Opportunities for Linking Biomonitoring to Risk Assessment and Public Health in the National Children's Study

EPA/ICCA Biomonitoring Workshop, Sept. 24-25, 2007

Jim Quackenboss
US EPA, ORD/NERL
NCS Interagency Coordinating Committee (ICC)
NCS Program Office
Today’s Presentation

- Overview of the National Children’s Study (NCS)
  - Background
  - NCS Research Plan
  - Proposed Measures
- NCS and Risk Assessment
- NCS and Public Health
National Children’s Study

• Largest long-term study of children’s health and development ever to be conducted in the U.S.
  • Approximately 100,000 children to allow study of important but less common outcomes

• Longitudinal study of children, families, and their environment
  • From before/early pregnancy to age 21

• Environment defined broadly
  • Chemical, physical, behavioural, social, cultural

• A platform for children’s environmental health research
Study Concepts

- **Aims**
  - Identify potential environmental effects: harmful, harmless, helpful
  - For important conditions and diseases of children, identify potential preventable causes

- **Hypothesis driven**

- **Exposure begins with pregnancy**

- **Has power to study high priority conditions (n~100,000)**

- **Gene environment interaction**

- **National resource for future studies**
Hypotheses Necessary for Framing the Study

• Assure answers to “big issue” questions
• Hypothesis required for costly elements
• Input from >2500 scientists, others
• Important for child health & development
• Requires and measurable with sample ~100,000
• Evolving with the science
• Updated hypothesis statements in Research Plan
# Priority Exposures and Health Outcomes

<table>
<thead>
<tr>
<th>Priority Exposures</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Physical Environment</td>
<td>Housing quality, neighborhood</td>
</tr>
<tr>
<td>Chemical Exposures</td>
<td>Pesticides, phthalates, metals, air &amp; water quality</td>
</tr>
<tr>
<td>Biologic Environment</td>
<td>Infectious agents, endotoxins, diet</td>
</tr>
<tr>
<td>Genetics</td>
<td>Interaction between environmental factors and genes</td>
</tr>
<tr>
<td>Psychosocial milieu</td>
<td>Families, SES, institutions, social networks</td>
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<table>
<thead>
<tr>
<th>Priority Health Outcomes</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Pregnancy Outcomes</td>
<td>Preterm, Birth defects</td>
</tr>
<tr>
<td>Neuro-development &amp; Behavior</td>
<td>Autism, schizophrenia, learning disabilities</td>
</tr>
<tr>
<td>Injury</td>
<td>Head trauma, Injuries requiring hospitalizations</td>
</tr>
<tr>
<td>Asthma</td>
<td>Asthma incidence and exacerbation</td>
</tr>
<tr>
<td>Obesity &amp; Physical Development</td>
<td>Obesity, Diabetes, altered puberty</td>
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</table>
2000-present  Pilot studies/methods development
2004             Developed Study Design and Study Plan; Posted Requests For Proposals: Coordinating and Vanguard Centers
2005             Awarded initial contracts (Coordinating and Vanguard Centers)
2007             Completion of the first phase of the Study protocol
2007             Award Wave I Study Center contracts
2008             Reviews and approvals (OMB, Peer review, IRB’s)
2008*            Repository and Laboratory procurements
2008-2009*       Additional Center and Location procurements (wave 2&3)
2008-2009*       Begin pilot cohort at Vanguard Centers (VCs)
2009-2014*       Begin full Study at VCs and additional Centers
2010*            First Study results become available (methods, pilots, preliminary findings)
2015*            Full data set for outcomes of pregnancy
*Pending funding
Funding for the NCS (as of April 2007)

• FY 2000-06: ~ $50m from existing budgets of NICHD/EPA/CDC/NIEHS
  • Infrastructure: Study Plan; Coordinating Center and 7 Vanguard Study Centers...
  • Scientific development: 30 workshops, 20 scientific reviews, 19 pilot studies; hypotheses, exposure and outcome measures, protocol in progress...

• FY 2007: $69m appropriated February 14
  • Prepare for recruitment and enrollment at VG Centers
  • Develop Information Management System
  • Establish additional centers for expanded locations toward full sample

• To conduct the full Study: FY ’08-’34 ~ $3 B
The NCS Research Plan

- The background, design and measures to describe what will be done and why.
- Designed for review
- 600+ pages
- On the NCS website: www.nationalchildrensstudy.gov
Study Sample

1. All Births in the Nation
   - ~4 million births in 3,141 counties

2. Sample of Study Locations
   - 105 Locations
   - Selection of neighborhoods

3. Sample of Study Segments
   - All or a sample of households within neighborhoods

4. Study Households
   - All eligible women in the household

5. Study Women
National Children’s Study Locations
Vanguard locations: Study Centers awarded (bold)

Lincoln, Pipestone, and Yellow Medicine Counties, Minnesota
and Brookings County, South Dakota

Salt Lake County
Utah

Waukesha County
Wisconsin

New York City (Queens)
New York

Montgomery County
Pennsylvania

Duplin County
North Carolina

Orange County
California
Schedule of Visits

- 13 face-to-face contacts over the 21 year study period
- Contacts most frequent early in the study
- Between visits ongoing data collection by phone, mail, etc.

Note: Frequency and type of follow-up for women (first 4 yrs) depends on their probability of becoming pregnant

<table>
<thead>
<tr>
<th>Schedule Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Trimester</td>
<td>5 years</td>
</tr>
<tr>
<td>2nd Trimester – Study Ultrasound</td>
<td>7 years</td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>9 years</td>
</tr>
<tr>
<td>Birth – Place of delivery</td>
<td>12 years</td>
</tr>
<tr>
<td>6 months</td>
<td>16 years</td>
</tr>
<tr>
<td>12 months</td>
<td>20 years</td>
</tr>
<tr>
<td>3 years</td>
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Home
Clinic
To be determined
Hypotheses->
Target Chemicals,
Routes, Life-Stage

Indirect Measures
(e.g., Community)
or Questionnaires?

Environmental & Biomonitoring?

Importance of Route
Time represented by environ. & biological
Completeness of combined environ. & biological measures

Environmental?
Biomarker not available
Route of exposure is critical
Exposures can be more reliably/efficiently assessed using environ.

Biomonitoring?
Route of exposure not important
Biomarker reflects exposure over critical life stage(s)
Exposures more reliably assessed using a biomarker

Based on Ozkaynak, et.al., “Exposure Assessment Implications for the Design and Implementation of the National Children’s Study” Environmental Health Perspectives 113: Aug. 2005
Proposed “Core” Environmental Measurements

<table>
<thead>
<tr>
<th>Indoor Air</th>
<th>Particulate Matter ($\text{PM}_{10}$) NO2, O3, VOCs, Aldehydes and Ketones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence, Child care locations</td>
<td></td>
</tr>
<tr>
<td>Outdoor Air</td>
<td>$\text{PM}_{2.5}$ NO2, NOx, SO2, O3</td>
</tr>
<tr>
<td>Community-level</td>
<td></td>
</tr>
<tr>
<td>House Dust</td>
<td>Allergens, endotoxin, mold, metals, pesticides (+archive for future analyses)</td>
</tr>
<tr>
<td>Potable water</td>
<td>Disinfection byproducts (BBPs), Metals, Coliforms, Nitrate, Pesticides</td>
</tr>
<tr>
<td>Soil &amp; Food</td>
<td>Metals, pesticides</td>
</tr>
</tbody>
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### Proposed Biomonitoring for Chemical Agents

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Chemicals Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>PCBs, Persistent and non-persistent pesticides, PBDE, Perfluorinated compounds, PBDE flame retardant; Perchlorate; Lead, Mercury, Cadmium; Bisphenol A</td>
</tr>
<tr>
<td>Urine</td>
<td>PFBS, Alkyl phenols, Hg(inorganic), As(speciated), perchlorate, halogenated phenols (PCP), phthalates, atrazine, OPs, carbamates, pyrethroids, EBDC/ETU, Cadmium</td>
</tr>
<tr>
<td>Breast milk</td>
<td>Dioxins/furans; Organochlorine Pesticides; PCBs</td>
</tr>
<tr>
<td>Meconium</td>
<td>Cotinine, Organophosphate Metabolites</td>
</tr>
<tr>
<td>Nails</td>
<td>Mercury (organic, inorganic)</td>
</tr>
<tr>
<td>Hair</td>
<td>Cd, Cotinine, Mercury, Nicotine</td>
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</tbody>
</table>
## Proposed Questionnaire
### Topic Areas in the NCS

<table>
<thead>
<tr>
<th>Housing characteristics</th>
<th>Building age, renovations, Heating/cooling systems/usage, Clothes dryer, Vaporizers, Air cleaners, Stove use, Water for drinking and cooking, Ozone sources, Vacuum cleaner use, Garage location and use, Gasoline exposure, Noise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation/hobby</td>
<td>Types of jobs, activities, exposures</td>
</tr>
<tr>
<td>Product use</td>
<td>Creams/lotions that are widely applied; Cleaning products</td>
</tr>
<tr>
<td>Pesticide use</td>
<td>Type, method, frequency of application, and use protective equipment; Number and types of pets, and exposure to flea/tick treatments</td>
</tr>
</tbody>
</table>
**Proposed Questionnaire, Diary, or Observation**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual assessment</td>
<td>Housing, neighborhood characteristics</td>
</tr>
<tr>
<td>Time and activity</td>
<td>Time spent at home, work/school, in-transit for work and non-work days</td>
</tr>
<tr>
<td>Diet</td>
<td>Food-frequency questionnaire 3-day checklist Infant feeding/intake Eating behaviors (child)</td>
</tr>
<tr>
<td>Exposure-Related Topics</td>
<td>Environmental tobacco smoke Take home exposures Physical activity Household composition and demographics</td>
</tr>
</tbody>
</table>
**Example Environmental Measures over Time**

<table>
<thead>
<tr>
<th>Simplified Summary of Measures by Visit - Environmental Measurements</th>
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</thead>
<tbody>
<tr>
<td><strong>Pre-</strong></td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td><strong>Indoor Air</strong></td>
</tr>
<tr>
<td>PM10/metals, carbon</td>
</tr>
<tr>
<td>Gaseous Air Pollutants</td>
</tr>
<tr>
<td><strong>House Dust</strong></td>
</tr>
<tr>
<td>Pesticides</td>
</tr>
<tr>
<td>Metals (store)</td>
</tr>
<tr>
<td>Allergens, Mold, Pollen</td>
</tr>
<tr>
<td><strong>Drinking Water</strong></td>
</tr>
<tr>
<td>Disinfection Byproducts (DBPs)</td>
</tr>
<tr>
<td>Nitrate (private wells)</td>
</tr>
<tr>
<td>Pesticides (private wells)</td>
</tr>
<tr>
<td>Perchlorate (Community Level)</td>
</tr>
<tr>
<td><strong>Soil</strong></td>
</tr>
<tr>
<td>Mid-yard - Metal, Pesticide</td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>Visual Assessment</td>
</tr>
<tr>
<td>Noise Survey</td>
</tr>
</tbody>
</table>
Other Data Collections

- Community samples
  - Water
  - Air monitoring
  - Possibly food

- Specific settings outside of the home
  - Child care locations (probably on a subsample due to costs)
  - School (specifics not yet developed)

- Medical Record Abstraction
  - Complete abstraction of the mother and infant records at the time of delivery
  - Likely additional abstractions for a subset of events and/or outcomes
Validation sampling provides a statistical basis to adjust for error in exposure assessment when investigating exposure-outcome relationships.

A validation sample is a small sample designed to provide information on the bias or error introduced by using alternative measures [or models] of exposure.

Need to develop optimal designs and identify surrogate measures [, questionnaires, or models] and their relationship to “true” exposure.

Collections and storage protocols based on analytes specified in the hypotheses

Many analyses will be deferred
  - Too costly and not necessary to have every analysis on every participant
  - Many hypotheses can be addressed with nested case-control studies

Limited set of analytes require immediate processing
  - Depends on stability of sample/analytes
Opportunities for Linking Biomonitoring to Risk Assessment and Public Health
Biomonitoring and the National Children’s Study

- Prime applications of biomarkers are epidemiological observational studies.
  - Relate biomarkers (at various times) to outcomes
- NCS requires and employs extensive use of biomarkers
  - Assays to test hypotheses
  - Repository of biological and environmental samples for future analyses and hypotheses
- Biomarker database - http://www.nationalchildrensstudy.gov/research/analytic_reports
- Evolving science and methodological developments = new improved measures & better science, e.g.:
  - EPA/NCER Early indicators of environmentally induced disease
  - NIEHS – Exposure biology Initiative
NCS and Risk Assessment

- NCS will address important issues for environmental risk assessment, such as:
  - Contribution of multiple exposures to childhood disease
  - Long-term health effects from early exposures
  - Factors that alter susceptibility (e.g., specific genetic polymorphisms, immune deficiencies)
  - Disparities in health outcomes (e.g., race, ethnicity, poverty, housing, income, nutrition)
  - Uncertainty factors and defaults in risk assessment for protecting children
NCA and Risk Assessment

- Directly links human exposure measures (biomonitoring and environmental) to health status, yielding better estimates for children, including the role of
  - Multiple “environments” and agents
  - Genetic factors and gene-environment interactions

- NCS will provide a rich data base for risk assessment, e.g.
  - Longitudinal exposure measures
  - Community-level cumulative risks
Conceptual Model: Exposures, Interactions, Mediators, and Outcomes

Exposures
- Chemical Exposures
- Physical Exposures
- Psychosocial Exposures
- Biological Exposures
- Genetics

Mediator Examples
- Gene Expression
- Health Care

Outcomes
- Pregnancy Outcomes
- Neurodevelopment and Behavior
- Asthma
- Obesity and Growth
- Child Health and Development
- Injury
- Reproductive Development
• The NCS will identify not only what is harmful but what is helpful to children’s health

• Provides a national dataset linking source-exposure-effect
  
  • Evidence on which to base decisions about practice and policy regarding children’s physical and mental health
  
  • Allows evaluation of the consequences/effectiveness of regulatory decisions

• Economic benefits: disease prevention; cost avoidance

• Resource for future research
Environmental Public Health Paradigm

Source: Danelle T. Lobdell, US EPA, NHEERL
Environmental Indicators

Data Available

Level 1: Actions by EPA, State, and other regulatory agencies
Level 2: Actions and behavioral changes by regulated community
Level 3: Reduced amount or toxicity of emissions
Level 4: Improved ambient conditions
Level 5: Reduced exposure or body burden
Level 6: Improved Human or ecological health

Data Unavailable at present Time

Output Measures

Measures of Human/Eco-Health
NCS and Public Health Research

- Training for clinical, epidemiological, and environmental health research
- Consortia for combined research
- Public use and secondary data analysis
- Complimentary, not competitive, with investigator initiated research
- Platform for *adjunct studies*
What are *Adjunct Studies*?

- Uses NCS data, participants or their samples
- Outside of the “core” NCS protocol
- Generally supported with non-NCS funding
- NCS Program Office coordinates review and approval
- Requires participation of an NCS investigators
  - Study Centers, NCS Program Office, or ICC members
- Benefit of adjunct studies
  - Enhances breadth, depth and value of the NCS
  - Could use for linking biomonitoring and other exposure measures to sources
Use of Data to Maximize Output

- Publicly available results available ~2015
  - Hypothesis-specific (exposure-outcome) data analysis
  - Public-use data sets with support
- Successive funding for investigator initiated research and analyses
- Expected translation of results into related prevention initiatives
- Data analyses and adjunct studies may be needed
  - to link biomonitoring and exposure measures to sources
For more information about the NCS

Web site:  www.nationalchildrensstudy.gov

Link on the home page that says “National Children’s Study Research Plan”

Click on link for “E-Updates” to join the listserv for news and communication

Email the study at  ncs@mail.nih.gov