Use of *In Utero* and Post-Natal Indicators to Predict Health Outcomes Later in Life

October 14-15, 2010
The Washington Club
Washington, DC
Environment Special: The oceans—why 70% of our planet is in danger

How the first nine months shape the rest of your life

The new science of fetal origins

BY ANNIE MURPHY PAUL

The Facebook Movie: The secret history of social networking
Use of Emerging Science for Environmental Health Decisions
A Standing Committee of the National Academies

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*Martin L. Stephens*, The Humane Society of the United States
*Helmut Zarbl*, Robert Wood Johnson Medical School
*Lauren A. Zeise*, California Environmental Protection Agency

Additional workshop and committee information can be found at:
http://nas.edu/envirohealth

* Members of the Planning Subgroup for this workshop.
** Chair of the Planning Subgroup for this workshop.
SESSION 1
- What is the range of adult disease states that have developmental origins?
- What are the possible mechanisms for persistent, adult-onset effects associated with developmental exposures?
- How good are current animal tests in detecting associations between early life exposures and later life effects? How relevant are the effects observed in animals for human exposures?
- How is genetic variation addressed in the context of developmental exposures and epigenetics?

SESSION 2
- What early life biomarkers are available to predict later life disease?
- Are there shorter-term animal tests or mode-of-action-based in vitro/human biomarker tests that detect early life events and are predictive of later life effects?
- Which media are the most promising for investigating early life indicators (e.g. target tissue, placental tissue, maternal blood, cord blood)?
- When is the optimal time to look for early indicators (e.g., during pregnancy, immediately after birth, during childhood)?
- Does exposure during development alter the sensitivity to later life exposure?
SESSION 3

Is our scientific understanding of these processes sufficient to inform weight-of-evidence-based risk assessments and regulatory practices?

1) How ready is the science?

   a) Can we find the right predictive events?
   b) Do we know enough to establish certain upstream events or processes involved in fetal or infant programming of disease? Are we able to define these as adverse?
   c) What approaches could be taken for use of upstream measures in dose-response assessments, including characterizing the impacts of human milieu?
   d) What types of technologies are best suited to give us information on upstream events for hazard identification and dose response?
   e) How should scientists weigh in to facilitate the acceptance of the new science?

2) What are the regulatory implications?

   a) What are the regulatory requirements for acceptance (such as validation of new models, assays, and biomarkers)?
   b) How do we know when the science is ready for regulatory use?
   c) How can this new science be implemented in the regulatory sphere?
   d) What are the political and societal issues involved in implementation?
Transgenerational Influences, Clinical Events, Lifestyle & Social Stressors, Environmental Chemicals, and Transgenerational Influences are components of Developmental Exposures. These exposures act through DNA Methylation, Histone Modification, MicroRNAs, and Imprinting. They influence Later Life Outcomes and Susceptibilities including Growth, Neurobehavior, Obesity, Reproduction, and Cancer.
In molecular terms; how is chromatin organised with respect to gene expression and repression?

Epigenetic mechanisms are intimately involved in setting up and maintaining the two major forms of chromosomal structure, heterochromatin and euchromatin, and in the structural switches of facultative heterochromatin between the two.

SESSION 1: INTRODUCTION

• Strategies for Detecting Later Life Effects Following Early Life Stressors in Humans
  Robert Lane, University of Utah

• Traditional Testing Strategies for Detecting Later Life Effects Following Early Life Stressors: Animal Models
  John Rogers, U.S. Environmental Protection Agency

• Novel Effects: From Research to Methods Development and Regulatory Acceptance
  Steven Bradbury, U.S. Environmental Protection Agency

Panel:
• Moderator: Helmut Zarbl, University of Medicine and Dentistry of New Jersey
• Bill Farland, Colorado State University
• Jerry Heindel, National Institute of Environmental Health Sciences
• Theodore Slotkin, Duke University Medical Center
• Session 1 speakers
SESSION 2: FETAL PROGRAMMING ON LATER LIFE EFFECTS

Emerging Science: *in utero* and post-natal indicators that predict endpoints such as obesity, insulin resistance, and hypertension.

• The Placenta: Influence on Fetal Programming and Useful After Birth?
  *Leslie Myatt, University of Texas Health Science Center*

• Obesogens, Stem Cells, and the Maternal Programming of Obesity
  *Bruce Blumberg, University of California, Irvine*

• The Role of Epigenetics in the Developmental Origins of Human Metabolic Disease
  *Karen Lillycrop, Southampton General Hospital*
Emerging Science: *in utero* and post-natal indicators that predict diseases caused by arsenic exposure.

- Hepatic Gene Expression Changes Associated with *In Utero* Arsenic Exposure Accelerated Atherosclerosis in the ApoE-Knockout Mouse  
  *J. Christopher States, University of Louisville*

- Fetal Arsenic Exposure and Adulthood Cancer in Mice  
  *Michael Waalkes, National Institute of Environmental Health Sciences*

- Consequences of Pre- and Post-natal Arsenic Exposure in Bangladesh  
  *Joseph Graziano, Columbia University*

**Panel:**  
- Moderator: Kim Boekelheide, *Brown University School of Medicine*  
- Kristina Thayer, *National Institute of Environmental Health Sciences*  
- Session 2 Speakers
SESSION 3: IMPLICATIONS FOR USING EARLY INDICATORS TO PREDICT HEALTH OUTCOMES LATER IN LIFE

• What and in What Areas is the Emerging Science Ready for Use in Risk Assessment?
  Robert Chapin, Pfizer

• What Difficulties Do We Face in Using This New Science for Risk Assessment Purposes?
  Ila Cote, U.S. Environmental Protection Agency

Panel:
• Moderator: Lauren Zeiss, California Environmental Protection Agency
• Bob Benson, U.S. Environmental Protection Agency
• Stan Barone, U.S. Environmental Protection Agency
• Deborah Hansen, U.S. Food and Drug Administration
• Sarah Janssen, Natural Resources Defense Council
• Reza Rasoulpour, Dow Chemical Company
• Session 3 Speakers
• Present the emerging scientific understanding of how developmental exposures alter later life health and disease.

• Identify early life biomarkers that predict later life health and disease.

• Identify gaps in mechanistic understanding, experimental techniques, conceptual approaches, and databases that are hindering progress.

• Think through and plan ahead for the challenges faced in implementing risk assessment and protective regulatory action in this new field.
Developmental Exposures

- Transgenerational Influences
- Clinical Events
- Lifestyle & Social Stressors
- Environmental Chemicals

EPIGENOME
- DNA METHYLATION
- HISTONE MODIFICATION
- MICRORNAS
- IMPRINTING

Later Life Outcomes and Susceptibilities
- Growth
- Neurobehavior
- Obesity
- Reproduction
- Cancer