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

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**Jim Quackenboss
US EPA, ORD/NERL
NCS Interagency Coordinating Committee (ICC)
NCS Program Office**



**US Department of Health
and Human Services**
NIH, CDC, NCHS, OS



**US Environmental
Protection Agency**
ORD, OCHP

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



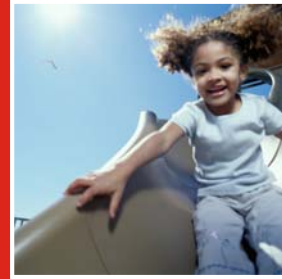
Study Concepts



- 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



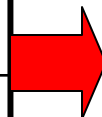
- Assure answers to “big issue” questions
- Hypothesis required for costly elements
- Input from >2500 scientists, others
- Important for child health & development
- Requires and measurable with sample ~100,000
- Evolving with the science
- Updated hypothesis statements in Research Plan



Priority Exposures and Health Outcomes



Priority Exposures	Examples
Physical Environment	Housing quality, neighborhood
Chemical Exposures	Pesticides, phthalates, metals, air & water quality
Biologic Environment	Infectious agents, endotoxins, diet
Genetics	Interaction between environmental factors and genes
Psychosocial milieu	Families, SES, institutions, social networks



Priority Health Outcomes	Examples
Pregnancy Outcomes	Preterm, Birth defects
Neuro-development & Behavior	Autism, schizophrenia, learning disabilities
Injury	Head trauma, Injuries requiring hospitalizations
Asthma	Asthma incidence and exacerbation
Obesity & Physical Development	Obesity, Diabetes, altered puberty



Time Line for the NCS



- 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



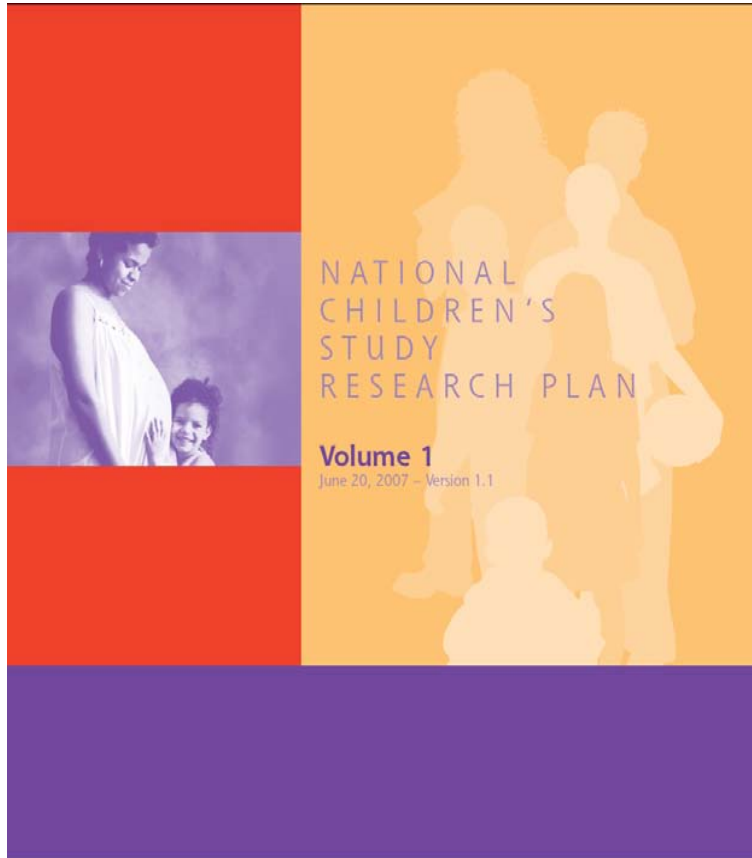
Funding for the NCS (as of April 2007)



- 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

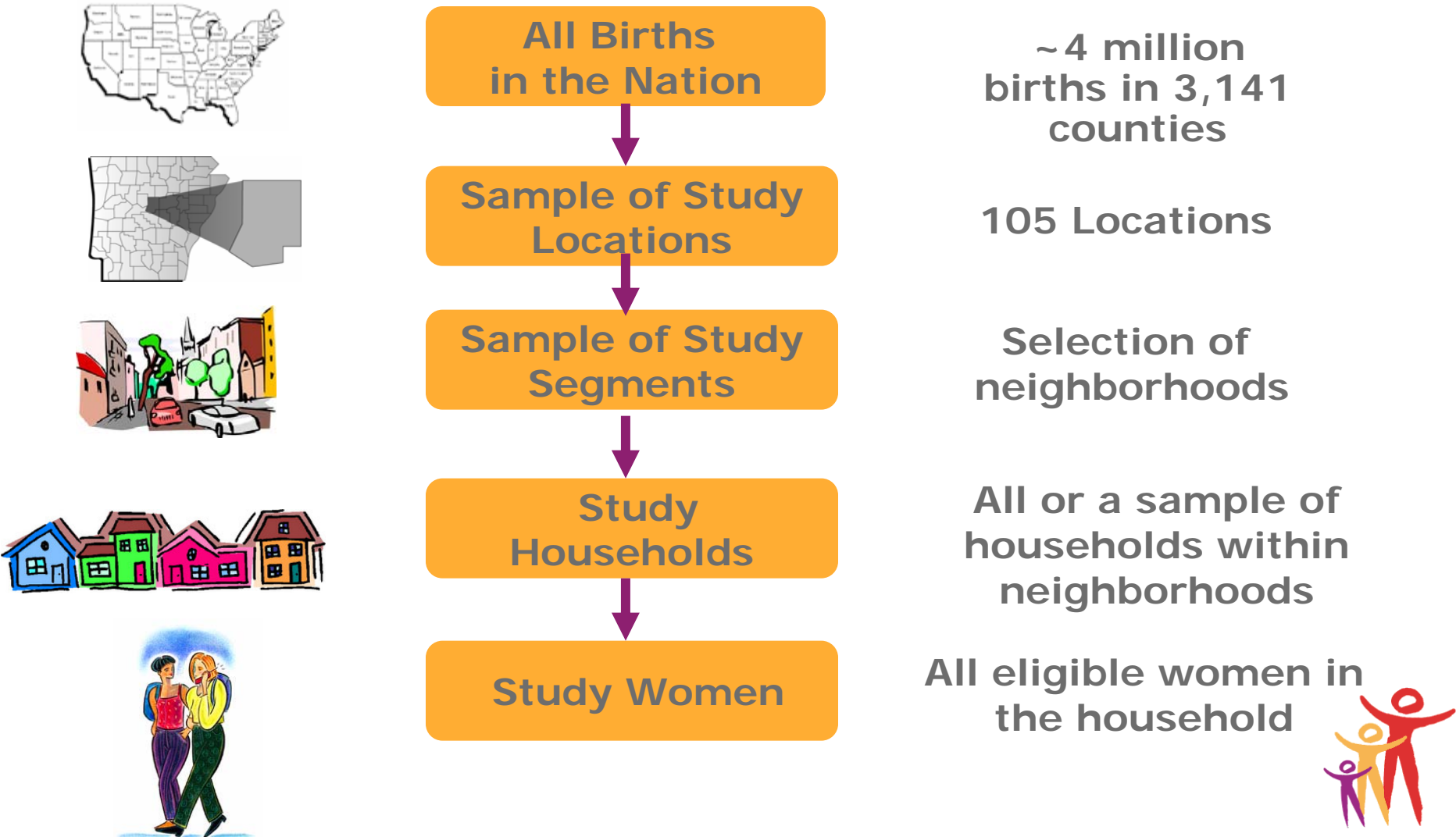


- The background, design and measures to describe what will be done and why.
- Designed for review
- 600+ pages
- On the NCS website:
www.nationalchildrensstudy.gov





Study Sample



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

Orange County
California

Duplin County
North Carolina



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.



Home



Clinic



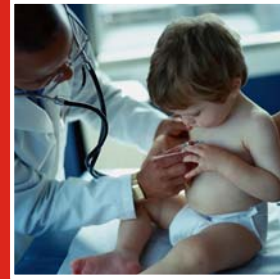
To be determined

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

1 st Trimester	5 years
2 nd Trimester – Study Ultrasound	7 years
3 rd Trimester	9 years
Birth – Place of delivery	12 years
6 months	16 years
12 months	20 years
3 years	



Hypotheses->
Target Chemicals,
Routes, Life-Stage



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

Environmental &
Biomonitoring?

Environmental?

Biomonitoring?

Importance of Route

Time represented by
environ. & biological

Completeness of
combined environ. &
biological measures

Biomarker not available

Route of exposure is
critical

Exposures can be more
reliably/efficiently
assesses using environ.

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



Indoor Air (Residence, Child care locations)	Particulate Matter (PM ₁₀) NO ₂ , O ₃ , VOCs, Aldehydes and Ketones
Outdoor Air (Community- level)	PM _{2.5} NO ₂ , NO _x , SO ₂ , O ₃
House Dust	Allergens, endotoxin, mold, metals, pesticides (+archive for future analyses)
Potable water	Disinfection byproducts (BBPs), Metals, Coliforms, Nitrate, Pesticides
Soil & Food	Metals, pesticides



Proposed Biomonitoring for Chemical Agents



Blood	PCBs, Persistent and non-persistent pesticides, PBDE, Perfluorinated compounds, PBDE flame retardant; Perchlorate; Lead, Mercury, Cadmium; Bisphenol A
Urine	PFBS, Alkyl phenols, Hg(inorganic), As(speciated), perchlorate, halogenated phenols (PCP), phthalates, atrazine, OPs, carbamates, pyrethroids, EBDC/ETU, Cadmium
Breast milk	Dioxins/furans; Organochlorine Pesticides; PCBs
Meconium	Cotinine, Organophosphate Metabolites
Nails	Mercury (organic, inorganic)
Hair	Cd, Cotinine, Mercury, Nicotine



Proposed Questionnaire Topic Areas in the NCS



Housing characteristics	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
Occupation/hobby	Types of jobs, activities, exposures
Product use	Creams/lotions that are widely applied; Cleaning products
Pesticide use	Type, method, frequency of application, and use protective equipment; Number and types of pets, and exposure to flea/tick treatments



Proposed Questionnaire, Diary, or Observation



Visual assessment	Housing, neighborhood characteristics
Time and activity	Time spent at home, work/school, in-transit for work and non-work days
Diet	Food-frequency questionnaire 3-day checklist Infant feeding/intake Eating behaviors (child)
Exposure-Related Topics	Environmental tobacco smoke Take home exposures Physical activity Household composition and demographics



Example Environmental Measures over Time



Simplified Summary of Measures by Visit - Environmental Measurements							
	Pre-	Pregnancy		After Birth			
		T1	T2/T3	6-Mo	12 mo	2-yr	3-yr
Indoor Air			(self)			(self)	(self)
PM10/metals, carbon	Blue	Blue	Green	Blue	Blue	Blue	Yellow
Gaseous Air Pollutants	Orange	Blue	Blue	Blue	Blue	Blue	Blue
House Dust							
Pesticides	Blue	Blue	Blue	Blue	Blue	Blue	Blue
Metals (store)	Orange	Blue	Green	Blue	Yellow	Blue	Blue
Allergens, Mold, Pollen	Orange	Blue	Green	Blue	Blue	Blue	Blue
Drinking Water							
Disinfection Byproducts (DBPs)	Orange	Blue	Green	Blue	Blue	Blue	Blue
Nitrate (private wells)	Blue	Blue	Blue	Blue	Yellow	Yellow	Yellow
Pesticides (private wells)	Blue	Blue	Blue	Blue	Blue	Blue	Blue
Perchlorate (Community Level)	Blue	Blue	Green	Yellow	Blue	Yellow	Yellow
Soil							
Mid-yard - Metal, Pesticide	Orange	Blue	Green	Blue	Blue	Blue	Yellow
Others							
Visual Assessment	Orange	Blue	Green	Blue	Yellow	Yellow	Yellow
Noise Survey	Orange	Green	Green	Yellow	Blue	Yellow	Yellow



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



Design Considerations for Exposure Assessment in the NCS



- 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

Strauss W, Lehman J, Morara M, Ryan L. 2003. Development of Exposure Assessment Study Design for the National Children’s Study: Project Overview, Results and Recommendations. Task 5. US EPA, National Exposure Research Laboratory. Available as Appendix C from: http://nationalchildrensstudy.gov/research/analytic_reports/



Analytes (Environmental and Biologic)



- 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



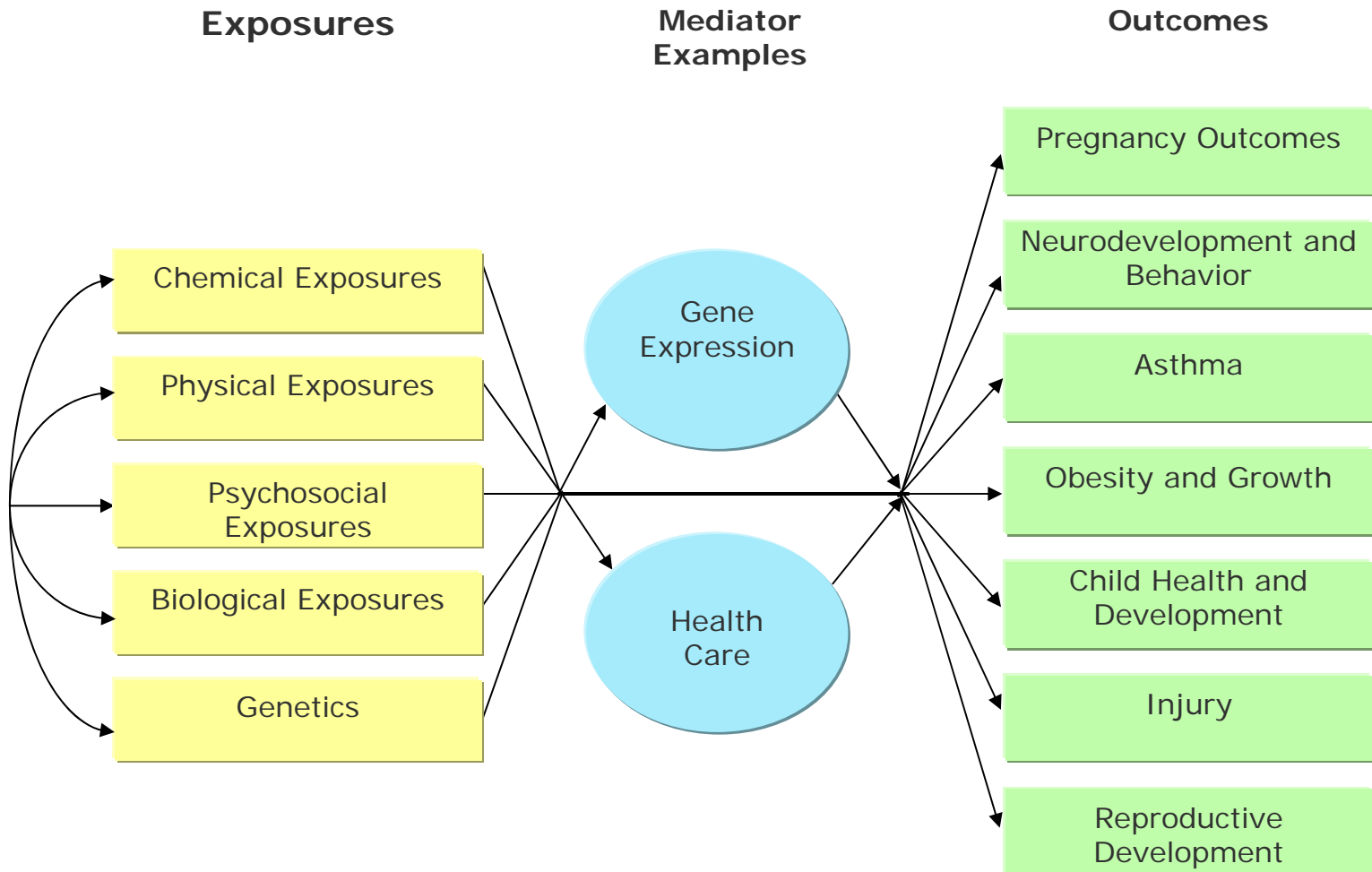
NCA and Risk Assessment



- 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



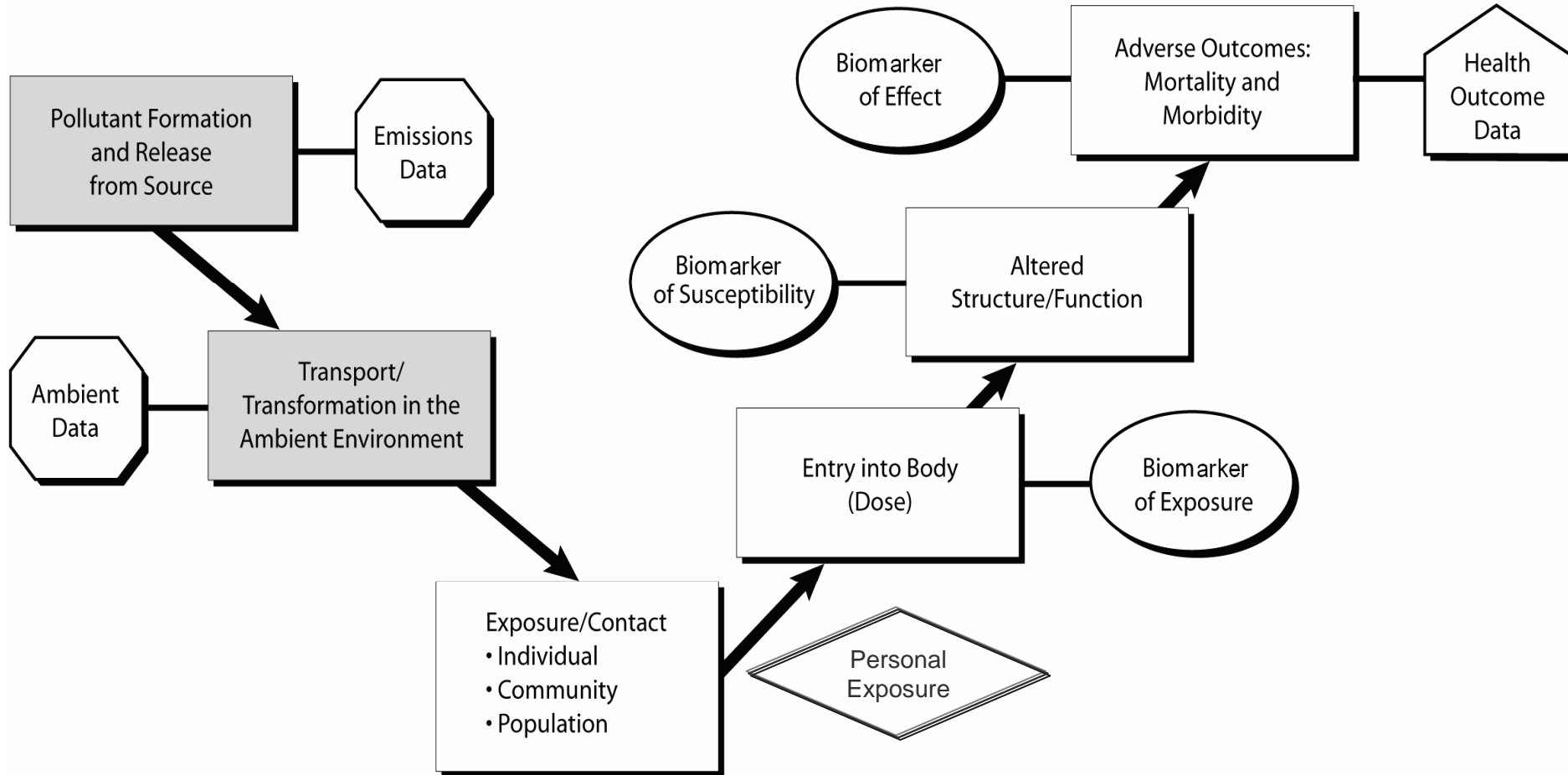
NCS and Public Health



- 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

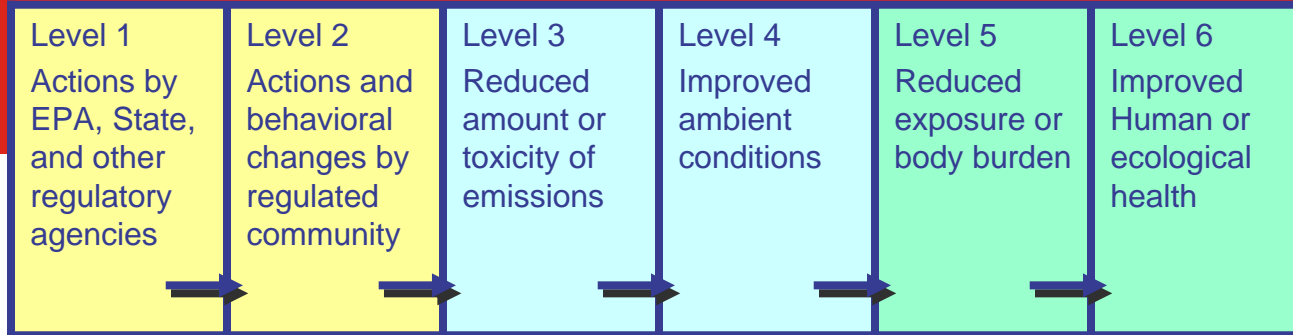


Source: Danelle T. Lobdell, US EPA, NHEERL

Environmental Indicators



Data Available



Data Unavailable at present Time

Output Measures



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

