

**National Children's Study  
Federal Advisory Committee 12th Meeting  
September 20–21, 2005  
Gaithersburg Marriott Washingtonian Center  
Gaithersburg, MD**

This meeting was held in conjunction with the National Children's Study, which is led by a consortium of federal agency partners: [the U.S. Department of Health and Human Services](#) (DHHS) (including [the National Institute of Child Health and Human Development \[NICHD\]](#) and [the National Institute of Environmental Health Sciences \[NIEHS\]](#), two parts of [the National Institutes of Health](#), and [the Centers for Disease Control and Prevention \[CDC\]](#)), and the [U.S. Environmental Protection Agency \(EPA\)](#).

## **Day One**

### **Welcome and Introductions**

*Alan R. Fleischman, M.D., NCSAC Chair, Senior Advisor, The New York Academy of Medicine*

Dr. Fleischman welcomed National Children's Study Federal Advisory Committee (NCSAC) members and other participants to the 12th meeting of the NCSAC. Highlights of Dr. Fleischman's presentation are as follows.

- There is a sadness because of the recent disasters in the south. However, man-made and nature-made catastrophic events provide opportunities to study the impact of such events on the psychosocial well-being of children, families, and communities. The challenge for the National Children's Study (Study) is to consider how to generate data in this kind of chaos and disarray, to follow subjects as they move across the country, and to better understand the impact that terror, trauma, and disaster have on the health and development of the nation's children.
- In regard to the NCSAC:
  - The federal government may obtain advice on long-range planning and development of programs from groups of outside experts through the formation of advisory committees.
  - The Federal Advisory Committee Act (FACA; Public Law 92-463; passed on October 6, 1972) creates standard and uniform procedures governing the operation of all advisory committees.
  - The function of the NCSAC, as with all federal advisory committees, is to advise—to think carefully and deeply about issues and to make recommendations and give advice.
  - The advice of the NCSAC goes to the Study Director, Peter C. Scheidt, M.D., M.P.H.; to the Director, NICHD, Duane F. Alexander, M.D., and to the Study's Interagency Coordinating Committee (ICC).
- The minutes of the April 27–28, 2005, NCSAC meeting reflect the tone and tremendous input from the NCSAC to each and every issue raised during the meeting.
- The presentations in the present meeting reflect how the Study Director; the Director, NICHD; the ICC; and others involved in the Study have considered and addressed recommendations made, advice given, and issues raised by the NCSAC during the April meeting, which included the following:

- The Study plan requires a quality management plan.
- Substantial thought and resources are required to seriously address community engagement and successful recruitment of diverse participants including immigrants, minorities, and rural populations.
- Integrity of the probability sample needs to be maintained even with additional sampling and adjunct studies.
- The North Carolina (NC) Herald Pilot Study is a complex undertaking but is consistent with the overall mission of the Study and worth the time, effort, and expense.
- With regard to NCSAC roles, responsibilities, processes, and procedures, four subcommittees were created and three have been activated: ethics, community engagement, and concept review.
- A procedure to review public-private partnerships is required to ensure that such relationships do not create conflicts of interest, affect the integrity of the Study, or create the impression of inappropriate influence.
- With regard to community involvement and cultural sensitivity, the Study must gain the trust and respect of the community as a whole, not just from community representatives or community-based organizations, but from all members of the community.
- The Study must be flexible in its community engagement strategies.
- The Study's research should be committed to being translational; the Study must find ways to convert results from raw data into policy changes, at both local and national levels, to benefit communities. The NCSAC is ready, able, and willing to help with this process.
- Ethical considerations on the use of incentives (payments and monetary compensation) to enhance recruitment and retention was discussed, but engaging the trust of participants is perhaps the greatest incentive to recruitment and retention.
- The Study needs to develop methods to convince participants that children and communities will ultimately benefit and that ultimately the data that are obtained will be used in positive ways to help future children, families, and communities.
- Incentives may differ among sites, and guidance about the ranges of incentives and approved gifts of appreciation should be provided.

## **Welcome and Overview of the National Children's Study**

*Peter C. Scheidt, M.D., M.P.H., Study Director, NICHD, NIH, DHHS*

Dr. Scheidt welcomed NCSAC members. Highlights of Dr. Scheidt's presentation are as follows.

- Coordinating and Vanguard Centers procurements
  - Negotiations for the Coordinating Center and 2005 Vanguard Centers are complete.
  - Negotiations for some Vanguard Centers will continue into October.
  - The first Steering Committee meeting is tentatively scheduled for November 9–10.
  - Dr. Scheidt will chair the Steering Committee.
- Awards for the Coordinating Center and some Vanguard Centers will be announced September 29, 2005, at 1:00 p.m., at the National Press Club in Washington, DC.
- U.S. Surgeon General, Vice Admiral H. Richard Carmona, M.D., M.P.H. (DHHS); Dr. Alexander (NICHD); EPA Administrator Stephen L. Johnson, M.S.; and CDC Deputy Director Dixie E. Snider, Jr., M.D., M.P.H., will attend the award announcement.

- Award announcement guests include the March of Dimes, the American Academy of Pediatrics, the National Medical Association, the National Hispanic Medical Association, and the Children’s Environmental Health Network as well as principal investigators for the Coordinating Center and Vanguard Centers.
- The Study plan will evolve into the Study protocol, which specifies the data collection processes and procedures and is essential for specific planning and resource allocation, peer review, institutional review board (IRB) review and approval, and Office of Management and Budget (OMB) review and approval.
- Program Office exposure and outcome teams have reviewed data collection approaches, considered an array of measures and instruments, and reviewed and provided references. A draft protocol will tentatively be ready in November for initial review by the ICC and for review by the Steering Committee at its first meeting.
- Key pilot studies and activities currently include:
  - The NC Herald Study
  - The EPA request for applications for Early Indicators of Environmentally Induced Diseases, which will entail two pilot projects for the Study
  - Informed Consent for the Study
  - Technology Assistance in Capture of Clinical Information
  - Development of the Study’s quality management plan
  - Use of “errors in measurement” concepts to guide selection of data quality objectives for exposure assessment.
- Upcoming workshops and planning meetings include:
  - International Childhood Cancer Cohort Consortium, with the National Cancer Institute and EPA
  - Pharmaceutical coding systems
  - Measures for infection and inflammation
  - Exposure assessment protocol team
  - Neurodevelopmental outcomes
  - Biological sample assessment.
- The Annual Study Assembly meeting, titled “Implementing the National Children’s Study: Scientific Progress, Challenges, and Opportunities,” will be held November 29–30, 2005, at the Omni Shoreham Hotel in Washington, DC.
- Study Assembly highlights will include introduction of the Coordinating and Vanguard Centers and updates on protocol development; the NC Herald Study; the International Childhood Cancer Cohort Consortium; and scientific, ethical, and design challenges.
- Scientific breakout sessions will include biological and psychosocial exposures; chemical and physical exposures; pregnancy outcomes, growth, and development; neurodevelopmental outcomes; community engagement; information technology and data collection; and international collaboration.
- Staff changes in the Program Office are as follows:
  - Kate Costella, M.S.W., Program Analyst
  - Regina Shih, Ph.D. (mental health epidemiology), Research Fellow
  - Laura Goetzl, M.D. (maternal and fetal medicine), interagency personnel agreement
  - Leni Buff, Program Analyst, detail from Smithsonian Institute completed
  - Beth Davis, promoted to Program Analyst training position.
- Project officer responsibilities are as follows:

- Ms. Davis, Project Officer for logistical support
- Dr. Scheidt, Project Officer for scientific support
- Sarah Knox, Ph.D., Project Officer for the Coordinating Center
- Ruth Brenner, M.D., Project Officer for the Vanguard Centers
- Warren Galke, Ph.D., Project Officer for the repository
- Larry Needham, Project Officer for the biological laboratory.
- Response of the Study Director to NCSAC April 2005 meeting statements include:
  - The Quality Management Plan is under development through an EPA contract and in the Coordinating Center contract.
  - The needed oversampling at the Study’s second stage will be addressed at the first Steering Committee meeting.
  - Recruitment and retention methodology will be developed and tested in the NC Herald Study, as will measures for environmental exposures, development, consent, and others.
  - A process for reviewing public-private partnerships is being developed.
  - Community involvement strategies are currently being reviewed, including the development of community-level reports and community advisory boards.
  - A number of possible incentives have been considered. NCSAC recommendations appear both reasonable and appropriate.
- The Study protocol will tentatively be completed in June 2006 and will be followed by public comment, peer review, IRB(s) review, and OMB approval.
- Requests for proposals for remaining Study sites will be issued in winter or spring 2006 for fiscal year 2006 funding or in fall 2006 for fiscal year 2007 funding.

**National Research Council/Institute of Medicine Report: Ethical Issues in Housing-Related Health Hazard Research Involving Children, Youth, and Families**

*Bernard Lo, M.D., Report Committee Chair, University of California, San Francisco*

Dr. Lo summarized a recent report from the National Academies Committee on Ethical Issues in Housing-Related Health Hazard Research Involving Children, Youth, and Families. The committee’s full report and executive summary are available at [www.nas.edu](http://www.nas.edu). The charge to the committee was (1) to review and synthesize existing approaches to conducting housing health hazards research involving children and the challenges and ethical issues that arise in conducting research and (2) to identify approaches to ensure the ethical conduct of that research. In response to this charge, the committee recommended the following:

- Involve communities and respond to concerns
- Ensure informed parental decision making
- Ensure voluntary parental decision making
- Consider other risks in the home
- Consider obligations to third parties
- Require and fund community involvement
- Require consent process focused on parental understanding
- Require appropriate anticipatory plans for risks observed in the home
- Ensure complete and adequate review
- Ensure uniform regulatory protections across federal agencies
- DHHS Office for Human Research Protections (OHRP) provide guidance on Subpart D terms

- OHRP provide guidance on economically and educationally disadvantaged participants.

In sum, researchers, IRBs, OHRP, sponsors, and representatives of relevant communities should work in partnership to ensure:

- Community engagement
- Parental understanding of essential elements
- Uniform regulatory standards
- Clear interpretation of regulatory terms
- Ethical conduct of research

### **Report from the Director, NICHD**

*Duane F. Alexander, M.D., Director, NICHD, NIH*

Dr. Alexander welcomed the NCSAC members, thanked them for their time and effort, and recognized the value of their input to the Study. He complimented the hard work of the many people who have been involved with the Study's recent procurements, including the Program Office, the ICC, and the NICHD contracts office. Dr. Alexander assured the meeting participants that the Coordinating Center and Vanguard Centers awards would be scientifically and fiscally sound.

- **Funding status/prospects.** Since 2000, the Study's four lead funding agencies have spent about \$39 million through fiscal year 2005 to plan, develop, and coordinate the Study. About \$12 million was spent in fiscal year 2005, with \$7.5 from NICHD, \$1.5 from NIEHS, \$500,000 from CDC, and from EPA, \$1 million in direct funding and \$1.5 of in-kind contributions. The spending to date does not include funding for staff salaries, staff and hiring activities, and details and loaned personnel from other agencies, all of which comes directly from the agencies' budgets. The President's fiscal year 2006 budget did not request any additional funding for the Study's implementation. The entire NIH budget received only a 0.6 percent increase for fiscal year 2006 in the President's Budget. With inflation rising within the biomedical arena at 3.5 percent per year, the NIH budget is about 3 percent below inflationary costs. NICHD's fiscal year 2006 base budget of \$1.2 billion is slated to receive a \$7 million increase in the President's Budget. Dr. Alexander said that the House of Representative passed the President's fiscal year 2006 budget request for NIH intact. To date, there has only been committee action in the Senate. However, with prodding from Senator Arlen Specter (R-PA), the Senate appropriations committee added \$1 billion to NIH's fiscal year 2006 budget. Of this, about \$41 million is slated for NICHD. The full Senate has not yet passed this budget, and if it does, the House and Senate may have to resolve their differences. Regardless, the fiscal year 2006 budget will be tight. No funding was designated for implementation of the Study. Dr. Alexander noted that given the recent natural disasters and the necessary reconstruction, there will be competition for available funding within the budget. Planning of the fiscal year 2007 budget has begun, and the recent natural disasters will affect this process.
- **AGES.** Dr. Alexander described three presentations on the impact of "big science" at a recent retreat of NIH institute directors: (1) the Study, (2) special initiatives from the National Cancer Institute such as nanotechnology applications and other diagnostics, and (3) the American Gene and Environment Study (AGES). NIH officials have previously discussed how AGES and the Study could develop a mutually beneficial relationship,

primarily through common participants. AGES tentatively plans to recruit about 500,000 participants, including some children. AGES would collect DNA samples for gene analysis for differences in single nucleotide polymorphisms (SNPs) and study the relationships between SNPs and the development of chronic diseases in adulthood that do have some genetic component but are not strictly Mendelian disorders. The projected total budget for AGES is about \$6.5 billion to \$7.5 billion, spread over 12 years as compared to the Study's 2.7 billion dollar budget over 25 years. NIH officials are examining whether cost savings would be realized by combining the Study and AGES. Dr. Alexander reported that there would be some cost saving through a joint recruitment effort, but the sampling methodologies of the two studies are not compatible.

- **Living with uncertainty.** Dr. Alexander noted that professionals in the health arena are familiar with dealing with uncertainty and that facing uncertainty is often an educational process. Although the Study is facing uncertainty, it will continue to proceed, primarily because both House and Senate appropriations committees direct the lead agencies to keep working on planning and implementing the Study, specifically, "to be ready for the field no later than 2007." The lead agencies, as well as Congress, will continue to consider all means by which the Study can be funded, and those who are involved with the Study will continue to move it forward.

### **Role of Behavioral and Psychological Factors in the Study**

*Sarah S. Knox, Ph.D., Behavioral Scientist, Study Program Office, NICHD, NIH, DHHS*

Input to the draft Study protocol has come from multiple sources including 22 working groups, a federal consortium, pilot studies, Study Assembly meetings, workshops, literature reviews, and white papers. White paper topics include psychiatric assessment in children from a longitudinal, epidemiologic perspective; neuropsychological assessments in children from a longitudinal perspective; assessment of social-emotional development in children from a longitudinal perspective; and a proposed motor development assessment protocol.

The psychosocial and behavioral exposure domains are as follows:

- **Demographics:** Nativity, age, household composition, languages spoken, marital status, race/ethnicity, residential history, socioeconomic status (SES)
- **Culture:** Background, beliefs, attitudes, practices
- **Family structure:** Including household composition
- **Family process:** Relationships, division of labor, conflict resolution, domestic violence
- **Neighborhood:** Social and economic characteristics
- **Religion/spirituality:** Identity, beliefs, practices
- **Parental competencies:** IQ, social competence, knowledge of child development, personality
- **Parenting practices:** Warmth, limit-setting, discipline techniques, cognitive stimulation, health care management
- **Psychological stress:** Social and economic stress, job strain, racism/discrimination, parenting
- **Social support:** Instrumental, emotional and network support
- **Parental psychopathology:** Depression, other diagnoses
- **Public policies:** Food stamps, benefits, health insurance

- **Child care:** Type, stability, ratio of adults to children, hours/day, quality
- **School:** Quality, ratio of students to teachers, SES, diversity of students, discrimination
- **Diet:** Maternal, child (including breastfeeding)
- **Smoking, alcohol consumption, substance abuse**
- **Physical activity.**

The Study's approach to psychosocial influences on health and development of children will use a multilevel interactive model that includes individuals, families, neighborhoods, schools, and communities. From this multilevel interactive perspective, exposures will include the following:

- Independent predictors of health and development
  - Neighborhood and community characteristics as predictors of behavioral outcomes (for example, violence)
  - Media exposure as a predictor of cognitive development and sensitivity to violence
  - Racism stress as a predictor of preterm birth
  - Family resources and process as predictors of school performance and social behaviors
  - Psychosocial stress during pregnancy as a predictor of birth weight and outcomes, difficult behavior at 3–8 months
- Interactions with other environmental exposures
  - Animal research indicates that maternal stress modulates the effects of maternal lead exposure in offspring.
  - Effects differ by gender: neither lead alone nor stress alone raised corticosterone in female offspring, but the combination of stress and lead did.
  - Neurohormones (such as dopamine, DOPAC) were higher in females than in males.
- Gene-environment interactions
  - Epigenetics (methylation, acetylation)
  - Serotonin transporter gene
  - Schizophrenia
  - Famine, infection, and schizophrenia
  - Parenting style alters gene expression (for example, in rats and monkeys).

*Stress* is defined as a feeling of distress experienced when demand exceeds an individual's ability to control what is happening in his/her life. Stress has consequences for physical health primarily when it is chronic, not acute.

Psychosocial factors as well as toxicants will be included in the investigation of exposures influencing gene expression-mediated outcomes in the Study. Basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes will be considered.

Psychiatric/mental health outcomes will include:

- Periodic screening of all children starting in infancy for signs of psychological and psychiatric dysfunction (for example, autism, depression, behavioral problems).
- More definitive testing for those with suspected problems.
- Assessments will be dimensional rather than dichotomous (normal/abnormal) classifications.

- Recording samples of behavior (such as videotapes) are being considered and may be “banked” for future analyses, such as case-control studies. These observations will also be coded directly so that simplified measures will be available on all children.

Neurobehavioral/cognitive outcomes will include omnibus IQ, executive function, language/verbal skills, academic skills, visuospatial abilities, learning/memory, attention, and motor skills.

Social/emotional health and development outcomes will include social competence, attachment, school readiness, emotional competence, temperament/personality, and aggression.

Exposures, outcomes, and mechanisms can be summarized as follows:

- **Exposures:** Psychosocial and behavioral factors interact with each other and with other environmental and genetic/biological factors to influence health and behavioral outcomes from molecular to systemic levels.
- **Outcomes:** Behavioral and psychosocial outcomes in the Study are complex and will be investigated from a perspective of multiple influences that vary in importance by developmental stage.
- **Mechanisms:** Mechanisms occur from the molecular to the systemic levels.

Study hypotheses involving psychosocial and behavioral factors include:

- Disparities in prevalence and severity of asthma by race and SES are explained in part by psychosocial and behavioral environmental factors.
- Exposure to psychosocial stressors during vulnerable periods of pregnancy and early childhood can interact with genotype to permanently alter gene expression, causing adverse neurobehavioral outcomes.
- Maternal stress during pregnancy is associated with increased risk of asthma.
- The amount, type, context, and content of media exposure from infancy through adulthood influence brain, cognitive, neurological and social/emotional development.
- Social institutions (for example, religious, schools, daycare) influence cognitive, social, and emotional development.
- Family resources and structure shape children’s home, childcare, and school experiences and economic opportunities, influencing developmental and health trajectories.
- Adolescent onset of aggression is associated with behavioral and contextual exposures.
- Public policies related to children differ across states and will have positive effects on child health and development.
- Dietary antioxidant constituents of diet decrease asthma risk.
- Breastfeeding is associated with lower rates of obesity and lower risk of insulin resistance than infant formula.
- Fiber, whole grains, and glycemic index are dietary predictors of obesity, insulin.

## **Ethical Considerations: Informing Participants, Families, and Communities of Information Learned**

*Myron Genel, M.D., Chair, NCSAC Ethics Subcommittee, Yale University School of Medicine*

The mission of the NCSAC Ethics Subcommittee is to provide advice and recommendations concerning various ethical concerns. In a conference call prior to the meeting, the subcommittee (Dr. Genel; Nancy Dubler, LL.B.; Cynda Rushton, D.N.Sc., R.N.; David Schonfeld, M.D.; and Peggy Shepard) was asked to discuss and respond to specific questions derived from the following statements:

- The Study plan is committed to revealing relevant and important information to participants and families.
- NIH policy on reporting results specifies that:
  - Informed consent must include information on what will and will not be offered or told to participants.
  - Under the Federal Privacy Act, an individual may not waive his or her right to obtain access to research records.
- The Study's data and safety monitoring board (DSMB) will assess scientific validity of findings.

The subcommittee developed the following recommendations during its conference call:

- Should the Study inform participants and families about aggregate findings?
  - Findings must be scientifically valid and clinically relevant.
  - The Study should inform participants, families, and the greater community of findings.
  - The Study has an obligation to develop methods to help participants understand and interpret the meaning of the information.
  - A Web site can provide updated information, perhaps with access to some information for the general public, and secure access for individuals/families.
- Should the Study inform participants and families about all individual findings, or only those that are medically or clinically relevant, or only those for which an intervention is available?
  - The Study should inform participants and families about all medically or clinically relevant individual findings whether or not there is an available intervention.
  - The Study should focus on how best to communicate this information so that it is useful to participants and increases knowledge without being unduly alarming.
  - There is a need for a system to assure that each participant is informed of such information.
  - Written communication (paper or secure e-mail) should accompany any oral discussions.

The NCSAC reached consensus and agreed to these recommendations.

The remaining issues for discussion include:

- Some information may be confusing and misleading or not particularly useful to the participant; should it be shared?
- How should the Study determine which information is medically or clinically relevant?
- Should families be advised about the potential negative impact of being informed about findings?

- Should participants be “offered” or “told” the information, or should information “be available on request”?
- What methods and frequency should be used to inform participants of findings? (What method should be used for clinically “critical” versus “relevant” information?)
- Who should do the informing? The Program Office? The Coordinating Center? Participating local centers? Personal physicians?
- How should the Study treat genetic information?
- What information should be shared with local communities?

The NCSAC also reached consensus on the following issues:

- Those elements of aggregate data that are shared should be presented thoughtfully, and reasons should be provided as to why they are being shared; that is, there should be purpose to the informing of aggregate data.
- The concept of “clinical relevance” may not be uniformly applicable across geographic regions, across communities, and across time.
- The categories of aggregate data need to be the same across regions.
- The Study may not always be able to determine the meaning and clinical relevance of aggregate data.
- What may not be clinically relevant today may become relevant in the future.
- “Clinical utility” may be a more important concept than clinical relevance; that is, the aggregate data should be used for a specific purpose such as improving health outcomes in individuals and communities.
- Too much data can be dangerous. Community engagement may be helpful to determine what is useful to the community and what is not.
- The Study needs a clearly articulated process to define categories of information, and the participants need to understand what the categories are.
- The Study needs to offer information to participants, and communities need to be involved to help determine what information is offered.
- The Study should have methods to identify in a timely manner clinically critical findings, with appropriate “red flags,” and as best as possible, involve personal physicians and families in dealing with these clinically critical findings.
- When there is a reason to think that participants and families might wish to know clinically relevant but not clinically critical findings at the individual level, the participants should be offered the finding, with some element of interpretation of meaning, ideally in a face-to-face setting where participants and families can ask questions and discuss the meaning of the findings.

The NCSAC Ethics Subcommittee will continue to discuss these issues, and further recommendations will be presented to the NCSAC at future meetings.

### **NCSAC Community Engagement Subcommittee Report**

*Bernice Pescosolido, Ph.D., NCSAC member, Indiana University*

- **Formal issues.** Dr. Balsam discussed the FACA regulations as they pertain to subcommittees of chartered federal advisory committees. She noted that subcommittees must work through the larger federal advisory committee. All recommendations from the Community

Engagement Subcommittee must be discussed and approved by the NCSAC before being presented to government officials. All but the most specific administrative subcommittee meetings are open; all substantive discussions will be shared with the NCSAC. Dr. Balsam said that the subcommittee's function is advisory, not regulatory. The subcommittee can make recommendations to the NCSAC, which in turn can make recommendations to the Study. Only the NICHD Director, Study Director, and the ICC can decide what recommendations to implement. The Study has accepted and implemented previous recommendations, for example, community engagement strategies such as those for secondary sampling, community needs assessments, and local communities' flexibility to adjust or augment the Study protocol.

- **Informal issues.** The Community Engagement Subcommittee asked for the list of invitees for the contract award announcements at the National Press Club on September 29. NCSAC members will be allowed to review and add to the list, but they will have to provide the additional invitees' appropriate contact information to the Program Office.
- **Issues for discussion:**
  - Recruitment will begin in 2007, giving each Vanguard Center a year to participate in protocol development and serious community engagement.
  - The Vanguard Centers are required to engage the community throughout the length of the Study.
  - Community profiles have been created to better understand community dynamics at the various sites.
  - The principal investigators from each Vanguard Center will be asked to introduce their program at the Study Assembly meeting on November 29–30, 2005. Each Vanguard Center is required to speak about its community engagement strategy.
  - Centers should report best practices to serve as a model for the group.
  - The Study is committed to a cross-site evaluation of the community engagement efforts.
- **Recommendations.** The NCSAC Community Engagement Subcommittee recommends that:
  - Contract awardees provide synopses or executive summaries of their community engagement plans so that the Community Engagement Subcommittee can review them and provide feedback to the NCSAC on best practices at the January 2006 meeting.
  - The Study should consider hosting future NCSAC meetings at Vanguard locations.

The NCSAC reached consensus and agreed to these recommendations.

### **Update from the ICC**

*Amy Branum, M.S.P.H., ICC Member, National Center for Health Statistics, CDC, DHHS*

- Ms. Branum reviewed the history and evolution of the ICC, and she summarized the legislation that authorized NICHD to conduct the Study.
- The current ICC structure comprises 13 federal employees with approximately equal representation from NICHD, NIEHS, CDC, and EPA. This composition assures adherence to the Congressional directive authorizing the Study, broad federal representation in the areas of child health and the environment, and continuity within the project as involvement of these organizations dates from the initial Study planning sessions. The current ICC representation is listed at the end of this document.

- ICC chairs include two co-chairs that rotate every 4 months (staggered in 2 month intervals) from CDC and EPA and one permanent co-chair from NICHD (currently Dr. Scheidt).
- Each agency now has an ex officio member on the NCSAC: William Farland, Ph.D., Office of Research and Development, EPA; Allen Dearry, Ph.D., Office of Research and Development, NIEHS, DHHS; and Lonnie King, D.V.M., Office of Strategy and Innovation, CDC.
- The current ICC roles include critical functions such as overseeing broad Study issues (scientific and administrative), ensuring interagency collaboration, and maintaining financial support and joint budget decision making; ongoing activities related to broad oversight; general administration and planning oversight; pilot project planning and coordination; drafting policy; and incorporating NCSAC considerations into Study planning.
- Upcoming activities related to broad oversight include protocol review, Steering Committee planning and preparedness, Study Assembly meeting, and Vanguard and Coordinating Centers announcements.
- The ICC has been a true interagency collaboration and has been successful working collaboratively across agencies.
- Since the last NCSAC meeting, EPA has begun developing quality assurance monitoring pilot projects, and the ICC has determined the Steering Committee chair (Dr. Scheidt). The ICC is receiving regular updates on the progress of and giving input to the NC Cohort Study, developing adjunct study guidelines, and planning community pilots.
- Interagency collaboration requires even more effort and attention as the Study moves into the field. Once sites are in the field and the Steering Committee is operational, those involved in the Study will have to see how roles evolve.
- The ICC will continue to benefit from and looks forward to interactions with the NCSAC.

## Day Two

### Welcome and Recap of Day One

*Dr. Fleischman*

Dr. Fleischman welcomed participants to the meeting's second day and reviewed the highlights of the first day and the agenda for the second day.

### Role of Genetic Information in the Study

*Cynthia A. Moore, Ph.D., Office of Genomics and Disease Prevention, CDC, DHHS*

- Genetic information is important because all human disease is the result of gene-environment interaction.
- A unique opportunity exists in the Study to determine how genes interact with the environment to influence the health and development of children.
- Studying gene-environment interaction requires consideration of potential uses of genetic information, collection and storage of biologic materials in an appropriate manner, and awareness of the ethical, legal, and social implications of the use of genetic information.
- According to the Secretary's Advisory Committee on Genetic Testing, 2001, the proposed definition of a *genetic test* is "an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or

karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes.”

- Genetic information identifies genetic predispositions and risk factors throughout the participant’s lifetime and provides information on others (for example, family, ancestral group) besides the study participant.
- A 2004 Study workshop on the collection and use of genetic information brought together experts in the federal government (NIH, EPA, CDC, and Food and Drug Administration) to explore opportunities and challenges, and provide recommendations to the Study. The workshop’s overall discussion focused on ensuring that biologic samples are appropriately collected and stored to provide sufficient quality and quantity of genetic information to study health outcomes over time.
- Potential uses of genetic information in the Study are to identify disease risk factors, assess exposures to environmental agents, and characterize disease outcomes.
- Genetic information can be used to identify risk factors, including the relation to disease susceptibility, severity, and prognosis; interaction with other risk factors; and response to therapeutics. This is the focus of most genetic research to date, which requires germ line DNA.
- Examples of DNA variation and relation to disease and health include (1) autism and GABA receptor subunit polymorphisms, (2) insulin resistance in obese children and peroxisome proliferator-activated receptor-gamma2 polymorphisms, (3) arsenic metabolism and polymorphisms in developmentally restricted arsenic (III) methyl-transferase, and (4) acute leukemia outcomes and polymorphisms affecting chemotherapy pharmacodynamics.
- Genetic information can be used to assess exposures: (1) changes in gene expression in response to, or changes in DNA structure as a result of exposure to, an environmental agent; (2) limited research in infants or children; and may be assessed in RNA, proteins, DNA.
- Examples of genetic studies of exposure to environmental agents include metallothionein gene expression and cadmium exposure and (2) carcinogen-DNA adducts in paired maternal and newborn blood samples.
- Genetic information can be used to characterize outcomes: (1) using biomarkers to stratify study populations into more homogeneous groups, (2) current studies focused on various malignancies such as childhood leukemias, and (3) assessed in DNA, RNA, and proteins.
- Examples of genetic studies to characterize outcomes include: (1) asthma phenotypes and  $\beta_2$ -adrenergic receptor polymorphisms and (2) acute lymphocytic leukemia subtype discriminating genes.
- Challenges include availability of biologic materials; instability of RNA; effects are often time-limited and may not be time-specific (for example, gene expression in response to exposure, at different developmental stages, DNA adducts may persist over time), and effects may be limited to certain tissues, some of which may not be readily accessible.
- Potential types of genetic analyses in the Study include variation in gene sequence, variation in gene expression, hypothesis testing, hypothesis generating, candidate genes, whole genome analysis, genetic information, and epigenetic information.
- Issues to consider in planning for collection of genetic information include types of specimens (essential, optional) from child and family members, timing of specimen collection, ensuring sufficient quantity of genetic material, and technology for genetic studies.

- Issues to consider in planning for collection of genetic information include (1) types of specimens (essential, optional) from child and family members (for example, peripheral blood, cord blood, buccal cells, placenta; sampling of parents, grandparents; sampling of subsets of participants for specific studies), (2) timing of specimen collection (for example, one or multiple collection points; integration with collection for other biologic studies), (3) ensuring sufficient quantity of genetic material (for testing core hypotheses, for testing in multiple studies over time), and (4) technology for genetic studies (rapidly evolving technology, increasing use of genome-wide scans, potential for whole genome sequencing at reasonable cost in near future).
- Workshop conclusions and recommendations are as follows:
  - It is essential to collect biologic materials to study both genetic variation and gene expression.
  - Collection, storage, and analytic approaches need to be reconsidered as studies are developed and new technologies become available.
  - Planning should focus on collection of high-quality biologic specimens for genetic studies and storage of sample aliquots for genomic DNA, RNA, protein; whole genome amplification; and cryopreservation.
  - Specimens to be collected from the child include cord blood collection (key), peripheral blood sampling in early and late childhood (key) and blood spot in infancy (desirable).
  - Family members should also be sampled, including mother, father, and, if possible, siblings enrolled in the Study.
  - Flexibility is desired to add other collections in certain situations such as acute, unpredicted exposures.

### **Research on a Complex Trait: Can the Task Be Accomplished?**

*Jeffrey C. Long, Ph.D., NCSAC member, University of Michigan*

- A complex trait is any trait whose expression is influenced by more than just the alleles at a single genetic locus. A complex trait shows familial aggregation; its transmission patterns do not follow Mendel's laws; and it can be continuous or dichotomous.
- Environment affects the trait's complexity. Many genes affect the trait with or without environment. This is interaction with nonadditive contributions from different genetic and/or environmental causes. Measurement, imprecision, scale, and categorization help to make a trait complex.
- There are several models for complex traits, including simple Mendelian, simple Mendelian plus environment, and genotype x environment interaction.
- There are two basic strategies for analysis of complex traits.
  - **Genetic linkage:** The strategy is to show that an unknown locus that contributes to the complex trait is linked to a genetic marker locus with a known location on the genetic map (that is, does not freely recombine with).
  - **Candidate gene association:** A candidate gene is a gene with a known physiological function related to the complex trait. In the broadest sense, it is any gene that might have a role in the etiology of a disease, that might regulate gene expression or protein formation, or that might be associated with a variant having any of the above effects.
- Data structures for complex trait analysis include (1) randomly sampled individuals (allows tests for association, sensitive to population stratification), (2) parent-offspring trios (allows

tests for linkage and association, robust to population stratification at cost of statistical power), (3) sibling pairs (allows tests for linkage and/or association, flexible but less powerful design), and (4) nuclear families or extended pedigrees (more powerful than sibling pairs, more difficult to collect data).

- Approaches to complex trait analysis include (1) improved phenotype definition (narrow phenotypes, endophenotypes, constellations), (2) targeted sampling designs (genetic isolates, extreme environments), and (3) ascertainment strategies (case-control, extended families, affected relatives).
- In sum, researchers cannot expect to understand the roles of either genes or environments in isolation of the other. A purely genetic approach may mislead; by the same token, a purely environmental approach may also mislead. Phenotyping is the rate-limiting step in both endeavors. Researchers should proceed simultaneously.

## **Human Subjects Review: Sample Storage and Biobanking**

*Dr. Fleischman*

- Important aspects of obtaining genetic information are the widespread belief in “genetic essentialism,”—the belief that genetic information is a basic part of being human—and “genetic determinism,” the belief that our health outcomes are determined primarily by our genes. In addition, genetic information affects our personal identity by relating to “FACE” (family, ancestry, community and ethnicity).
- It is important for the Study to be aware, concerned, and responsive to these ethical considerations.
- Important aspects of human subjects review include:
  - What is being studied?
  - Disclosure of results (yes, no, maybe)
  - Description of genetics-related risks (for example, breach of confidentiality, considerations of “group” harms)
  - Future use of samples or data
  - Withdrawal of samples or data.
- A critical challenge in human subjects review is idiosyncratic local IRB review and informed consent style concerning genetic information, including disclosure; stored samples/future studies; minimizing risks of breach of confidentiality; right to withdraw from study/samples from storage/data from bank; and development, in the future, of new information that is clinically relevant.
- Important aspects of biobanking include identified samples/deidentified samples, obtaining general consent for future studies, and the Health Insurance Portability and Accountability Act of 1996 Privacy Rule (HIPAA), which specifies that all direct identifiers must be removed. What is not clear is whether a participant can give a single consent for the collection of future medical records and the long-term storage of biologic samples.

## Comments from the Genetics Panel

- The clinical validity of gene-disease associations is likely to be unknown for most Study participants. Findings need to be replicated. There is a great potential for spurious findings.
- Predictive limitations need to be clearly conveyed to Study participants and health care providers. Although genetic information has limited predictive value, it can sometimes be valuable in indicating risk.
- There are a variety of potential uses of genetic information. Associations of genetic risk factors with therapeutic outcomes may prove valuable to health care providers. The Study may help to develop clinically significant applications of genetic information.
- Analytical strategies may influence Study approaches. Will the Study test all participants? Will the Study test for specific outcomes? When outcomes become evident, will the Study retrospectively examine genetic information? Will the Study follow potential risk factors over time to assess associated outcomes?
- There is no obligation to do the genetic testing at the moment of collection.
- The Study needs to anticipate that clinically or socially important findings could be discovered inadvertently, and it needs to plan appropriate responses to such discoveries.
- Laboratories need to be Clinical Laboratory Improvement Amendments (CLIA) certified to provide individual findings to the Study participants who request it.
- The Study provides an opportunity to explore large study designs in a vulnerable population—children.
- It is critical that researchers learn how to conduct large population studies, and the Study will greatly influence future research.
- The Study should provide valuable findings on genomics, proteomics, transcriptomic, epigenetics, and DNA modification.
- Studying family structure is important but adds ethical complexity.
- One of the most effective genetic tests is family history. The Study should collect accurate family history information.
- Findings on pharmacogenetics and pharmacogenomics will help to improve efficacy and decrease adverse events and side effects due to genetic variation, particularly in children.
- The Study should attempt to use national review committees instead of local IRBs.
- The Study should educate participants and families on the role of genetics in the Study and educate the public on avoiding the trap of genetic determinism.
- The Children's Oncology Group provides an example of a central IRB collaborating with many local IRBs; local IRBs may cede their authority to a central or national IRB but have no legal obligations to do so.
- The Study will use the NICHD IRB, but it will also attempt to bring together IRBs from the Vanguard Centers and Coordinating Center through cooperative agreement to collaborate and address issues such as informed consent, liability concerns, and legal risks.
- An innovative approach with the help of OHRP may provide appropriate regulatory support to centralize diverse institutions and their IRBs.
- A process to protect human subjects must be established that is both consistent with the original consent and intent of the Study.
- The Study began creating an Information Management System (IMS) two years ago to adequately protect individual data in accordance with confidentiality standards and HIPAA regulations.

- Study participants may refuse genetic testing. This decision will not make the individual ineligible.
- Study participants may choose to leave the Study for a period of time and then wish to re-enroll after a period of absence.

## **Peer Review of the Study Protocol: Potential Mechanisms**

*Dr. Fleischman*

- The Study protocol is being developed with input from many groups and sources, including working groups; the ICC; the Program Office; development of hypotheses, exposures, and outcomes; and the Study plan.
- Additional development will come from Steering Committee input and review, ICC review, and potentially peer review.
- All R01, R03, R15, R21, and P01 subprojects receive peer review through a formal NIH committee structure.
- Special emphasis panels (formed on an ad hoc basis for reviews requiring special expertise or in special circumstances) provide review for scientific and technical merit, qualifications of principal investigators and research team, availability of resources, budget, and other factors (for example, human subjects).
- Peer review criteria include:
  - **Significance:** Does this study address an important problem?
  - **Approach:** Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project?
  - **Innovation:** Does the project use novel concepts, approaches, or methods?
  - **Investigators:** Is the principal investigator appropriately trained and well suited to carry out this work?
  - **Environment:** Does the scientific environment contribute to the probability of success?
- Questions posed for NCSAC discussion were:
  - Should the National Children’s Study Protocol undergo peer review?
  - If yes:
    - What is the most appropriate mechanism for review?
    - What are the most appropriate criteria for review?
  - Could the Institute of Medicine (IOM) review?
  - If yes, can the Study be fast-tracked through the IOM?

## **NCSAC Recommendation**

The NCSAC reached consensus and agreed on the need to peer review the Study protocol. Peer review will give the National Children’s Study scientific credibility within the scientific community. How the peer review will proceed (that is, the actual peer review process) and the group that will do the peer review need to be further evaluated. The timeframe for the peer review process and the independence of the peer reviewers are important concerns.

## Adjunct and Core Study “Outside” Proposals and Public-Private Partnerships: Review Process

Marion J. Balsam, M.D., NCSAC Executive Secretary, Study Research Partnerships Program Director, Study Program Office, NICHD, NIH, DHHS

- Adjunct study and public-private partnership concepts were discussed at the April 2005 NCSAC meeting, including ethical issues and plans to develop the review and approval process.
- The Program Office and ICC subsequently discussed the need for a review and approval process for outside proposals of additions to the core protocol.
- The conclusion was to develop a single review and approval process for both the adjunct studies and the additions to the core protocol (largely applicable to public-private partnerships as well).
- Issues to consider in the review and approval process include:
  - Sheer volume of proposals anticipated (for core protocol, adjunct studies, public-private partnerships)
  - Communication requirements and the back-and-forth reworking of the iterative review process
  - Breadth and complexity of the science and proposals
  - Various levels of review as appropriate for Study structure
  - Various proposal types require different reviews (thus, many steps in the process are “as indicated”)
  - Retain the integrity of the Study (quality, ethics, burden, and so on)
  - Streamline the process and facilitate timely review to the extent possible.
- Review of adjunct studies, “outside” proposals, and public-private partnerships is an iterative review process that will be coordinated by the Program Office.
- Steps in the iterative review process could occur concurrently, in a parallel manner.
- Basic concepts of the iterative review process include:
  - **Program Office:** Initial general review, tracking, communications, facilitating the review process
  - **ICC:** Formal review for scientific fit/merit, burden (participant and study), cost, ethical considerations, refer for technical review as indicated
  - **NCSAC:** Concept review as indicated
  - **Steering Committee:** Review (fit/merit, burden, logistics, and so on)
  - **Program Office:** Preliminary approval; facilitates peer review and funding; coordinates with Study Centers; facilitates OMB; IRBs (NICHD/local); data use plan; contract modifications
  - **Program Office:** Final approval
  - **Study Centers:** Implementation.
- Proposals involving specific Study centers would be coordinated early in the process with the relevant principal investigators.
- Participant burden will be a major issue of consideration for all proposed adjunct studies.
- Maintaining the integrity of the Study is a key issue in considering all adjunct studies.

The Concept Review Subcommittee met during a working lunch session on September 21, 2005.

## Potential Impact of the National Children’s Study on Priority Health Outcomes

*Dr. Scheidt*

- Research findings have led to successful prevention/intervention measures and have subsequently led to significant declines in targeted health outcomes.
- Case studies on the impact of research on health outcomes include:
  - **Sudden infant death syndrome (SIDS):** There was a 57 percent decline in the U.S. SIDS rate from 1991 to 2001.
  - **Framingham Heart Study:** Mortality rates from cardiovascular disease fell 42 percent; researchers estimated that one-third of this decline was attributable to Framingham (13–20 percent) and estimated \$455 billion in annual savings from 1970 to 1990.
  - **Lead poisoning:** There was an 87 percent decrease in geometric mean blood lead levels, with lifetime economic benefits ranging from \$110 to \$318 billion per annual cohort.
- The bases of analyses for estimating the potential economic impact of the Study include:
  - For economic burden, *Revised Annual Costs to the U.S. from Selected Disease Burden*, April 6, 2004
  - Analysis attempted to underestimate potential reductions in health outcomes (not all hypotheses will be verified)
  - Estimates are imprecise with a wide range of error.
- An analytical study of potential Study impact on 10 selected health outcomes estimated significant cost reductions.
- The conservative estimate of the total annual economic savings attributable to Study impact on the 10 health outcomes ranged from \$4.6 to \$10.7 billion.
- The researchers made the following conclusion on the Study’s economic impact: It appears that a beneficial impact from the Study on the priority outcomes of any measurable level would more than compensate for the cost of the Study.

## The National Children’s Study: A Clinician’s Perspective

*Donald J. Dudley, M.D., NCSAC member, University of Texas Health Science Center at San Antonio*

- The patient in need may ask her clinician the following questions:
  - “Why did I have a miscarriage?”
  - “Why was my baby born premature?”
  - “Why did I have preeclampsia?”
  - “Why does my child have asthma?”
  - “Why does my child have diabetes?”
  - “Why is my child autistic?”
- The physician in need answers: “I don’t know.”
- A brief historical perspective of the Collaborative Perinatal Project (CPP) follows:
  - From 1959 to 1965, about 59,000 pregnancies were recruited (42,000 women; about 7,000 had more than one pregnancy).
  - CPP collected extensive data regarding pregnancy, labor, and delivery.
  - The study’s goal was to determine the degree to which perinatal events contributed to cerebral palsy, mental retardation, and epilepsy.

- CPP was a multicenter study with 12 sites. It tested children up to age 8, collected extensive amount of data collected on mothers and their children, and produced tangible results (738 papers published, with data still untapped).
- CCP changed obstetric practice:
  - Mid-forceps delivery ceased
  - Showed that episiotomy was not useful
  - Cerebral palsy from antepartum events, not intrapartum (85 percent)
  - Inflammation associated with prematurity
  - Maternal hypothyroidism and poor outcomes
  - Drug use during pregnancy
  - Dangers of adolescent pregnancy.
- CPP changed pediatric practice:
  - Unparalleled data on growth and development of children
  - Changed management of neonatal jaundice
  - Changed management of febrile seizures
  - Led to the development of the rubella vaccine.
- Now is an appropriate time to implement the Study because of problems with CPP (not hypothesis driven; too many collaborators hindered progress; does not address contemporary problems) and recent advances in medical care (before ultrasound, fetal monitoring, widespread use of cesarean delivery and epidural analgesia, and development of neonatal intensive care units).
- There are three advantages of the Study:
  - It will be the largest study ever done of obstetrical complications such as miscarriage, stillbirth, preterm birth, and preeclampsia.
  - It will be the largest study ever done of pediatric diseases and problems such as asthma, diabetes/obesity, autism, injury, and fetal origins of adult disease.
  - It will be the largest study done of healthy children; it will examine determinants of child health and normal and abnormal development.
- The Study is analogous to the Human Genome Project because it is a bold initiative that is expansive in scope, expensive to perform, controversial, and criticized. The Study will be a landmark achievement that affects almost all aspects of biomedical research, and it will produce many major spin-off studies (such as studies that focus on gene-environment interactions).

## **Clinical, Economic, and Regulatory Implications of the National Children's Study**

*Jerome A. Paulson, M.D., George Washington University*

- Primary care pediatricians are often confronted with environmental health questions from patients and families that they cannot answer:
  - What is the impact of the mercury consumed from fish on breastfeeding children?
  - What is a child's risk of developing cancer from pesticides sprayed near schools?
  - Are there any risks associated with a baby's exposure to fragrances from plug-in air fresheners in the baby's room?
  - Are there any risks associated with chemicals released from a newly purchased crib?
- Questions such as these can be answered through a long-term, prospective study that tracks a very large number of factors, including social factors; naturally occurring and man-made

influences; physical factors, including chemical and other physical factors; biological exposures; psychological factors; educational factors; genetic factors; and cultural influences.

- The Study will answer numerous other questions, many of which researchers and clinicians do not even know to ask today.
- Another prospective study, CPP, answered questions about relationship between events occurring during labor and delivery and the risk of developing cerebral palsy. It also answered a number of other questions. For example, the minimally increased risk of developing epilepsy and the nominal risk of becoming retarded as a result of febrile seizures.
- As co-director of the Mid-Atlantic Center for Children's Health and the Environment, Dr. Paulson manages 1 of 11 Pediatric Environmental Health Specialty Units in the United States. The unit provides education on issues related to children's health and the environment, and it responds to questions from parents, physicians, and public health officials about children's health and the environment.
- Pediatric Environmental Health Specialty Units are funded by the Agency for Toxic Substances and Disease Registry and EPA to answer questions from parents and professionals about the impact of the environment on a child's health. The Study will help answer to these questions.
- The Study, both in the short and long term, will generate information about the links between the genetic makeup of human beings and the differential outcomes that occur when different individuals sustain the same or similar exposures.
- Because the Study will have data and biological specimens stored for the long term, researchers will be able to retrospectively study episodes of exposures that were not recognized prospectively. For example, a researcher will be able to test a hypothesis about the possible link between a child's exposure to a newly developed chemical and later health outcomes.
- The Study will be a major undertaking, but the United States excels at major undertakings (for example, space exploration to the moon, the Hubble Space Telescope, mapping the human genome).
- The Study's cost is dwarfed compared with the cost of treating diseases or disabilities associated with low birth weight and preterm birth, asthma, diabetes, and obesity—all of which have environmental components.
- NICHD estimates that the major chronic diseases the Study will address directly cost the United States \$269 billion per year. If the Study were to result in only a 1-percent reduction in those costs, the expense of the entire Study could be recouped in a single year.
- Patients who are cared for by pediatricians of the future will be healthier as a result of the information gathered from the Study.
- Pediatricians of the future will be much better physicians as a result of the information gathered from the Study.
- The information that will be derived from the Study will be of great importance to the health of children in the United States and to the health of children around the world.

## Science in Support of Environmental Protection: Regulatory Implications of the National Children's Study

William H. Farland, Ph.D., Acting Deputy Assistant Administrator for Science, EPA

- Research and Development at EPA consists of 1,900 employees; a \$600 million budget; \$70 million extramural research grant program; 13 laboratory or research facilities across the United States; and credible, relevant, and timely research results and technical support that inform EPA policy decisions.
- Making decisions with sound science requires relevant, high quality, cutting-edge research in human health, ecology, pollution control and prevention, and decision sciences; proper characterization of scientific findings; and appropriate use of science in the decision process.
- Research and development contribute uniquely to health and ecological research, as well as research in pollution prevention and new technology; in-house research, partnerships, and an external grants program; and problem-driven and basic research.
- The data needs for risk assessment can be pollutant specific and can include methods development.
- Data for risk assessment are generated by EPA scientific research and data collection, external input into research and assessment, and collaboration among government agencies, academia, industry, and private groups.
- The field of risk assessment began in the 1970s with an emphasis on oral administration routes per FDA precedence and now integrates the concept of life stage and variable susceptibility.
- The Food Quality Protection Act of 1996 and the Safe Drinking Water Act, as amended 1996, authorized risk assessment in infants, children, and pregnant women.
- In 1994, the National Research Council urged EPA to assess risks to infants and children whenever it appears that their risks might be greater than those of adults.
- Although “children’s risk” can mean different things to different people, EPA is interested in both the effects manifested during childhood and early-life exposures that can contribute to effects at any time later in life.
- The *Child-Specific Exposure Factors Handbook* provides a summary of the available and up-to-date statistical data on various factors assessing children’s exposures. These factors include drinking water consumption; soil ingestion; inhalation rates; dermal factors including skin area and soil adherence factors; consumption of fruits, vegetables, fish, meats, dairy products, homegrown foods, and breast milk; activity patterns; body weight; consumer products; and life expectancy.
- EPA develops supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogens to analyze the data pertinent to cancer risks following early-life exposures; develops approaches that are consistent with the state of the science and health-protective when critical information is absent or uncertain; and allows these approaches to be updated when there is new information or new understanding.
- Key features of the Study include (1) environmental samples and observations (for example, air, dust, soil, water, biologic; age-related human activity patterns) and (2) child development outcomes (for example, functional, physical growth, motor/sensory development, physiologic, cognitive, social, emotional, psychiatric).
- Computational toxicology involves genomics/proteomics, computational methods/bioinformatics, and variability in exposure and susceptibility.

- Applications of toxicogenomics to risk assessment include pattern recognition for exposure assessment, cross-species extrapolation, understanding mechanisms of toxic action, input to biologically-based toxicokinetic and toxicodynamic response models, and identification and characterization of sensitive life stages or individuals.
- The science of risk assessment is evolving to focus on the “real world” need to address complex chemical exposures in the environment.
- To meet this challenge, better and different data and innovative tools and approaches must be developed.
- Based on current trends, future regulatory mandates will use and further the development of such assessment approaches.
- A partnership of environmental health professionals in the public (local, state, federal) and private sectors (environmental, academia, industry) will be needed to address these emerging challenges.

### **Support of the National Children’s Study: National Medical Association**

*Renée R. Jenkins, M.D., F.A.A.P., Past Chair, Pediatric Section, National Medical Association*

- The National Medical Association (NMA) was established in 1895. Its mission statement includes commitment to the elimination of health disparities. It represents the interests of 25,000 African-American physicians in all medical fields, with 100 affiliate societies in the United States and its territories. NMA policy is formed through a house of delegates. The association publishes the *Journal of the NMA*. Its Web site is [www.nmanet.org](http://www.nmanet.org).
- The NMA organized the Commission to End Health Disparities with the American Medical Association and National Hispanic Medical Association and 34 other health professional organizations, and it formed the Cobb Institute—an internal division to coordinate health disparities program activities.
- The Pediatric Section has about 700 members who are primarily African Americans. The pediatric section evolved from a practicing physician majority to a more diverse group including health administrators, academicians, and pediatric subspecialists. The research practice network, Advocacy Committee, is chaired by Earnestine Willis of the University of Wisconsin. An annual program addresses health disparity issues.
- A Pediatric Section resolution, adopted in July 2005, recognizes the opportunity for inclusion of protective as well as risk factors (that is, asset approach) within subgroups and inclusion of fathers. The resolution supports the community engagement process in planning, promotes community-based participatory research principles in the design, and endorses the Study as a unique opportunity to advance biomedical and neurobehavioral science for child health guidance, intervention, and policy for the future.
- To improve Study opportunities, the Pediatric Section will support the Study through organizational policy (resolutions); disseminate information through the NMA newsletter; encourage membership to join the Study Assembly and participate in regional forums; and continue its dialogue with the NCSAC to identify topics, research questions, and approaches as the Study progresses.
- The NMA promotes an integrative model of developmental competencies for minority children, which includes the impact of social position as mediated through racism, prejudice, discrimination, and oppression; segregated contexts as defined by residential, economic,

social, and psychological dimension; and concepts representing “nonshared” experiences, with mainstream populations defining unique developmental pathways for children of color.

### **The National Children’s Study: A Unique Opportunity**

*Lee Salamone, Director, Public Health and Science Policy Issue Group, American Chemistry Council*

- The American Chemistry Council (ACC) is a trade association that represents the leading companies engaged in the business of chemistry, which provides innovative products and services to make peoples’ lives better, safer, and healthier. Chemical manufacturing is a \$450 billion enterprise and a leading exporter. Chemistry companies invest more in research and development than any other business sector.
- The ACC’s mission is to improve environmental, health, and safety performance through responsible care; apply common sense advocacy designed to address major public policy issues; and promote health and environmental research and product testing through programs like the High Production Volume Challenge and the EPA Voluntary Children’s Chemical Evaluation Program pilot.
- ACC board-approved principles on children’s health since 1999 include protecting children, relying on science for risk-based decision making, focusing resources on issues of greatest concern, providing relevant information in an appropriate context, and building on existing government and industry research and testing.
- The Study is important because of the need for information on changing patterns of disease in children and the need for a scientific basis for public policy. Researchers and clinicians want to know what contributes to healthy and unhealthy development in children and want to improve children’s lives. The time is right for the Study, new tools are available, and there is a new understanding that environment as a whole needs to be assessed and addressed.
- ACC supports the Study because it uses a broad definition of environment (physical, chemical, biological, social), has a long-term approach, uses a large, national probability sample, focuses on gene-environment interactions, provides the opportunity to answer important questions, and will produce a national resource.
- The ACC supported the Children’s Health Act of 2000. Its scientists participated in working groups and on the NCSAC. ACC outreach is aimed at raising awareness of the Study on Capitol Hill and within ACC membership. The ACC provides yearly support for appropriations for the development of the Study as defined in legislation. The ACC maintains active partnerships with other groups that support the Study, making for a stronger overall coalition.
- The ACC continues to support the Study and is willing to partner with other organizations to increase the collective likelihood of success.

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Juanita Sims Doty, Ph.D., University of Mississippi  
Alexa Fraser, Ph.D., Westat  
Eugenia Guardia, Booz Allen Hamilton Inc.  
Doris B. Haire, American Foundation for Maternal and Child Health  
Roy Hoffman, M.D., M.P.H., FAAP, Office of Disease Prevention and Health Promotion, DHHS  
Anne E. Imrie, Science Applications International Corporation  
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Susan S. Lundquist, M.Sc., Office of Environmental Information, EPA  
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Jennifer Stempel, Education Development Center, Inc.  
Warren J. Strauss, Sc.M., Battelle Memorial Institute  
Ritu Tuteja, M.P.H., National Center for Environmental Research, EPA  
Cindy S. Ziker, Ph.D., Arizona Department of Education

*I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.*

\_\_\_\_\_  
Date

\_\_\_\_\_  
Alan R. Fleischman, M.D.  
Chair  
National Children's Study Federal Advisory Committee