National Institute of Environmental Health Sciences

NIEHS Strategies in Biomonitoring and Low Dose Exposures

Science Guidance Panel Meeting for Biomonitoring
Oakland, California

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Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director
National Institute of Environmental Health Sciences and
National Toxicology Program

Why Environmental Health Matters

- 13 million deaths could be ***prevented*** per year by improving our environment
- Environmental factors influence 85 out of the 102 non-communicable diseases in WHO report
- Environmental factors account for at least 2/3 of cancer cases in the United States
- You can't change your genes, but you ***CAN*** change your environment

WHO Global Health Report (2010); Horton, R., Lancet (2013)

Environmental Exposures: One Size Does Not Fit All

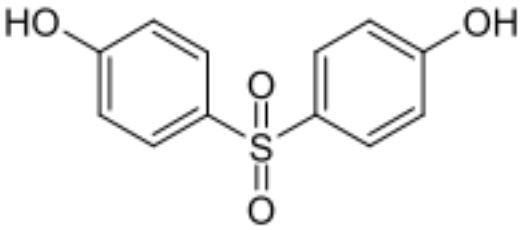
- Thousands of chemicals in our environment:
  - EDCs, Mixtures…
- Many modes of exposure:
  - Air, water, food, pathogens, etc…
- Exposures differ depending on,
  - Dose, timing, the individual
- Disease and dysfunctions are not the same:
  - Many disease endpoints and mechanisms
  - Occur over a long range of time

Early Life Exposures Can Have Lasting Effects: Developmental Basis of Adult Disease

- Early life is a sensitive time for exposure:
  - Organs are forming
  - Gene expression programs are being established
  - Epigenetic reprogramming is occurring
  - Changes occurring during development permanently alter the potential of an organ

Persistent Effects

- New and “replacement” chemicals are rapidly proliferating
- Many of these chemicals are untested or appear to be no safer than the chemicals they are replacing
- Some chemicals are persistent and can cause long term environmental and health consequences
- Studies are showing that exposure certain chemicals (i.e., phthalates, PAHs or flame retardants) before birth can lead to long term health effects



BPS

Chicago Tribune

TRIBUNE WATCHDOG

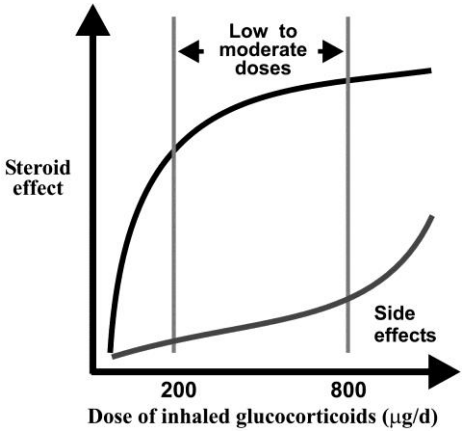
Playing with fire

A deceptive campaign by industry brought toxic flame retardants into our homes and into our bodies. And the chemicals don't even work as promised.

The Low Dose Hypothesis

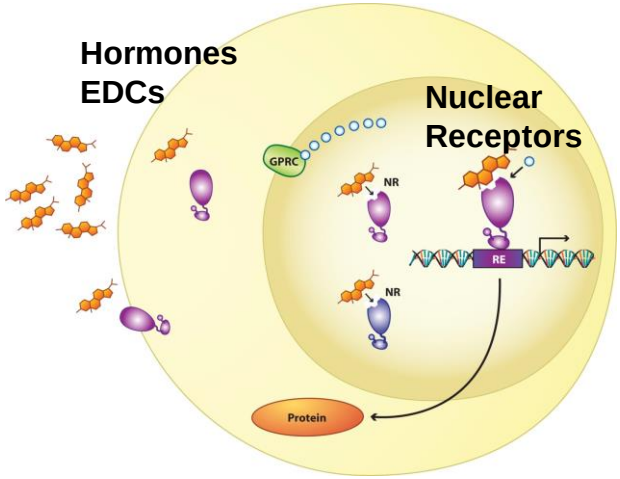
Proposes that:

- EDCs have effects, especially on reproduction and development, at low doses
- Effects observed in exposed animals are occurring at doses similar to human exposures (i.e. at doses that are thought to be safe)
- **Humans environmentally exposed to EDCs are affected by low doses**

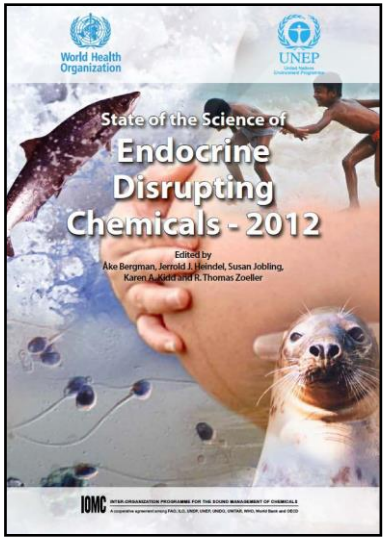


Endocrine Disrupting Chemicals

- *"An **Endocrine Disruptor** is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action."*
  – The Endocrine Society, 2012

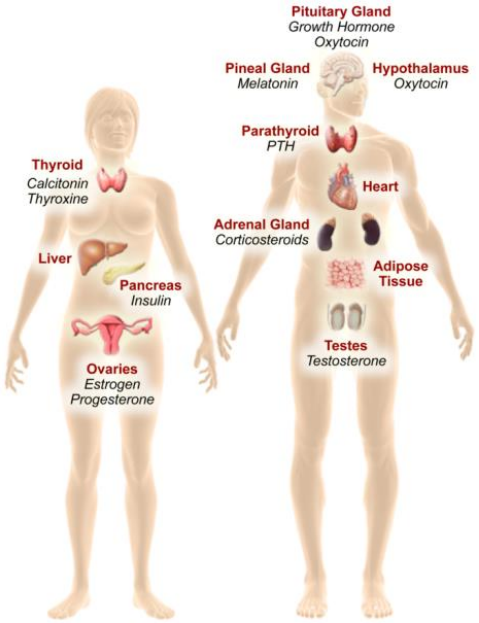


- New report from The United Nations Environment Programme (UNEP) and the World Health Organization (WHO), *"State of the Science of Endocrine Disrupting Chemicals"*
  - *EDCs are becoming a "global threat" that should be addressed*



Low Dose EDC Research at NIEHS

- We are studying many EDC chemicals across a wide-range of exposures and disease endpoints:
  - BPA, dioxins, metals, PBDEs, phthalates, many others…
  - Preconception, pregnancy (mother), prenatal (baby), early childhood, puberty
  - Reproductive health, behavior, cancer…
- Replacement Chemicals
  - Need for 21st Century testing



Hormones Act at Very Low Doses

- ***Tiny*** amounts of hormones have profound effects on development and health (ppb-ppt)
- As a result, EDCs have major effects at low doses

Measured adult blood levels of hormones and EDCs

free testosterone (men):
0.04-0.244 ng/ml

free estradiol (women):
0.05-0.250 ng/ml

PCB180: 0.6 ng/ml

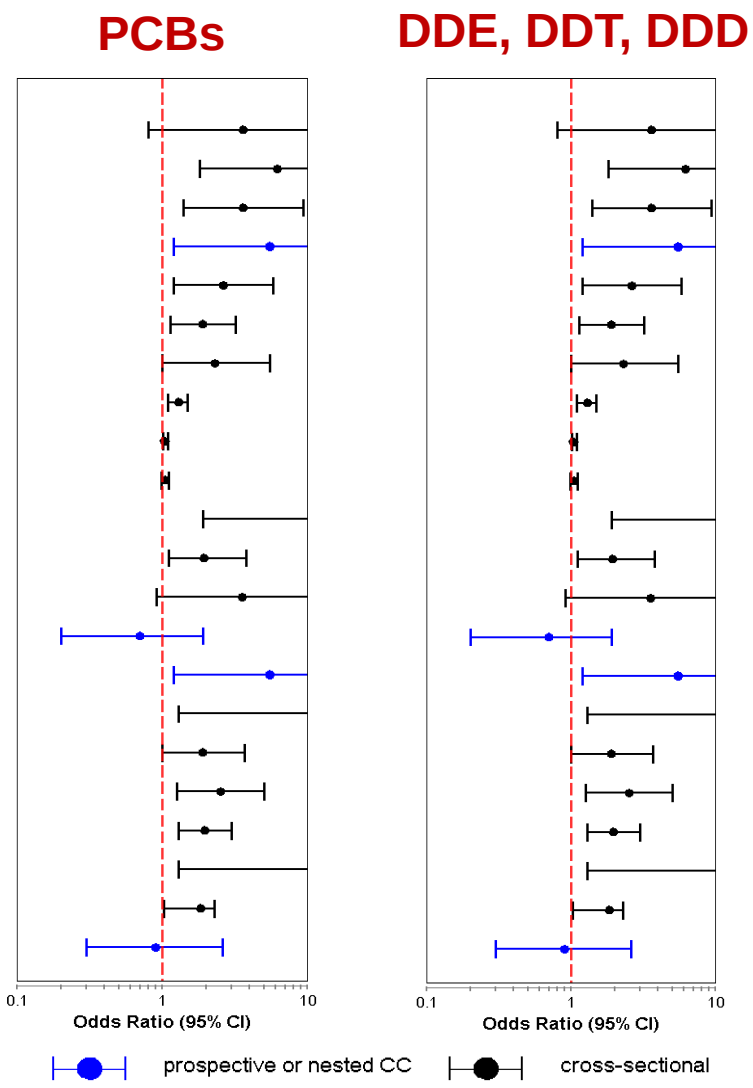
MEP (phthalate):
150-180 ng/ml

BPA (Human PK Study):
1.1 ng/ml

Examples of Chemical Effects at Low Doses: POPs and Diabetes in Humans

- Studies have shown correlation between high levels of PCBs and the distribution of body fat in the abdomen
  Uppsala (Lind Group)
  Roos et al., *Obesity* 2012

- Many studies show positive association between diabetes and certain POPs



PBDE Health Effects in Humans

- Neurodevelopmental Effects
  - PBDEs-cord blood associated with neurological deficits in children (motor perf., cognition (↓IQ), behavior)

    (Eskenazi et al., 2013; Herbstman et al., 2010; Roze et al., 2009)
- Thyroid Homeostasis
  - Altered circulating THs, TSH in adults

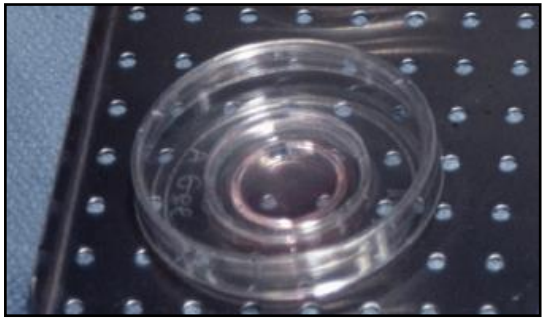
    (Meeker et al., 2009; Turyk et al., 2007; Stapleton et al., 2011; Bloom et al., 2008, Chevrier et al., 2010)
- Reproductive Development/Toxicity
  - Cryptorchidism in infants
  - Early menarche
  - ↓androgens, LH, FSH; ↑inhibin
  - ↑estradiol, inhibin in male infants (BDE-154)
  - ↓sperm counts, testis size (BDE-153)

    (Akutsu et al., 2008; Chen et al., 2011; Main et al., 2007; Meeker et al., 2009; Meijer et al., 2012)

BPA Exposure in Humans

Assisted Reproductive Technologies (ART)

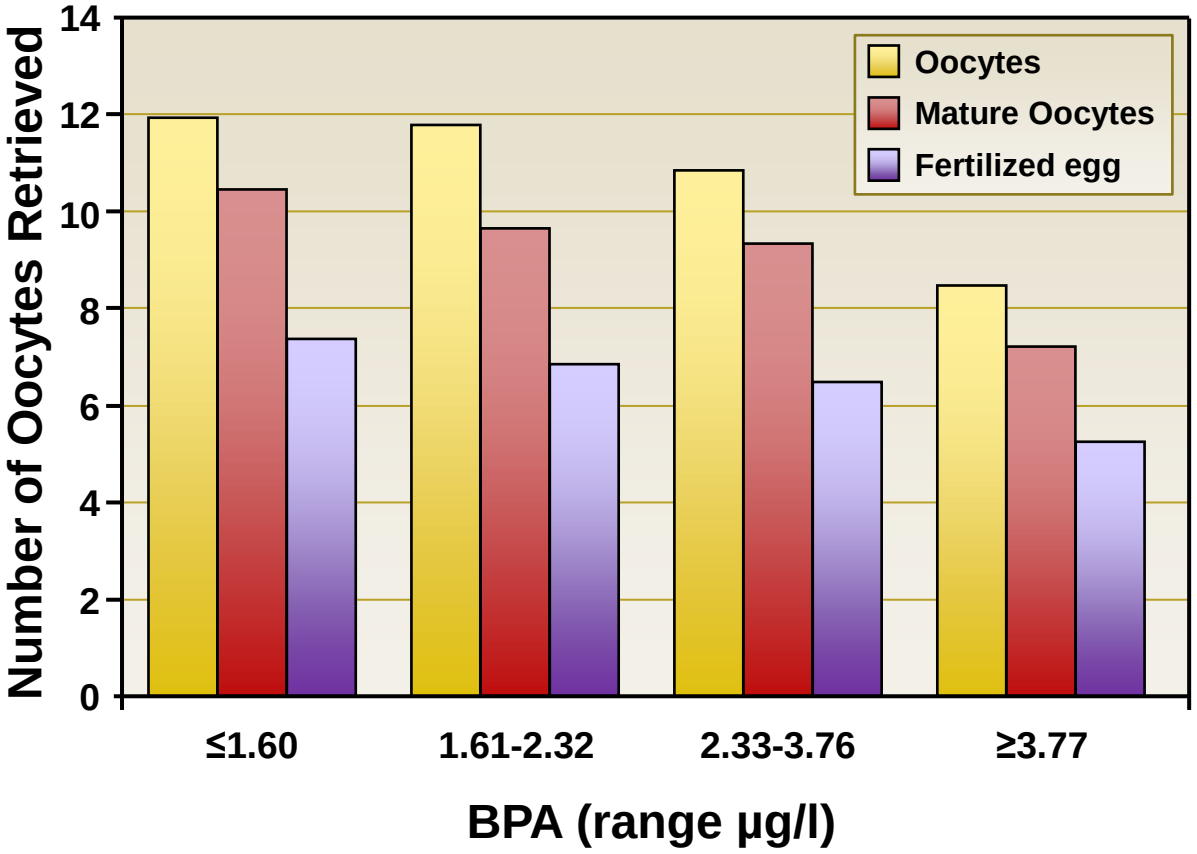
- Urinary BPA from ART clinical study population were similar to those measured in NHANES
- Urinary BPA associated with a reduced ovarian response:
  - Decrease in number of oocytes retrieved
  - Decrease in peak serum estradiol
- Urinary BPA associated with an increased odds of implantation failure



Ehrlich et. al., *Hum Reprod*. (2012)

Effects of BPA on Fertility

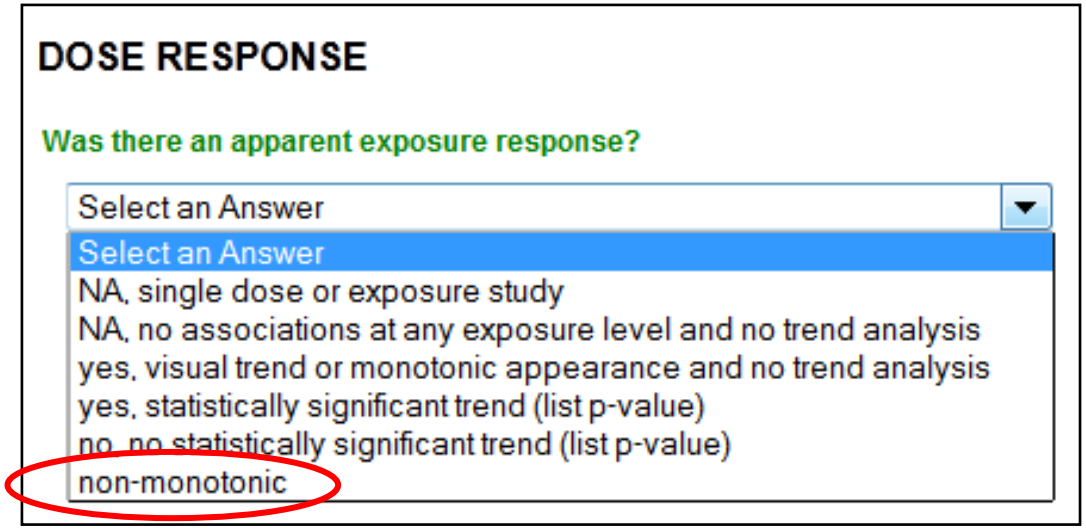
* Average BPA levels ~1.97 µg/l for females in NHANES 2007–2008



Ehrlich et. al., *Hum Reprod*. (2012)

OHAT Developing Tools to Analyze Low Dose Responses

- Characterize Shape of Dose Response for Each Health Outcome or Endpoint
- Human, animal, *in vitro* studies



New Research and New Programs at NIEHS

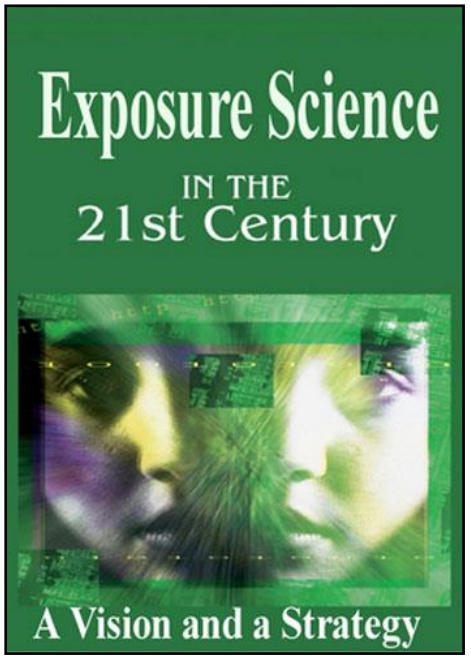
Joint Extramural and NTP Research Program on BPA

CLARITY-BPA (2011-2015)

- **C**onsortium **L**inking **A**cademic and **R**egulatory **I**nsights on BPA Toxici**ty**
- GLP-compliant study of BPA toxicity in rats
  - Includes developmental exposure
  - Broad dose range: 2.5 – 25,000 µg/kg bw/day
  - 2 doses reference estrogen
- 12 grantees involved in planning, studying specific disease endpoints

Measuring Individual Susceptibility

- *The **Exposome***: A tool to discover associations between the environment and disease
- Focusing on what is ‘doable’ today, while building capabilities for tomorrow
- 2012 NAS workshop on underlying individual susceptibility



National Research Council (NRC)
September 2012

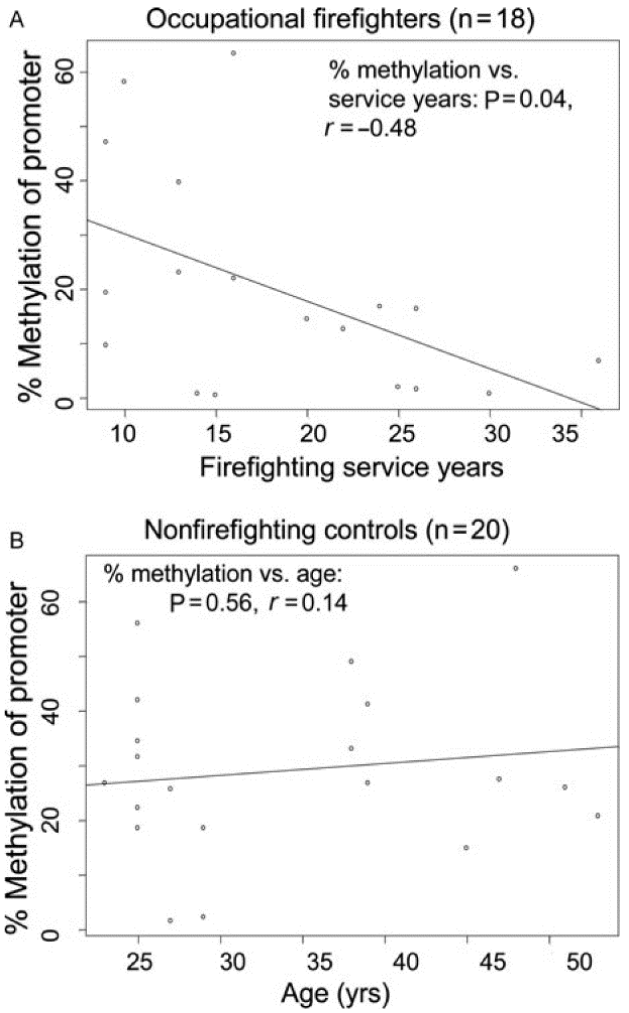
Tackling Chemical Mixtures: PAHs at NTP

- Preliminary chemical analysis of Deepwater Horizon samples
  - Source oil
  - Environmental samples

- PAH toxicity testing
  - Short-term *in vitro* & *in vivo* testing battery
    - Assess a broad range of structurally diverse PAHs and PAH mixtures
    - Include a robust suite of endpoints
    - Evaluate available models for predicting mixture toxicity, such as PAH exposure on road crews

PAH research in Cells and in Humans

- PAH biomarker predicts years of service for firefighters
- Reduced promoter methylation and increased gene expression in vitro and in blood DNA from cells and firefighters exposed to high levels of PAHs
- Methylation status relates to years of service, not age of firefighter



Ouyang *et al*., *J. Occup Environ Med;* University of Cincinnati (Ho Group)

New Efforts in Toxicology Testing

- Toxicity for the 21st Century or "Tox21"
  - High throughput screening using nuclear receptor and stress response pathways assays was initiated
    - 12174 substances, 8307 unique
- The 1000 Genomes *In Vitro* Project
  - Tox21 robot, 1086 cell lines, representing 9 racially distinct populations, were screened in a cell viability assay with 179 chemicals
- The Diversity Outbred (DO) Mouse
  - A New population-based mouse model to identify, characterize, and quantify hazard

A New Vision and Mission for NIEHS and NTP

- Our ***vision*** is to provide global leadership for innovative research the improves public health by preventing disease and disability
- Our ***mission*** is to discover how the environment affects people in order to promote healthier lives

The New NIEHS Strategic Plan

- The new Plan is a blueprint for the entire Environmental Health Science Community
- ***6 Themes*** that brush a broad scientific context
- ***11 Goals*** that are more specific and target high impact areas of science
- ***2 Crosscutting Themes*** that integrate overlapping areas of science

Strategic Themes

- Studying ***basic mechanisms*** and ***windows of susceptibility***
- Linking ***individual and population exposure*** to risk
- Creating better ***predictive models*** and 21st Century tools
- Enhancing ***communication*** and ***diversity*** in all aspects of research

- ***Training*** a multidisciplinary group of scientists
- Improving ***coordination*** between gov't agencies and other groups

Thank you!

NIH National Institute of Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

NIEHS Strategic Plan Website
http://www.niehs.nih.gov/strategicplan