National Children's Study Assembly Meeting
Breakout Session Summary: International Collaboration
November 29, 2005
Omni Shoreham Hotel
Washington, DC

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).

Co-Chair: Danuta M. Krotoski, Ph.D., Acting Associate Director, Prevention Research and International Programs, NICHD, NIH, DHHS

Co-Chair: Jenny Pronczuk, M.D., Medical Officer, Department of Protection of the Human Environment, World Health Organization, Geneva

Invited Participants:
Sheryl Bartlett, Ph.D., Healthy Environments and Consumer Safety Branch, Health Canada
Terry Dwyer, M.D., M.P.H., Murdoch Children's Research Institute, Royal Children's Hospital
Tye Arbuckle, Ph.D., Biostatistics and Epidemiology Division, Health Canada
Margaret Jean Golding, Ph.D., D.Sc., F.S.S., Avon Longitudinal Study of Parents and Children, University of Bristol
Susan Morton, Ph.D., MBChB, School of Population Health, University of Auckland
Georges Salines, Environmental Health Department, National Institute for Public Health Surveillance, France
Lorenza Mariscal Servitje, M.Sc., Health Promotion Department, Mexican Secretariat of Health

(Two sessions of this breakout session were held on November 29, 2005.)

Welcome and Introduction

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Dr. Krotoski began by showing a video developed as an outcome of collaboration between the National Children's Study IIG and the World Health Organization (WHO). She noted that many longitudinal studies are in industrialized countries, and there is a need to learn more about the situation in developing countries. Information in the video included:

Dr. Salines said that the ELFE study design is quite different from the international children's study: ELFE will enroll all the babies born on certain days of the year and send people to collect data and blood samples on these specific days. He noted that the beauty of that system is the definition of the sample; however, exposures during pregnancy must be assessed retrospectively. This compromise resulted from merging the two studies. Older studies can be used as validation samples to validate the measurements obtained in ELFE. The specific Web site for this project is: http://www.elfe.ined.fr. The site includes links to many longitudinal studies in Europe:

- http://www.birthcohorts.net/
- http://www.fhi.no
- http://www.generationr.nl.

Healthy Environments and Consumer Safety: Canadian National Children's Study

Tye Arbuckle, Ph.D., Biostatistics and Epidemiology Division, Health Canada, and Sheryl Bartlett, Ph.D., Healthy Environments and Consumer Safety Branch, Health Canada

Drs. Arbuckle and Bartlett described their vision for a national children's study in Canada, something planned and dreamed about since 2000. The long-term goal would be to reduce the disease burden for children caused by environmental risks such as asthma, various cancers, adverse pregnancy outcomes, birth defects, and adverse effects on the immune system. Achievement of two objectives would move toward this goal:

- Objective 1: Improve management of known risks to children's health.
  - Key environmental risks to children's health involve poor air quality; contaminants in food, water, indoor air, and consumer products; radon and UVB radiation; and noise. Canadian children spend a lot of time inside, making indoor air quality and radon especially important.
  - Existing legislation and federal programs should be strengthened to better protect child health.
  - Parents, communities, industry, and health professionals can be enabled to manage risks to children's health and/or provide advice to reduce these risks.
- Objective 2: Improve understanding of environmental risks and children's health. Key gaps in knowledge include:
  - The effects of low level exposures to chemicals and chemical mixtures
  - Exposure levels in real life settings (especially indoors)
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  - Research on children's environmental health issues within government and universities.

They were excited about becoming a partner with the National Children's Study. Canada does not have centers for children's environmental health, even though there was mounting concern that the environment was impacting children's health. The limited Canadian data were based on small, localized studies, and there was limited research capacity in this area.

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- Access to the wealth of preparatory work done for the National Children's Study

behavior, among others. The study tried to collect as much information as possible from the community and the families in the study.

Self-completion questionnaires were used, which were validated by many pilot projects. Four questionnaires were sent during pregnancy, with charming interviewers who cajoled responses out of 94 percent on the first questionnaire, slightly less on later ones. Children began to ask for their own questionnaires, so coloring books were used for 5-year olds and real questions as they got older. Questionnaires were also sent to teachers.

Other sources of information included:

- Health records
- Biological samples
- Environmental monitoring (done in a subset of homes)
- Education records and examination results
- Hands-on assessments (after the age of seven, the whole cohort is invited to come be examined every year, getting information you could not get any other way).

Biological samples included maternal blood and urine, umbilical cord blood and slices, placentas, and children's hair and nail clippings, blood, and urine. DNA has been extracted from the blood of the mother and the children. Surprisingly, there has been no problem getting people to agree to genetic studies. In this study, researchers looked at the chemicals people spray around their houses (such as disinfectant, carpet cleaner, aerosols, air fresheners, paint stripper, and pesticides). These comprise part of the total chemical burden (TCB) a child is exposed to. The statistical relationship between TCB and the occurrence of "persistent wheeze" was found to be very tight. Also, there was a tight association of birth weight with TCB: babies with the heaviest TCB (above the 90th percentile) averaged 100 grams lighter than the rest of the newborn population.

Dr. Golding said that the researchers have tried to collaborate with people in many fields. They started with 14,500 pregnancies, and 11,500 are still being followed. The popularity of the study among the participants is great. The children get something out of it, the parents think they get something out of it, and they are convinced that they are helping the future. The Web site (http://www.alspac.bris.ac.uk) includes a list of 230 publications and a copy of every questionnaire used in the study.

Discussion

Session participants asked questions and commented about the following issues:

- *Inclusion of genetics and gene-environment interactions in proposed studies and what has been done or will be done with DNA samples.* Dr. Golding responded that when ALSPAC study researchers started with the genetics, they had a long learning curve and gradually got won over. They are just at the beginning of working on that. A number of projects are ongoing to see how the environment interacts with candidate genes. For example, the study has interesting results that show that parents who take paracetamol during pregnancy have

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- Each year, approximately 11 million children in developing countries die before the age of 5.
- Key mortality and morbidity risks are in the air, water, food, and soil.
- Concern is growing about the adult health impact of physical, chemical, and biological risks encountered during critical periods of development.
- Children in developing countries are at increased risk of exposure to infections and insect-borne diseases, smoke, toxic waste, and environmental degradation.
- New and emerging diseases, hormonal disruption, physical and social environment are compounded by poverty, industrialization, and civil strife.
- Children are not just small adults, but require special concern because their central nervous, digestive, and reproductive systems are more vulnerable than in adults. Children are also naturally curious and live closer to the ground.
- There is an urgent need to explore the hazards affecting development and behavior of children and parents in a systematic way.
- Long-term studies track the same individuals, follow their life trajectories, and make ongoing comparisons including the relationship between factors and the cumulative effects of multiple exposures. Such studies have the potential to identify harmful and helpful effects of many factors.
- In conclusion: Every child has the right to grow up in a healthy and safe environment.

The video was produced for the National Children's Study IIG/WHO Working Group by Thea De Wet at the University of Johannesburg in South Africa to raise awareness of the need for long-term studies in low and middle income countries.

National Children's Study: International Activities

Dr. Krotoski emphasized the goal of the long-term studies (LTS) interest group as harmonization of data in order to be able to pool data and thus leverage individual studies. International cooperation permits studies to include a broader range of questions and approaches; global LTS can provide a larger range of exposures as well—different continents, populations, areas. These studies will also provide a basis for identifying genetic and cultural factors in children's health.

The National Children's Study IIG was established in 2002 and has collaborated with the WHO working group on LTS to examine the impact of the environment on children's health in developing countries. They identified the feasibility of longitudinal cohort studies (LTCS) in developing countries and are establishing a common core protocol for all international LTCS to harmonize across cohorts. Twenty countries and the WHO are currently participating in IIG-related international activities. Dr. Krotoski noted the threefold purpose of the breakout session:

- To hear the report from the WHO working group on LTS and the impact of the environment on children's health in developing countries
- To hear reports from new or planned cohort studies
- To recognize the challenges and opportunities for collaboration among cohorts.

Longitudinal Cohort Studies on Children's Health and the Environment

The WHO working group on LTS on environmental threats to the health of children in developing and industrialized countries works to stimulate studies that will identify environmental threats to children's health. They also ensure comparability of data collected across countries by use of a common protocol for LTS to be undertaken in low and middle income countries. Dr. Pronczuk presented an update on the National Children's Study IIG/WHO collaboration.

Children represent the present and the future of our societies. She observed that children in developing countries are particularly sensitive to environmental threats. The unhealthy, unsafe, degraded environments contribute to the loss of approximately 11 million children younger than age 5 who die from perinatal causes, diarrheal diseases, and other health problems compounded by malnutrition, infections, and unregulated chemicals in the environment. A graph produced by WHO compared the basic, modern and emerging environmental factors influencing children's health:

- Basic: Unsafe water and food, indoor air pollution, and vectors
- Modern: Unsafe use of chemicals, traffic and industry, environmental degradation
- Emerging: Climate change, ozone depletion, nanoparticles, endocrine disrupters, radiation.

Children in developing countries are subjected to a combination of the basic risks typical of less developed countries and modern risks as a result of industrialization and globalization.

For children younger than age 5, the disease burden is strongly linked to environmental factors that include unsafe water, sanitation, and hygiene, indoor smoke from solid fuels, lead exposure, climate change, and ambient air pollution. All of these contribute to the major underlying cause of childhood morbidity and mortality, being underweight.

The Working Group on LTCS established in conjunction with the IIG of the National Children's Study has as its goal to stimulate international cooperation in LTCS. These efforts were cosponsored by the EPA, the NIH, and the CDC. Four consultations were held from October 2003 through August 2005. The first consultation discussed the feasibility of undertaking long-term studies in developing countries and identified challenges and benefits. The second identified the key issues, the third proposed core hypotheses, and the fourth developed a set of measurements and a matrix to be used in preparing the core protocols for studies in low and middle income countries.

Planned or existing LTCS in North America, Europe, South America, Africa and Thailand provide opportunities for collaboration and harmonization. Coordination among these studies will provide an opportunity to address rare conditions and environmental changes, as well as the effects of rapid socio-environmental change (obesity, dyslipidemia, diabetes, and cardiovascular disease). Such studies can also address prenatal influences on the baby's development such as the mother's nutrition and health (such as hypertension and diabetes).

LTCS offer collateral benefits to the public health systems of developing countries by:

- Improving children's health care
- Strengthening surveillance services
- Transferring new technologies
- Improving data management
- Building/coordinating research capacity.

Dr. Pronczuk noted that LTCS address two of the Millennium Development Goals:
- Goal #4: to reduce child mortality, and
- Goal #7: to ensure environmental sustainability.

Participation in LTCS would require adoption of internationally agreed-upon systems for such factors as sampling and storage, analytical methods, and data management. Participating countries should have accurate health records, low migration, and good public education. Finally, LTCS should involve partners from academia, national and international organizations, recognized nongovernmental organizations, the private sector, and participating communities.

Seven core hypotheses have been agreed upon:
- Respiratory effects
- Pregnancy outcome
- Neurodevelopment
- Growth and development
- Injuries
- Birth defects
- Childhood cancer.

Each of these hypotheses requires identification of specific hypotheses, background global data, main risk factors, knowledge gaps, and potential benefits.

One of the challenges identified at the fourth consultation in August 2005 was specimen collection. How should specimens be collected? How should they be stored? When should sampling take place? One recommendation is that samples could be collected at the time of vaccination—but this varies from country to country. Other challenges include data collection. A model questionnaire is being tested in Argentina that contains a concise set of questions that summarizes basic environmental information and could be extended to other countries though would need to address cultural differences. The Working Group has developed a matrix for sampling and data collection, which will be refined over the next year agreeing on definitions and terminology, informatics support, ethical aspects, community involvement incentives, and other factors. A white paper is planned for publication in 2006.

Longitudinal cohort studies on the environment are receiving increased political support. At the June 2005 meeting of the Health and Environmental Ministers of the Americas countries in Mar del Plata Argentina, the ministers issued a declaration advocating pursuit of long-term studies on the environment and children's health. It is hoped that the next ministerial meeting in Southeast Asia in 2006 will result in a high level declaration endorsing the importance of these types of

long-term studies. A partnership is needed between health and environmental sectors. Health and environment should work together.

ELFE: French Birth Cohort Study

Georges Salines, Environmental Health Department, National Institute for Public Health Surveillance, France

Dr. Salines described the ELFE program (French Longitudinal Study since Childhood), a cohort study that will enroll 20,000 children beginning in 2008 or 2009, a representative sample of newborns in France. Its dual objectives are in social science and public health with an emphasis on environmental health. ELFE resulted from a merging of two major earlier projects. In the field of social sciences, questions addressed the effects of poverty and social policies, consequences of family composition, mother's employment, and long distance commuting. In the field of health, questions addressed exposure levels to physical, chemical and biological factors during pregnancy and early childhood, the origins of obesity, and the early origins of violent behavior and risk-taking. In July 2002, Dr. Henri Leridon (INSERM) proposed a cohort project in the social sciences, and in 2004 the French government adopted a health action plan, which included an epidemiologic study of children. This latter plan was linked to the National Children's Study and had the objective of describing the growth and development of children, their exposure to pollutants, and their health. In June 2005, these two initiatives merged. Although their objectives were different, they had the same outline: a cohort of 20,000 children, nationally representative, starting in 2008 with long-term follow-up.

The main characteristics of the study are:

- Nationally representative sample of birth that includes all babies born on certain days of the year, which makes it easy to follow the children
- Integration of social and health concerns, retaining emphasis on environmental health
- Strong links with various existing surveys and registries: Birth Survey, Health Survey of School Children, Ministry of Education Panel, INSEE Permanent Demographic Sample, Specialized Mother-Child Cohorts
- Great variety of data collection methods, including a brief face-to-face interview with the mother soon after the baby's birth; after 6 weeks another face-to-face interview, then a series of interviews and exams.

The large cohort has advantages and limits. Advantages include:

- Statistical power
- Designed to be representative of births in the general populations
- Can address different kinds of objectives and pool various projects and partners.

Limits of the study are:

- Participation (and thus representative character) is difficult to maintain.
- Data collection, particularly for biological samples, has to be very restricted.
- Inclusion at birth.

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Benefits of a Canadian collaboration with the National Children's Study include:

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- Broader collaboration on research questions of mutual interest
- Shared protocols, which would allow for pooling data to increase sample size, as well as exploring the differences between the experiences of the countries with respect to climate, policies, ethnic make-up, culture, and other factors
- Opportunity to share new technology and techniques and build capacity in Canada in a number of research areas
- The breadth of health determinants of interest in the National Children's Study; can explore research areas of mutual interest
- Contributing to the international cohorts and communities of practice.

Concerns regarding the Canadian collaboration with the National Children's Study are:
- Research and laboratory capacity and expertise: there are always funding problems
- Sustainability over the length of the study: funding, personnel, and governance
- Issues of confidentiality, privacy, and transport of specimens across borders
- Is the National Children's Study model flexible enough to excite Canadian researchers?
- Concordance of timelines.

Potential Canadian hypotheses include such topics as the influence of Canadian national daycare program on child growth and development, and environmental exposures and genetic variation interactions and the risk of asthma.

The options available to Canada seem to be:
- Collaborate with the National Children's Study in developing a core protocol and minimal dataset using similar sampling strategy
- Develop a uniquely Canadian study
- Cheer from the sidelines.

In light of upcoming changes in Canada's government, the presenters expressed hope the political climate would allow Canada to join the National Children's Study and the international cohort.

Cohort Studies in Mexico

Lorenza Mariscal Servitje, M.Sc., Health Promotion Department, Mexican Secretariat of Health

Ms. Mariscal Servitje discussed advances that have occurred in Mexico and noted that Mexico has had experience in cohort studies. Although primarily done at the state level, they were helpful in building capacity. Dr. Cravioto worked out development curves with a 10-year follow-up to establish the growth curves used in Mexico. Dr. Rothenberg studied the effects of lead exposure before pregnancy up to 5 and 10 years, and Dr. Olais studied the effects of ozone exposure on pulmonary growth and development.

Mexico also has extensive experience with national surveys. The fields of health, nutrition, and serology have each carried out three surveys in the past 20 years, and serologic banks have records for 10–15 years.

In 2004 in Cuernavaca, the Secretariat of Health began to develop hypotheses about environmental exposures in order to determine which environmental factors to study. These hypotheses focused on the classical physical and chemical exposures. Plans were also made for planning the cohort study; however, no further progress has been made due to financial and organizational changes. Among the environmental health factors considered, some of the less common ones were:

- Built environment
- Media impact
- War and conflict
- Social network and participation
- Life crises.

The current under-secretary of health is very interested in developing this study, as well as a health promotion policy. There are financial concerns with respect to the federal resources for the long term, but the Secretariat of Health is looking at external resources for 2006 from the Pan-American Health Organization and two other foundations. Partnerships are needed for such a large project. Possible partners include Mexico's Children's Hospital, the National Institute of Genomic Medicine, the National Institute of Public Health, and the Center of Infancy and Adolescence.

Future plans at the national level involve a workshop with the partner organizations in March 2006 to develop the outline and programming for the study. At the international level, the Secretariat of Health wants to collaborate with the National Children's Study to see what problems were experienced with the Vanguard Centers, get help with laboratory and technical issues, and explore the possibility of forming a pilot center in Mexico.

Children of the 21st Century: Rationale for a New New Zealand Longitudinal Study

Susan Morton, Ph.D., MBChB, School of Population Health, University of Auckland

Dr. Morton reported that New Zealand is about to start a longitudinal study on children's development. The ministry of social development proposed a longitudinal study some years ago that would cover statistics, education, and labor among other areas. The new study is looking at associations between early life and later status. Association studies from two points in a life, or two studies done in the same sector have been done, but studies that looked across disciplines and crossed the domains of development have been lacking. What was needed was to understand multilevel influences on children related to the environment and in the context of the family and socioeconomic, cultural, and other factors. It is a challenge to create a study that looks across all those variables.

Dr. Morton described a life course approach that crosses domains. Childhood disadvantage can stem from parents' background, physical and mental health, health behaviors, and social, cognitive, and educational factors and may lead to poor adult circumstances or poor health. The rationale behind needing a new life course study is that how all the multifactorial influences act

and interact is not understood. Catching antenatal and intergenerational influences on development will inform prevention strategies directly.

The New Zealand longitudinal study to begin in 2007 or 2008 will require:

- Recruiting a cohort of children from before birth
- Following development over time in the context of their families and the wider environment
- Successful recruitment and retention.

The study will allow a better understanding of the influences on children's developmental trajectories and will provide an evidence base to direct policy to optimize development.

Dr. Morton noted that past longitudinal studies—the internationally acclaimed Christchurch and Dunedin studies in the 1970s—showed continuities in behavior across the life course. They allowed discrimination between associations and possible causal factors and identified risk factors and protective factors across a population. These studies are still going on 30 years later. But the global environment and technology have changed dramatically, and New Zealand is very different from the 1970s. The Asian population of New Zealand increased by 140 percent from 1990 to 2000, and Maori and Pacific populations also increased while the European population changed very little. A new study would capture the population changes. Because prevention is better than cure, the emphasis would be on:

- Promoting healthy development
- Recognition that early intervention is more effective than later remedial action
- Producing healthy adults, which is dependent on having healthy families who grow healthy infants.

Part of the problem is finding a way to develop this study in a short timeframe. Study planners want to allow collaboration and comparison across countries and to see what is unique to New Zealand and what the differences are. For instance, the multiethnic dimension is a characteristic of New Zealand in the 21st century. The goal is to optimize development of pathways for children of future generations.

Children of the 90s

Margaret Jean Golding, Ph.D., D.Sc., F.S.S., Avon Longitudinal Study of Parents and Children, University of Bristol

Dr. Golding said that the overall objective of the Avon Longitudinal Study of Parents and Children (ALSPAC) was "to understand the ways in which the physical and social environment interact, over time, with genetic inheritance to affect health, behavior, and development in children and then into adulthood." The study recruited women from a population of about 1 million people in the area, half in Bristol and half in the surrounding area. To be eligible for the study, a woman had to be expecting a baby between certain dates in 1991 and 1992.

Environmental influences under consideration included weather, hygiene (a factor often ignored in developed countries), housing, socioeconomic circumstances, stress, diet (nutrients as well as pollutants), medication (including over-the-counter medications), and parental attitudes and

behavior, among others. The study tried to collect as much information as possible from the community and the families in the study.

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Discussion

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children more at risk of developing asthma. Does genotype determine how it is metabolized? The study can help sort out cause and effect. Dr. Morton commented that the New Zealand researchers were trying to work this out and that it is a challenge to transport samples elsewhere for analysis. She noted that the government wanted to look at the genetics and how the environment may modify gene expression. New Zealand is not a developing country, but it does have some diseases, like meningitis, that are common in developing countries. Researchers can ask why some diseases like meningitis are differently displayed in the development of the disease and interaction with the environment and genetics.

- *The relationship between birth weight and total chemical burden.* A participant commented that a cohort of people who were within one-half mile of the World Trade Center was compared to children uptown (controlling for economics), and researchers found an effect. There were similar findings in a study in Poland. It is interesting that very nonspecific pollutants seem to have a similar result.

- *Lack of mention of cognitive and mental retardation, fetal ethanol exposure, and neonatal bloodspots (although cord blood was mentioned).* Dr. Golding noted that her study did not use neonatal bloodspots as a source of DNA. Dr. Morton said that cognition is one of the outcomes, one of the eight things they looked at among the factors. Dr. Salines noted that they were still in the planning process, but typically everyone should address these issues.

- *Whether the children in the ALSPAC study may feel different about themselves and that will affect the outcomes (the Hawthorne effect).* Dr. Golding replied that the study has been monitoring this. These children are just as likely as other children to get different conditions. Maybe their self-esteem is better. The researchers could test that by looking at school outcomes (the easiest way of doing it).

- *The argument for creating the Study related to the advantage of research for future analytical investigations and plans to make this resource available to the extramural research community.* The participant mentioned interest in newborn screening resources and large blood collections for genetic studies, noted that some studies will shed light on rare disorders, and expressed hope that there will be interaction with investigator-initiated resources around the world. Dr. Salines noted that a lot of statistical power is needed to look at cancer. Dr. Krotoski said that within the cancer consortium, there will be groups that want to address certain diseases or birth defects. She asked whether anyone had looked at resources for newborn screening in their countries. Dr. Morton responded that newborn screening is just coming in New Zealand. There is concern about collation of data from different sources. Some people would not want their samples to be shared outside the country. A participant noted the same issue occurs with Native Americans and commented that there has to be some sort of opt-in or opt-out option.

Additional Participants

Session A:

Phil Baird, Business Development, Fisher BioServices
Martha Berger, Office of Children's Health Protection, EPA
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