by the three lead organizations (CDC, EPA, NICHD). These projects range from development of methods for assessing exposure to new techniques for assessing health status, and approaches for involving the communities in the efforts.

Exposure: Sample Collection, Analysis and Archiving

Developing laboratory capability in ultramicroanalytic techniques (CDC)

The LCS will establish an extensive bank of biologic samples (e.g., blood, urine, amniotic fluid, saliva, hair) collected from study participants during pregnancy and childhood. These stored samples may be used to measure the exposure of individuals to a variety of environmental, biologic, and pharmacologic substances, as well as evaluate individual genetic factors and physiologic functioning. This pilot study will establish laboratories and laboratory expertise needed to successfully conduct a unique microanalytic technique (developed by Phillips et al.) which could then be applied on a larger scale as part of the LCS. This technique will expand the longevity and value of the LCS biobank, permitting the measurement of dozens of analytes on very small quantities of sampled tissue. The ability to measure multiple analytes on a single sample will also enhance our understanding of the interaction of multiple markers in the disease process.

Budget: \$70 K per year (proposed)

Exposure-Related Research for the Longitudinal Cohort Study (EPA)

This research will develop low cost, reliable exposure measurement methods that will have optimal predictive power in three interrelated tasks:

Task 1: Use existing data to determine the best measures of personal exposure using regression models to evaluate the respective predictive power different approaches (i.e., questionnaires, environmental and personal samples).

Task 2: Economize methodologies for obtaining the various exposure measures, taking into account level of participant involvement and reliability of measurements.

Task 3: Review and develop time-integrated and other measurements needed to improve measurements and classification of exposure during vulnerable developmental periods.

Budget: FY00 \$610K, FY01 \$350K (FY02 \$300K proposed).

Defining the timing of first trimester biological monitoring for environmental chemicals that may negatively impact birth outcome (CDC)

Many metabolites are detectable for limited periods of time post-exposure, laboratory analysis is expensive, and there are no validated questionnaire responses that predict exposure. A series of pilot projects would perform intensive sampling and laboratory analysis to determine the frequency of sample collection necessary during pregnancy to accurately describe exposure to environmental chemical contaminants that may impact a fetus and develop an validate

questionnaire data that correlate with quantified chemical exposures during pregnancy. Three pilot studies will be done in two locations (Imperial Valley, CA, Atlanta, GA) to provide critical information regarding the problem of when to collect biological samples during a cohort study of pregnant women. Each pilot will collect different information, but the studies will build on each other in order to achieve the goal of contributing to a cohort design that will accurately, efficiently and economically define exposures to environmental contaminants during pregnancy.

Budget: \$300 K per year (proposed)

Participant Recruitment and Retention, Community Involvement

Development of approaches for participant enrollment and follow-up for the LCS (CDC)

The scientific validity of the LCS depends on enrolling a representative sample of the target population for the cohort and thereafter retaining enrolled participants for the duration of the study in order to obtain complete data. There are numerous social/communication obstacles to obtaining these goals. The ability to successfully conduct the LCS is dependent upon designing an effective approach for subject enrollment and retention that will overcome these obstacles. The pilot study would fund two sites (through RFAs) to design, pilot test and evaluate techniques for participant enrollment and retention. A number of incentives (cash, free medical care, etc.) could be explored in the pilot study.

Budget : \$400 K per year (proposed)

Testing Methods of Recruitment, Retention of Participants and Community Involvement (EPA)

The recruitment and retention of participants are critical for any human study. For a longitudinal study, it is critical to keep them interested and involved in the study. Support from community and professional stakeholders is of great importance to the acceptance and success of the study, generating a sense of community pride in participation.

Problem: In the 30 years since the last comparable study, concerns over privacy have substantially increased and most population-based research studies have had to expend increasing efforts to encourage participation in health studies. Participation may be enhanced with relevance of the study to participants, altruism, and incentives.

Approach: In cooperation with our interagency partners, this project will begin to identify the community and professional stakeholders important to the success of the study, and evaluate various methods to keep the community involved over the course of a long term study.

Budget: FY00 \$40K, FY01 \$110K (FY02 \$110K proposed)

Accessing previously recorded community-based information (medical, education, social service records) to support the LCS (CDC)

Issues of privacy loom large today. The LCS will depend upon the ability of practitioners as well as lay persons to agree that accessing information previously deemed confidential is necessary to accurately describe exposures and life events for the parents and children of the cohort. A pilot study in three communities is being proposed to establish

mechanisms for the retrieval of medical, educational and other data that would be part of a larger population-based study of birth defects or developmental disabilities of childhood. In addition to determining mechanisms for accessing data, types of data to be collected, storage of data and protocols for sharing data among multiple sites could be explored.

Budget: \$300K per year (proposed)

Method Development (+Other)

Reliable and Stable Measurement of Learning Disabilities for Longitudinal Study (NICHD)

Subtle and small scale effects on neurological and cognitive development are of great concern regarding possible consequences of environmental exposure. Learning deficits may not be apparent until school age. They are often difficult to measure and change with developmental progression. To advance the identification, measurement, and understanding of dyslexia and other learning disabilities, a network of research centers is supported to identify how children learn to read and why some children do not learn to read. For example, to enhance the detection and measurement of learning problems, a sample of 379 children, comprised of normal and various learning disabilities, including dyslexia and attention deficit, will be followed and studied from age 7 through age 14. This work will redefine and refine classification of learning disabilities for accurate identification, apply new measurement methodology for detecting and quantifying learning disabilities, and improve the stability of measurements of learning disabilities over the longitudinal trajectory their evolution. This study should substantially improve the sensitivity for the Longitudinal Cohort Study to detect possible environmental influences on learning ability and disorders as the cohort moves through school age. (Relevant ongoing project)

Budget: FY00-FY01 \$163K/yr

Development of Measures of Gene Expression (NICHD)

Environmental factors are known to play a role in a number of diseases thought or known to be genetically based, such as Type I diabetes mellitus. The incidence for this condition has increased about 3% a year for the past 40 years, largely in children under 5 years of age, strongly suggesting the influence of environmental factors. This suspected environmental-genetic interaction is a model of the importance of studying the influence of environmental exposure on genetic expression and disease susceptibility in the Longitudinal Cohort Study. Studies are underway and proposed to develop improved methodology to assess genetic expression using microarray techniques and proteomic methodology that would be important and applicable in the LCS. In infants with genetic predisposition to Type 1 Diabetes Mellitus the interaction of genetic, immunological and exogenous factors are being assessed using state-of-the-art microarray technology. This longitudinal cohort study of Diabetes will identify the earliest manifestations of factors affecting genetic expression of Diabetes, similar to design of the LCS. Similar work is also underway defining the genetic Epidemiology of obesity in childhood and factors that affect expression of children genetically predisposed obesity in a longitudinal cohort sample. Conversely, application of assessments of genetic expression in the LCS will serve to enhance understanding of the processes influencing genetic expression by providing substantial samples for study, quantitative rather than descriptive measures of phenotypic expression and extensive measures of environmental exposures. (Relevant ongoing project)

Budget: Diabetes FY00 and FY01: \$717K/year
Obesity FY00 through FY03: \$700K/year

Identification of Emerging and Innovative Technologies for Use in the Longitudinal Cohort Study. Phase I: Evaluation of the state of the science. (EPA)

A longitudinal study of 100,000 children presents challenges for data collection and management. Current and future technological innovations may make data collection and management more efficient, accurate, and consequently, more cost effective. Innovative technologies could enhance this effort in at least three areas:

1. Measurement and analysis of health/medical characteristics.
2. Collection of questionnaire data using innovative technology (e.g. internet, electronic devices) to reduce the respondent burden, while increasing the quality of the data.
3. Measurement and analysis of exposure using novel approaches.

Approach: This project would gather information from the scientific literature, technology journals, and other venues (e.g., trade shows) with information on existing and cutting-edge technologies, and technologies currently in development.

Future activities: A consultation with experts to identify and prioritize those items with immediate utility for the study, and those which require additional development.

Budget: FY00 \$55K

Other Projects:

EPA also has several smaller projects to develop/assess methods for measuring behavioral/neurodevelopmental endpoints, development and evaluation of biomarkers, and testing of methods for archiving specimens. (FY2000: \$175K)

A SAFE AND HEALTHY ENVIRONMENT FOR CHILDREN

A National Longitudinal Cohort Study of Environmental Impacts on Children and Families

June 2000



The President's Task Force on Environmental Health Risks and Safety Risks to Children

EXECUTIVE SUMMARY

Executive Order 13045 (April 21, 1997) directs Federal agencies to make it a high priority to identify, assess, and address children's environmental health and safety risks, and created **the Task Force on Environmental Health Risks and Safety Risks to Children**. Co-chaired by the Secretary, HHS, and Administrator, EPA, the Task Force was charged to recommend strategies to protecting children's environmental health and safety, and chose four priorities: (1) asthma; (2) unintentional injuries; (3) cancer; and (4) developmental disorders. The Developmental Disorders (DD) Workgroup recognized that a large, prospective cohort study of children could offer a comprehensive approach to understanding how the environment, family, and society interact with the genetic constitution of the developing fetus and child. Large longitudinal studies of U.S. children were conducted 40-50 years ago, but the feasibility of conducting a modern-day longitudinal cohort study of children was in question.

On **January 12, 2000**, the Planning Committee of the DD Workgroup convened an expert panel to present state-of-the-art exposure assessment techniques and alternative study structures and methods to about 90 invited participants from government, academia, and private sector. Presentations highlighted issues to be considered in deciding the feasibility of such a study.

General conclusions of participants' discussion were:

- General support and extremely positive encouragement for conducting a large cohort study.
- Realization that children cannot be studied apart from their parents and their families and that studies should be sensitive to behavioral, social, and cultural aspects of the children and families.
- Need to develop specific hypotheses using a longitudinal cohort approach.
- Critical need for broad-based support within the communities proposed to be studied.
- Need to address from the beginning ethical issues regarding collection, storage, and eventual distribution of information, biologic specimens, genetic material, and environmental samples.
- Observation that the study should take advantage of the latest in information technology.
- Need for resolution of issues of internal versus external validity, particularly regarding follow-up.
- Need for diversity of the study population; need for a "representative" sample was not resolved.
- Modern bio-analytic and environmental monitoring techniques should be planned into the study.
- Need for interaction/collaboration among all the Federal agencies.
- Need for new money to conduct the study.
- Need for a strong, central, small directing group dedicated solely to designing/conducting the study.

On January 13, the Planning Committee developed the following recommendations to the Task Force:

- (1) The Task Force should plan a national longitudinal cohort study of children's environmental health.
- (2) New money for this study is imperative.
- (3) Full-time personnel are required to organize/oversee movement into the pre-pilot study planning phase.

THE PRESIDENT'S TASK FORCE ON ENVIRONMENTAL HEALTH RISKS AND SAFETY RISKS TO CHILDREN

President William Jefferson Clinton issued Executive Order 13045 on April 21, 1997, directing each Federal Agency to make it a high priority to identify, assess, and address children's environmental health and safety risks. In issuing this order, the President also created the Task Force on Environmental Health Risks and Safety Risks to Children, co-chaired by Donna E. Shalala, Secretary of the U.S. Department of Health and Human Services, and Carol M. Browner, Administrator of the U.S. Environmental Protection Agency. The Task Force was charged with recommending strategies for protecting children's environmental health and safety.

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THE LONGITUDINAL COHORT PLANNING GROUP

The Longitudinal Cohort Planning Group was organized under the auspices of the Developmental Disorders Workgroup of the President's Task Force on Environmental Health Risks and Safety Risks to Children.

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INTRODUCTION

Evaluating the link between environmental exposures and developmental disorders in children is a difficult research challenge. The range of developmental disorders is extremely wide, as is the range of exposures that might effect a child's intellectual, physical, emotional or social growth and development. Many exposures have different effects when they occur at different times, either before or after birth; for some exposures this critical window may be short. Short critical windows make the retrospective study of exposures that might cause developmental disorders in children very difficult. A prospective, longitudinal study of pre- and post- natal growth and development, in which information is collected at multiple points in time about pregnant women and subsequently about their children and families, is the optimum design with which to study the dynamic nature of growth and development. However, longitudinal cohort studies of pregnancy and childhood are difficult to carry out. The last such large cohort studies in the United States were begun in the 1950s and early 1960s, and the feasibility of conducting such a study in present times is uncertain.

To explore the feasibility of conducting a large, longitudinal cohort of pregnancy, childhood and adolescence, the Centers for Disease Control and Prevention, U.S. Environmental Protection Agency and National Institutes of Health, under the auspices of the President's Task Force on Environmental Health Risks and Safety Risks fo Children, conducted a consultation on January 12 and 13, 2000. Experts from within and outside the Government who have experience in the design and conduct of large, longitudinal cohort studies were invited to provide advice regarding the feasibility of conducting a longitudinal cohort study, as well as regarding issues that must be considered is such an undertaking. This report details the background of this consultation, as well as its results.

A SAFE AND HEALTHY ENVIRONMENT FOR CHILDREN

A growing body of science indicates that a child's growth and development are enhanced by a healthy and safe environment. Conversely, children may suffer disproportionately from environmental health and safety risks. Some normal childhood behaviors may result in exposures to physical, chemical, biological, or psychosocial threats, contaminants, and safety hazards. Pound for pound, children eat and drink more food and liquids, and breathe more air than adults. Children grow rapidly, and their absorption, distribution, metabolism, and excretion of various substances change over time, affecting how well they tolerate environmental exposures. Children by their very nature - small in size and weight - are less able to withstand the energy forces associated with injury and are less well protected by adult/standard safety features.

A child's environment represents more than hazards related to a specific exposure. It characterizes the totality of conditions and milieu in which a child grows and develops. The consequences of an unsafe and unhealthy environment may have long latency periods that result in untoward outcomes later in time. Thus, the scope of securing a safe and healthy environment

for children is broad and encompasses the tenets of protection, prevention, and promotion throughout the life cycle.

The President's Task Force on Environmental Health Risks and Safety Risks to Children is guided by a directorate comprised of a senior staff planning committee and workgroups on (1) program implementation and (2) data needs and research. In addition, four workgroups were formed to address the following priority areas: (1) asthma, (2) unintentional injuries, (3) cancer, and (4) developmental disorders.

Collectively, these priority areas represent key sentinel conditions concerning childhood morbidity and mortality. They also represent important opportunities for disease prevention and health promotion to prevent or relieve lifelong injury, illness and disability. In addition, their successful resolution requires broad cooperation and support from quality health and human services, environmental and legal protection, quality education, nutritious and safe foods, and safe and clean transportation. A safe and healthy environment for children requires safe labor and industry practices, safe and appropriate housing, safe consumer products and energy, as well as sound complementary fiscal, economic, domestic, and science policy.

The President's Task Force on Environmental Health Risks and Safety Risks to Children has employed four principles in directing its efforts: (1) primary prevention - eliminating the threat of exposure to harmful events or hazardous substances; (2) secondary prevention - providing screening, treatment, and follow-up care before the condition deteriorates to irreversible morbidity or mortality; (3) surveillance and monitoring - providing data for evaluation, decision making and resource allocations; and (4) research - generating new knowledge for effective primary prevention and quality treatment.

STRATEGIC SCIENCE

Evaluating the link in humans between environmental exposures and developmental disorders is a major research challenge given the range of outcomes that may arise from one exposure and the variety of factors that can result in a given outcome. The range of developmental disorders affecting children is wide and includes intrauterine growth retardation, infant mortality, birth defects, suboptimal postnatal growth and development, functional deficits (e.g., neurobehavioral, immune, reproductive, respiratory) and possibly the foundations for chronic diseases of adulthood. The factors that might be responsible for these outcomes are equally diverse. Prenatally, they range from genetic disorders to *in utero* exposures to infectious agents, poor maternal nutrition, tobacco, alcohol, drugs, and other chemicals. Even before conception, exposures of parents to radiation and chemotherapeutic agents have been linked with developmental disorders. In early childhood, exposures of concern run the gamut from lead and environmental tobacco smoke to lack of a nurturing and stimulating environment. The timing and pattern of these exposures impacts the types of effects that are seen, and the degree to which children are affected.

It is estimated that more than 150,000 babies in the U.S. (about 4 percent of all live births) are born with significant birth defects each year. Ranging from severe to mild, 2% to 17% of children in the U.S. have a developmental disorder, such as cerebral palsy, mental retardation, autism, or a hearing impairment. While the exact proportion attributable to environmental factors is unknown, exposure to environmental hazards often have lasting and profound consequences for children's growth and development that may not manifest themselves until adulthood. A child's nervous system, reproductive organs, and immune system grow and develop rapidly during the first months and years of life. As organ structures develop, vital connections between cells are established. These delicate developmental processes in children may be easily and irreversibly disrupted by environmental substances, such as lead, mercury, and polychlorinated biphenyls (PCBs), producing lasting changes in intelligence, behavior, and reproductive capability.

The consequences of both prenatal and postnatal lead exposure demonstrate the importance of investigating both acute and life-long toxicity and harmful effects in several domains. Lead is a neurotoxic metal that affects areas of the brain associated with regulating behavior by altering the output of neurotransmitters and disrupting the development of nerve cells. Exposure of pregnant women to lead may result in transfer of the metal to a developing fetus, resulting in developmental problems, while exposure of children, even to low levels, can cause lowered intelligence, reading and learning disabilities, impaired hearing, reduced attention span, hyperactivity, and antisocial behavior. Many of these problems last a lifetime and impact the quality of life of the child and his or her family.

Consequently, the President's Task Force on Environmental Health Risks and Safety Risks to Children seeks to establish and coordinate efforts of a unique multi-agency strategy to implement a longitudinal cohort study of environmental impacts on children and families. This national effort will assess the effects of early and ongoing exposures to physical, chemical, biological and psycho-social environmental influences on children's well-being, identifying both risk and protective factors.

SCOPE AND NATURE OF THE INVESTIGATION

In principle, the study design that can best define the effects of multiple environmental exposures, occurring at multiple points during development, on a wide array of possible outcomes is the prospective cohort study. A prospective cohort study can evaluate both chronic and intermittent exposures while avoiding many of the difficulties that alternative study designs have when attempting to reconstruct this information. However, few cohort studies of children have actually been carried out. The only U.S. studies to take a longitudinal approach to examining multiple facets of exposures and specific health outcomes in children were the Federally sponsored Collaborative Perinatal Project, Child Health and Development Studies, and Kauai Child Development Study, all of which were done about 40 years ago. In other countries, such studies are currently underway (e.g. the Avon Longitudinal Study of Pregnancy, Adolescence and Childhood; and the Danish National Birth Cohort Study) or are being planned

(e.g. a study of Norwegian children). A similar cohort approach has been used to study chronic health conditions in adults, e.g., the Framingham study.

U.S. researchers have considered conducting a similar present-day study of children, but no planning for such an effort has been undertaken to date due to the expense and time required to plan and conduct a longitudinal study. However, given the recent developments in biomarkers of exposures and outcomes and the experience gained in cohort studies with a narrow scope, it is desirable to now consider conducting a large, prospective cohort study of children, their parents and their families. This would represent a more comprehensive approach to understanding how the environment, family and society interact with the genetic constitution of the developing fetus and child to foster optimal childhood growth and development, and how environmental exposures can adversely affect that growth and development.

Understanding the complexity of human growth and development requires special investigative approaches. Conducting a longitudinal cohort study of children and families is such a special vehicle and it is a unique and necessary approach to assess the effects of prenatal, postnatal, and early childhood exposures to physical, chemical, biological, and psycho-social environmental influences on children's well-being. Central to understanding children's growth and development are the biological, behavioral, social, emotional, educational, and contextual consequences for identifying both risk and protective factors.

The longitudinal study represents a major legacy effort inaugurated by the Task Force. This effort will create an extensive national scientific resource and an interactive and collaborative research infrastructure for basic and applied scientists that will accelerate the pace of gaining new knowledge to improve the health and well-being of children for successive generations. It will enable maximum advantage of new developments in measurement, instrumentation and specimen preservation in the discovery of new knowledge integrated with information garnered from the genome project. This new investment will complement the existing children's environmental health research centers supported by this nation. Funding this research will represent a major commitment to discovering basic mechanisms of developmental disorders and environmental factors that influence growth and developmental processes.

The expertise of several agencies has been combined to explore the possibilities for developing a longitudinal cohort study of children. The study will begin during pregnancy and is intended to follow the children into adulthood. Assessments and data collection will include adverse physical, functional, and psycho-social consequences of environmental exposures. During FY1999 and FY2000, experts were consulted to assess the feasibility and benefits from various designs of longitudinal studies to guide future development of planning a study, conducting pilot tests, and providing information, including cost projections and scope, on which to base design decisions.

ASSESSING FEASIBILITY

On January 12, 2000, a group of experts with experience in conducting large cohort studies was convened in Washington, D.C. by the Planning Group. Two presentations were made as background to the discussions, one on exposure measurements by Dr. Maurice Berry (EPA/ORD/NERL), and one on biological specimen collection, analysis and storage by Dr. Terry Phillips (NIH/OD). Subsequently, experts on various types of cohort studies presented background on their respective approaches. These included a review of 1) the National Collaborative Perinatal Project by Dr. Karin Nelson (NIH/NINDS); 2) the Danish national cohort study by Dr. Jorn Olsen (Danish Epidemiology Science Center); 3) the Bogalusa Heart Study by Dr. Gerald Berenson (Tulane University); 4) the Avon Longitudinal Study of Pregnancy and Childhood by Dr. Jean Golding (University of Bristol); 5) HMO-based studies by Dr. Barbara Cohn (The Public Health Institute, Berkeley) and Dr. Diana Petitti (Kaiser Permanente, Southern California); and 6) the Nurses Health Study by Dr. Frank Speizer (Harvard University). Presentations highlighted issues that need to be considered in deciding to commence such a study, including specific advantages and disadvantages of each study type, and its overall feasibility. The experts were asked to provide information regarding the value and feasibility of a large, longitudinal study of children and the environment. Invited discussants commented on each approach and general discussion of all of the approaches was held at the end of the day. The following points and suggestions were made:

- ▶ While the specific nature of the longitudinal cohort study will require time and careful consideration of nominal hypotheses, there was general support and extremely positive sentiment for the possibility of conducting a large cohort study.
- ▶ Since children cannot be separated from the families in which they live, a longitudinal study must be a study of children, parents and families, and not just a study of children. The study should both collect information on and be sensitive to the behavioral, social and cultural aspects of the children and their families.
- ▶ Before giving further consideration to the settings and structure for the study, hypotheses must be developed. There was agreement that a large, long-term longitudinal study must address questions that are of importance to public health and the health of children, and that would be difficult or impossible to address with a smaller, shorter-term and less expensive design. A benefit of a longitudinal design is the ability to evaluate biomarkers of exposures and environmental measurements during critical windows of development, which continue throughout the life course, and to link exposures at particular times in development with their effects.
- ✓ There was considerable discussion, both from the experts and within the Planning Group, regarding how narrowly or broadly focused the hypothesis should be. However, it was recognized that a study intending to address the health, growth and development of children must collect a wide range of

information, from direct assessments of the immediate environment to indirect factors that may relate to a child's ultimate growth and development. Wide-ranging data collection does not mean such a study is merely a "fishing expedition."

- ✓ Rather than specifying a particular setting for the study, such as within an HMO, a University hospital clinic, a geographic region, etc., the consultants believed that it was preferable to specify the study design, the common protocol, etc., and let investigators representing different institutions and settings submit proposals describing how they would carry out the protocol.
- ✓ One design feature to be considered is a "core protocol" that all participants would follow, with the opportunity to incorporate modular components or "special studies" based on the characteristics, interests and expertise of the individual sites.
- ▶ Building support for a large cohort study both within the technical communities and study participants will be critical. In particular, two similar cohort studies planned or underway in Europe were either severely delayed or required major modification due to failure to build support within the community of general practitioner physicians. The support for the study within the community of parents is as crucial as the support from the medical and research communities. Input from all of these communities (parent, medical and research) should be obtained early in the process.
 - ✓ Ethical issues regarding collection, storage and eventual distribution of information, biologic specimens, genetic material, and environmental samples are paramount and must be addressed from the beginning of the planning process.
 - ✓ The need to garner support for the study should not be allowed to determine the type of information collected. In particular, simply allowing interested parties to exchange their support for questions or topics to be included will result in a poorly designed and unfocused study.
- ▶ Consideration should be given to the external and internal validity of the study, particularly with respect to longitudinal follow-up. Individuals who can be identified before conception, who present early for antenatal care, who can be followed successfully over time, or who have exposures of particular interest, are probably not representative of the general population. During the planning phase, the potentially conflicting issues of "representativeness" versus the requirements to carry out long-term follow up successfully and to address hypotheses of particular interest must be resolved. The consultants themselves could not agree whether the study population should be chosen to be representative of a given area or whether it should be selected to be diverse in its composition and in environmental exposures, but not necessarily representative. All agreed that regardless of this conflict, diversity of the study population was

important.

- ▶ The study should take advantage of the latest in information technology, particularly the Internet. Modern information technology should be incorporated into the design and conduct of the study from the beginning of planning, rather than being added after the study has already been designed.
- ▶ Similarly, modern bio-analytic and environmental monitoring techniques should be incorporated into the study during the planning phase. Some of these techniques already exist, but many may need to be developed specifically for this study. Banking samples for future use as technology evolves was discussed; its successful implementation will require resolution of many issues, particularly in logistics and ethics.
- ▶ Provisions and policies for public use of the collected information-- the data on the study forms, the biological specimens, and the environmental samples -- should be incorporated during the design phase, rather than added later. In this context, "public" is defined as both the research community and the general public. However, concerns were raised about the misunderstandings that can occur when individuals unfamiliar with a complex study are allowed to try to analyze the collected data without appropriate guidance and assistance.
- ▶ Long-term maintenance and ownership of both the study data and particularly the biological and environmental specimens should be addressed during the planning of the study. Provision should be made to assure adequate funds and facilities to store the biological specimens after the designers and investigators of the study have retired. The plan should be sensitive to the wishes of the study subjects, even years after the data and specimens have been collected.
- ▶ Several organizational issues were raised:
 - ✓ Opportunities for public-private (foundations, industry, etc) partnerships should be explored.
 - ✓ Interactions among the Federal Agencies involved will be crucial to the success of this project. More than one presenter expressed concern that conflicts among Agencies for control of the study might doom the entire project.
 - ✓ The presenters, discussants and Planning Group all believed that "new money" must be allocated for a large, longitudinal cohort study to proceed. If Agencies were required to fund this large and expensive cohort from existing allocations, the accompanying reduction in funds available for both Extramural and Intramural research is likely to erode the support of both the Federal and University research communities. Erosion of this critical support would be a serious threat to any planned study.

- ✓ A strong, central and probably small directing group, dedicated solely to the design and conduct of the study, will be necessary to avoid the pitfalls raised during the consultation.
- ▶ Since a large, longitudinal study of parents and children, beginning prenatally and continuing through childhood has not been done in the United States since the 1960s, the designers of the proposed study were encouraged to think boldly. This study should be a trail-blazer in the areas of ethics, data collection, information technology, biological analytic techniques and other areas.

RECOMMENDATIONS AND NEXT STEPS

The Longitudinal Cohort Study Planning Group met on January 13, 2000, to review the discussions at the consultation and to draft recommendations to the Task Force. The following general recommendations are made:

- ▶ **Based on the consultation and discussions in the Planning Group, the Task Force should move ahead with the planning of a national longitudinal cohort study on children's environmental health.**
- ▶ **To conduct a study of such magnitude and importance will require new money that does not reduce current research funds of the various agencies involved.** The Planning Group is in complete agreement with the expert consultants on this point. If current research funds are reduced in order to carry out this study, the general research community would be adversely affected and would not be willing to support the study and its goals.
- ▶ **Full-time personnel are required to organize and oversee the numerous activities that will be required to move into the pre-pilot planning phase of the process.** In order to set up the various activities necessary to keep the process moving and to prepare for launching a national cohort study within the next 5 years, an **Interagency Coordinating Team** of a small number (2-3) of full-time individuals must be assigned to this effort. This could be accomplished, for example, by detailing an individual from agencies involved in the activities (e.g., EPA, NIH, and CDC) to a central location in the Washington, DC, area for coordinating these activities. This group would be advised by the Interagency Planning Group, and would be responsible to the Executive Secretariat of the Task Force, as well as their own agencies.

The team would be responsible for the day-to-day management of all aspects of the pre-pilot phase. This would include planning the various additional consultations and committees (described below); compiling an inventory of other already planned studies that are related to the longitudinal cohort study, including instruments/techniques that are already being developed; setting up meetings/conference calls of the larger Planning

Group when needed; writing RFPs or other documents for soliciting proposals for funding of the pre-pilot efforts; communicating with the Task Force, and other appropriate entities on a regular basis; and PR functions such as answering inquiries about the study and producing materials that can be distributed to appropriate interested parties, e.g., government agencies that have not been a part of the planning process to date, academic institutions, parent groups. Maintaining the “spirit” of interagency collaboration at all levels was cited as being extremely important. It is hoped that this proposed structure for coordinating the planning process can be in place in the **next 3 months**.

CONCLUSION

As scientific and technological advances are made, the environment will undoubtedly change. More chemicals and pesticides designed to add comfort and productivity will be introduced. New emissions will alter air quality. High tech innovations will likely add to the number of known and unknown hazards. The interaction between these environmental influences and the biological and psycho-social environment of the child is not known. However, the risk to our planet, particularly our children, likely will rise each year. Consequently, the need for new knowledge to promote well-being and to protect and prevent untoward outcomes similarly rises. Fundamental research, surveillance, and program evaluation on such critical topics as the relationship between the environment and the effect it has on children’s health arises from many scientific disciplines and is supported through several mechanisms. The special nature of children, with their dynamic developmental trajectory, requires a longitudinal approach to assure maximum scientific information on and understanding of adverse health and safety risks in children resulting from exposure to a broad range of environmental agents. Such an enterprise is not only feasible but essential.

The President’s Task Force on Environmental Health Risks and Safety Risks to Children has been successful in coordinating multi-disciplinary efforts and the skills of multiple governmental agencies to achieve one common goal – making the future for our children brighter, healthier, and safer. The implementation and execution of a national longitudinal cohort study of children and their families will generate new knowledge critical for new and innovative interventions to bridge the gulfs between different scientific disciplines and assure a safe and healthy environment for children in the coming millennium.