NIEHS
National Institute of Environmental Health Sciences

Endocrine Disruption

Where do we go from here?

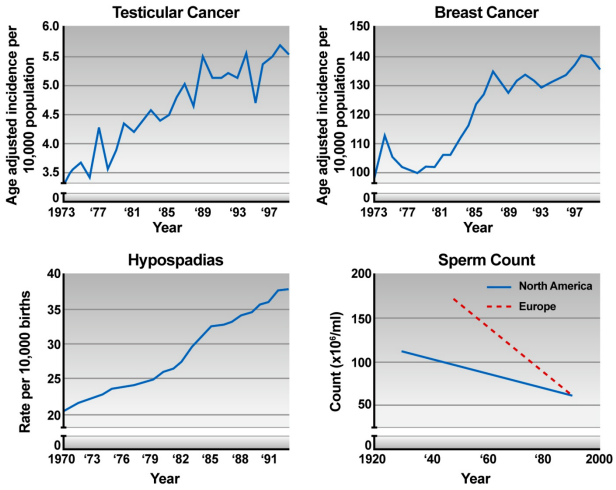
Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director
National Institute of Environmental Health Sciences
National Toxicology Program

EU Conference on Endocrine Disruptors
Monday, June 11, 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIEHS
National Institute of Environmental Health Sciences

Should We Be Concerned?

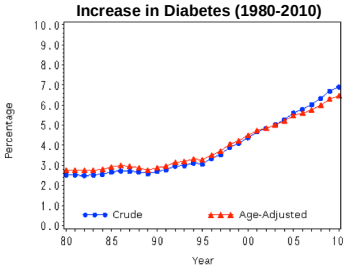


Sharpe and Irvine, 2004

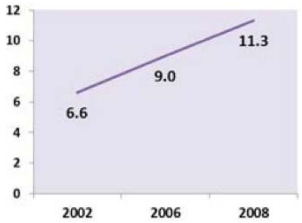
NIEHS
National Institute of Environmental Health Sciences

Should We Be Concerned?

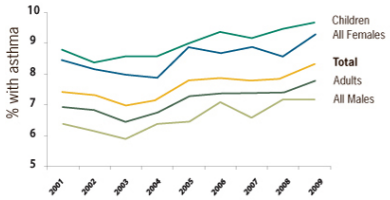
Increase in Diabetes (1980-2010)



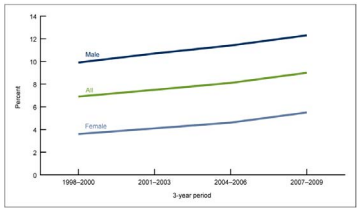
Increase in Autism Prevalence



Increase in Asthma



Increase in ADHD

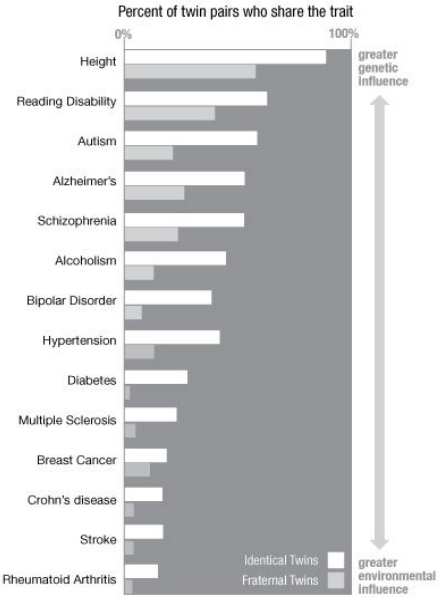


Data from CDC / National Center for Health Statistics

NIEHS
National Institute of Environmental Health Sciences

Genetics of Disease

- Strongly Genetic Diseases
  - Sickle cell anemia
  - Cystic fibrosis
  - Hemophilia
  - Marfan syndrome
  - Huntington's disease
- Not Strongly Genetic Diseases (from ID twin studies)
  - Fragile X syndrome
  - Prader-Willi syndrome
  - Scleroderma
  - Autism
  - Schizophrenia
  - Inflammatory bowel disease
  - Cancer (e.g. melanoma)



NIEHS
National Institute of Environmental Health Sciences

"ENVIRONMENT" Includes:

- Industrial chemicals
- Agricultural chemicals
- Physical agents (heat, radiation)
- By-products of combustion and industrial processes (dioxin)
- Infectious agents
- Microbiome (gut flora)
- Foods and nutrients
- Prescription drugs
- Lifestyle choices and substance abuse
- Social and economic factors

NIEHS
National Institute of Environmental Health Sciences

Gene-Environment and Disease

- Why have some diseases increased in incidence over the past 40 years?
- Genes have not changed over that time
- Recent "epidemics" of diabetes, asthma, ADHD, obesity due to environmental, dietary and behavioral changes
- We will never understand the etiology of diseases without an understanding of the role of "environment

NIEHS
National Institute of Environmental Health Sciences

Diseases with a Known or Suspected Environmental Component Include:

- Cancers
- Birth defects (cleft palate, cardiac malformations)
- Reproductive dysfunction (infertility)
- Lung dysfunction (asthma, asbestosis)
- Neurodegenerative diseases (Parkinson's)
- Neurodevelopmental disorders (autism)

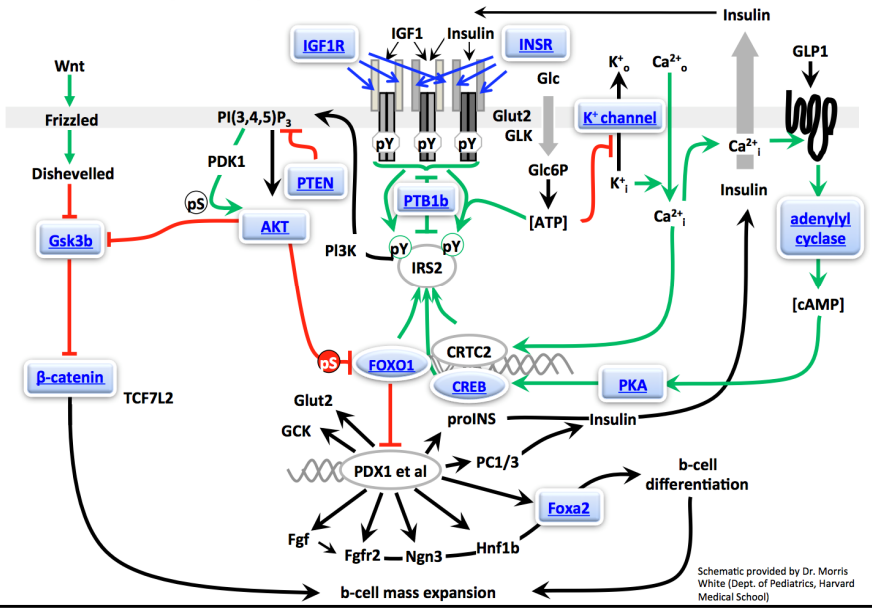
NIEHS
National Institute of Environmental Health Sciences

What is the Endocrine System?

- Complex system of hormones and receptors
  - Multiple receptors (cellular/nuclear)
  - Multiple cofactors
  - Receptor cross-talk
  - Hormones active at pM-nM concentrations
  - SERMs
- Multiple modes of action over a wide dose response
  - Non-monotonic dose responses
  - High doses do not predict low dose effects
  - High doses cause negative feedback
- Doses examined must be in the range of agent binding to receptor system
- Highly conserved across species

NIEHS
National Institute of Environmental Health Sciences

Insulin Signaling in Peripheral Tissue

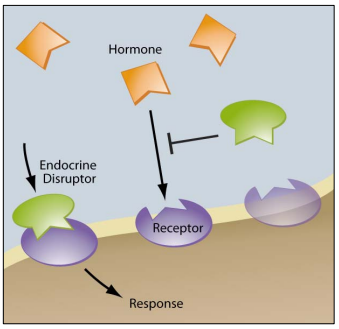


NIEHS
National Institute of Environmental Health Sciences

Some Chemicals Disrupt the Endocrine System

"Endocrine Disruptors"

Exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes

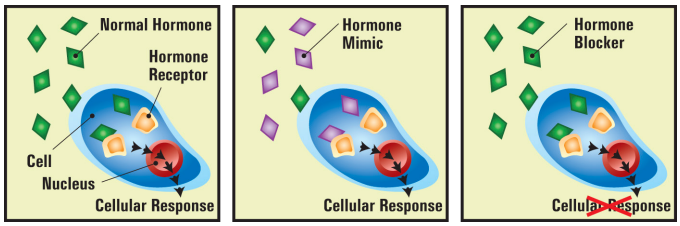


EPA definition modified from Crisp et al, "Environmental Endocrine Disruption: An Effects Assessment and Analysis," *EHP* 1998.

NIEHS
National Institute of Environmental Health Sciences

Why We Study Endocrine Disrupting Chemicals

- Low doses can have big effects
- Wide range of effects on our health
- Early life exposures can have persistent effects
- Endocrine disrupting chemicals are ubiquitous



NIEHS
National Institute of Environmental Health Sciences

Exposure to Endocrine Disruptors:
Effects in Wildlife (Fish, Frogs, Reptiles And Birds)

Decreases
- Survival
- Immune system - resistance to disease

Increases
- Size of thyroid
- Size of liver
- Abnormal testes and ovaries
- Spontaneous abortions
- Abnormal sexual behavior

Disruption
- Thyroid hormones
- Estrogen - ovarian hormones
- Androgen - testicular hormones

- Canaries in the coal mine…

NIEHS
National Institute of Environmental Health Sciences

Endocrine Disrupting Chemicals

HERBICIDES
2,4,-D
2,4,5,-T
Alachlor
Amitro
Atrazine
Linuron
Metribuzin
Nitrofen
Trifluralin

FUNGICIDES
Benomyl
Ethylene thiourea
Fenarimol
Hexachlorobenzene
Mancozeb
Maneb
Metiram - complex
Tri-butyl-tin
Vinclozolin
Zineb

METALS

INSECTICIDES
Aldicarb
beta-HCH
Carbaryl
Chlordane
Chlordecone
DBCP
Dicofol
Dieldrin
DDT and metabolites
Endosulfan
Heptachlor / H-epoxide
Lindane (gamma-HCH)
Malathion
Methomyl
Methoxychlor
Oxychlordane
Parathion
Synthetic pyrethroids
Transnonachlor
Toxaphene

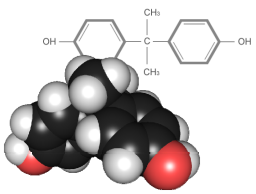
INDUSTRIAL CHEMICALS
Bisphenol - A
Polycarbonates
Butylhydroxyanisole
Cadmium
Chloro- & Bromo-diphenyl
Dioxins
Furans
Lead
Manganese
Methyl mercury
Nonylphenol
Octylphenol
PBDEs
PCBs
Pentachlorophenol
Penta- to Nonylphenols
Perchlorate
PFOA
p-tert-Pentylphenol
Phthalates
Styrene

Testosterone synthesis inhibitor — *Estrogen receptor agonist*
Thyroid hormone disruptor — *Androgen receptor antagonist*

NIEHS
National Institute of Environmental Health Sciences

Low Dose

- Our endocrine system: ***tiny amounts*** of hormones with profound effects on development and normal health
- Chemical exposures, even at low doses, can disrupt delicate endocrine system and create a mechanism for disease



- For some endocrine disruptors, biological changes can be seen at low doses, but not at high doses
- For example, low doses of BPA can change brain structure, function, and behavior in rats and mice exposed during critical periods of development. Some evidence from epidemiology studies.

NIEHS
National Institute of Environmental Health Sciences

Non-Monotonic Dose-Response Curves

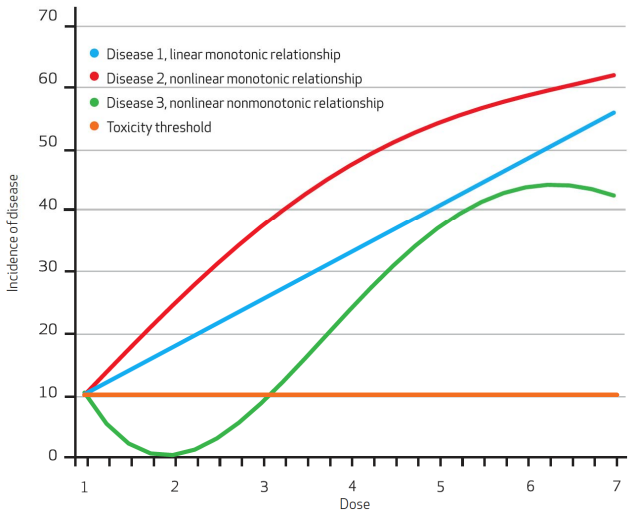
- It's not just about Bisphenol A (BPA)
- NMDRCs in hormones
  - Cortisol
  - Estradiol
  - Progesterone
  - Insulin
  - Growth Hormone
  - Prolactin
  - Testosterone
  - Thyroid Hormone
  - TSH
- NMDRCs in Endocrine Disruptors
  - Atrazine
  - Bisphenol A (BPA)
  - Chlorpyrifos
  - DDT
  - DES
  - Dioxin (TCDD)
  - PBDE-99
  - PCB 180 and PCB Mixtures
  - Perchlorate
  - Sodium fluoride
  - Tributylin oxide
  - Triclosan
  - And others…

NIEHS
National Institute of Environmental Health Sciences

Non-Monotonic Dose-Response Curves

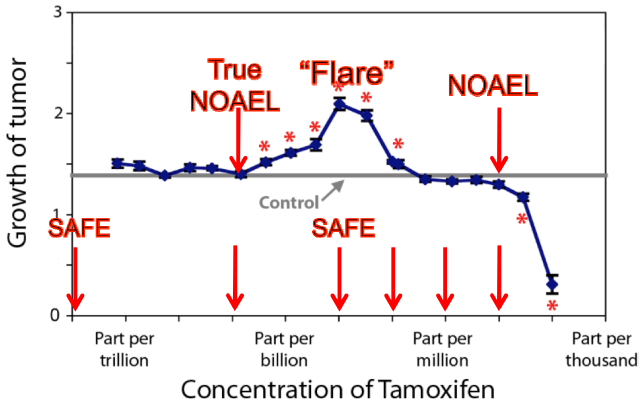
EXHIBIT 1

Depiction Of Various Hypothetical Dose-Response Relationships



NIEHS National Institute of Environmental Health Sciences

A Practical Example: Tamoxifen Flare



Modified from Vandenberg et al, "Hormones and EDCs: Low-Dose Effects and Nonmonotonic Dose Responses," *Endocrine Reviews* 2012.

NIEHS National Institute of Environmental Health Sciences

Wide Range of Health Effects

- Endocrine signals govern ***every organ & process*** in body
- When chemicals interfere, effects can be seen in many different conditions and diseases

- Recent work on endocrine disruption shows potential health effects including immune function, metabolism, brain development and behavior
- Animal studies identified exposure to environmental endocrine disruptors can cause weight gain later in life
- Endocrine Disruptors have also been linked to cancers, altered behavior, diabetes, immune dysfunction, reproductive dysfunction, and cardiovascular disease

NIEHS
National Institute of Environmental Health Sciences

Endpoints / Outcomes

- Cancer and birth defects are not the only endpoints.
- Complex diseases have complex causes.
- The environment is a contributor to: obesity, diabetes, cardiopulmonary disease, cancer, birth defects, autoimmune disease, reproductive dysfunction, neurodevelopmental disorders, schizophrenia, addiction, Alzheimer's Disease, and depression.

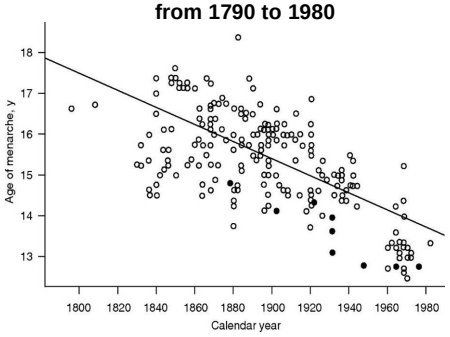
NIEHS
National Institute of Environmental Health Sciences

Decreasing Age of Puberty

US expert panel concluded:

- Earlier breast development and onset of menarche
- "Suggest … endocrine-disrupting chemicals …and body fat are important factors associated" with the change
- African American and Mexican American girls enter puberty earlier than white girls

Age of Menarche in Europe and the US from 1790 to 1980



Euling et al. Pediatrics 2008.

NIEHS National Institute of Environmental Health Sciences

Decreasing Age of Puberty

- The proportion of white girls in the Breast Cancer and the Environment Research Consortium who attained breast stage >2 at age 7 years **significantly greater** than reported in Pediatric Research in Office Settings (PROS) network in 1997.
  - White girls: 10.4% vs 5.0% (z = 3.72, P = .001)
  - Black non-Hispanic girls: 23.4% vs 15.4% (not significant)
- The proportion of white girls at breast stage >2 at age 8 also significantly greater than PROS.
  - White girls: 17.9% vs 10.5% (z = 3.77, P < .0002)
  - Black non-Hispanic girls: 37.0% vs 36.6% (not significant)

Biro et al, Pediatrics 2010.

NIEHS National Institute of Environmental Health Sciences

Decreasing Age of Puberty

Exposure to three chemical classes (phenols, phthalates, and phytoestrogens) in multiethnic longitudinal study of 1,151 girls:

- High-molecular-weight phthalate metabolites and triclosan weakly associated with pubic hair development
- Daidzein with breast stage
- Low-molecular-weight phthalate biomarkers associated with breast and pubic hair development
- Enterolactone attenuated BMI associations with breast development

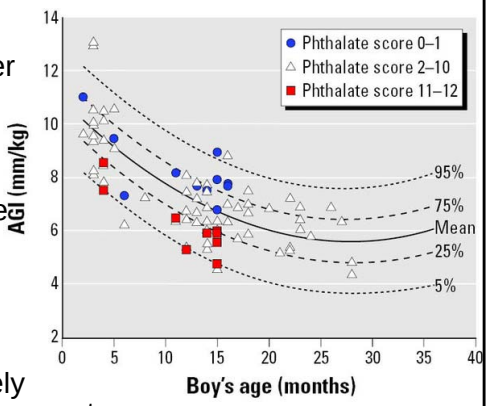
Weak, hormonally active xenobiotic agents had small associations with pubertal development, mainly agents detected at highest concentrations.

Wolff et al, EHP 2010

NIEHS
National Institute of Environmental Health Sciences

Phthalates and Anogenital Distance

- Higher exposure to phthalates (phthalate score) results in lower anogenital index (AGI) in boys.
- Association between AGI and phthalate exposure consistent with phthalate-related syndrome reported in prenatally exposed rodents.
- Data support hypothesis that prenatal phthalate exposure at environmental levels adversely affects male reproductive development.

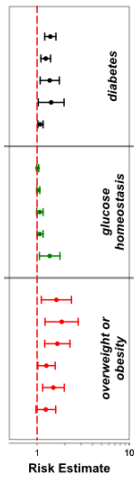


Swann et al, 2005. EHP;113(8):1056–1061

NIEHS
National Institute of Environmental Health Sciences

Bisphenol A & Diabetes / Obesity (Human Studies)

- **BPA and Diabetes, Glucose Homeostatis, Obesity**
  - NTP Review of 8 Studies
  - Studies range from 2008 – 2011
  - Risk Estimates show:
    - All Odds Ratios > 1.00 for diabetes
    - All OR > 1.00 for glucose homeostatis
    - All OR > 1.00 for overweight & obesity
    - No pooled OR available yet



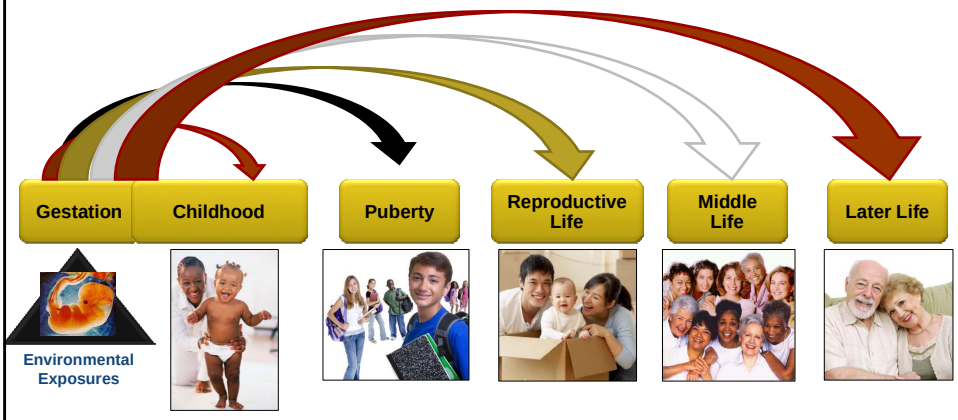
NIEHS
National Institute of Environmental Health Sciences

Persistence of Biological Effects

- Health effects of exposure to endocrine disruptors can be observed ***long after*** the actual exposure has stopped
- This is especially true when exposures occur during growth and development, processes that are very sensitive to endocrine regulation
- Animal researchers discovered that endocrine disruptors can produce latent effects by subtly altering the structure of DNA molecules (epigenetics)
- The NIEHS is conducting human studies on the latent effects of EDC exposure, including studies of children with behavioral, mental and physical abnormalities who were exposed to phthalates or PBDEs before birth

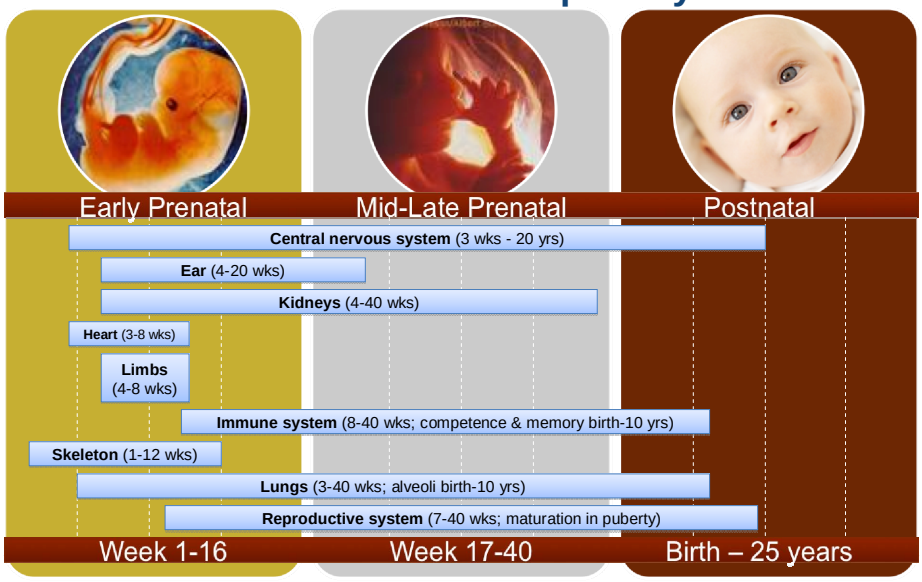
NIEHS
National Institute of Environmental Health Sciences

Developmental Origins of Disease:
Developmental Stressors Lead to Disease Throughout Life



NIEHS
National Institute of Environmental Health Sciences

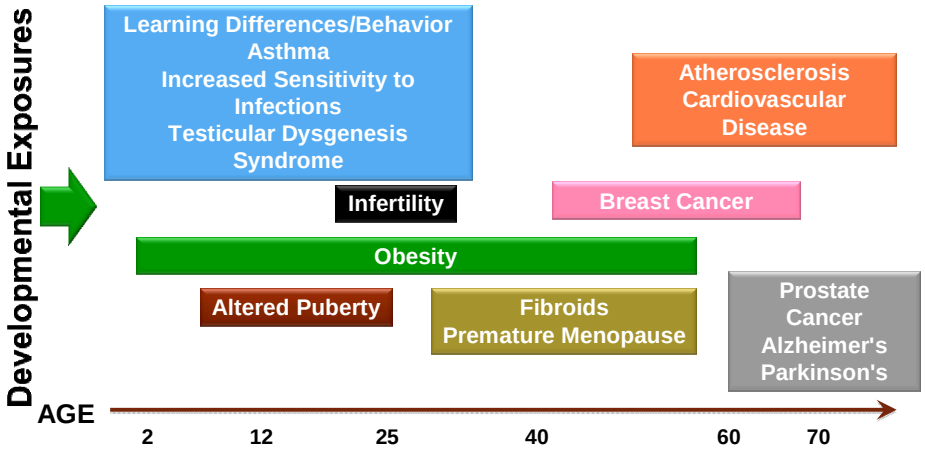
Windows of Susceptibility



Source: Altshuler, K; Berg, M et al. *Critical Periods in Development*, OCHP Paper Series on Children's Health and the Environment, February 2003.

NIEHS
National Institute of Environmental Health Sciences

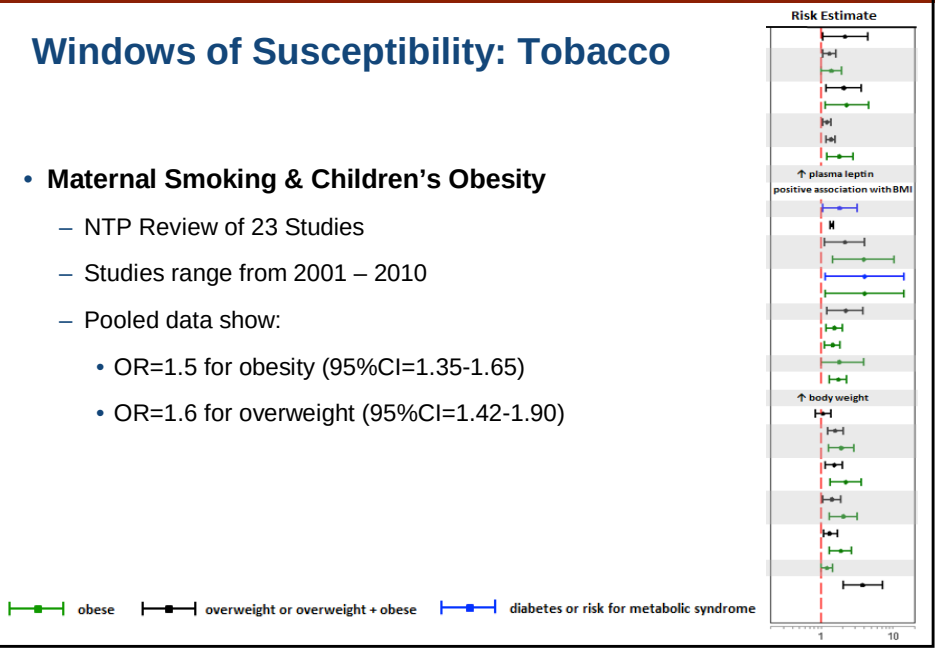
Examples of Developmental Origins of Health and Disease (DOHAD)



NIEHS
National Institute of Environmental Health Sciences

Windows of Susceptibility: Tobacco

- **Maternal Smoking & Children's Obesity**
  - NTP Review of 23 Studies
  - Studies range from 2001 – 2010
  - Pooled data show:
    - OR=1.5 for obesity (95%CI=1.35-1.65)
    - OR=1.6 for overweight (95%CI=1.42-1.90)



NIEHS
National Institute of Environmental Health Sciences

Ubiquitous Exposure

- Chemicals with endocrine disrupting activity are ***widely dispersed in our environment***
- Endocrine disruptors are often dispersed at biologically effective levels, and exposure to humans is common
- This is well documented by the CDC's National Exposure Report

NIEHS
National Institute of Environmental Health Sciences

Mixtures

- Exposures do not occur singly
- All of us are exposed to many different chemicals, and other environmental stressors, at the same time
- Several exposures at once can have synergistic effects on various metabolic pathways
- One exposure can also alter the body's response to later exposures
- The "exposome" is the totality of exposures that a person is subjected to from the environment

NIEHS
National Institute of Environmental Health Sciences

Public Health Implications of Environmental Effects

- Most environmental health assessments are made at the individual level.
- However, a small effect in individuals can aggregate into huge effects in a population.
- An example by David Bellinger shows the total, population-wide loss of full-scale IQ (FSIQ) points from medical conditions vs. environmental chemical exposures.
- When viewed from a population standpoint, environmental exposures can exact a huge toll.

Table 2. Estimated FSIQ point losses associated with different risk factors in a population of 25.5 million children.

Risk factor	Total no. of FSIQ points lost
Medical conditions	
Congenital heart disease	104,805
Preterm birth	34,031,025
Type 1 diabetes	185,640
Acute lymphocytic leukemia	135,788
Brain tumors	37,288
Duchenne muscular dystrophy	68,850
Neurodevelopmental disorders	
ASDs	7,109,899
Pediatric bipolar disorder	8,164,080
ADHD	16,799,400
Postnatal traumatic brain injury	5,827,300
Socioeconomic, nutritional, psychosocial factors	
Nonorganic failure to thrive	5,355,000
Iron deficiency	9,409,500
Environmental chemical exposures	
Methylmercury	284,580
Organophosphate pesticides	16,899,488
Lead	22,947,450

NIEHS
National Institute of Environmental Health Sciences

Need for Chemical Testing

- Over 80,000 chemicals in commerce today
- Majority of chemicals in commerce are untested
- About 12 chemicals (alcohol, lead, mercury, etc.) have been closely associated with human cognitive impairment
- About 100 chemicals have been shown to impair brain development in animal models



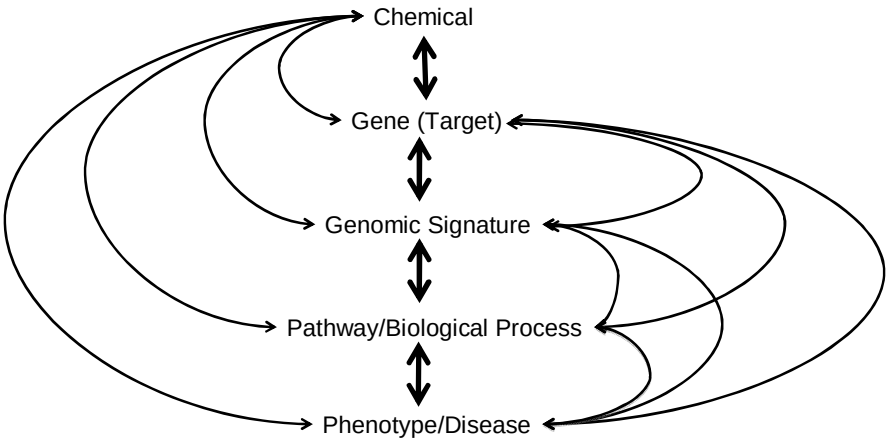

NIEHS
National Institute of Environmental Health Sciences

Toxicity Testing in the 21st Century

- Advancing Technology
  - In vitro screening
    - Human tissues more readily available
    - Increases in through-put
      - From 10's to 100,000 chemicals/year/assay
  - Omics
    - Genomics, Proteomics, Metabolomics
      - From single endpoints to high content data (10's of endpoints to 10,000,s)
  - Bioinformatic advances and challenges
    - How do we use all this high content data?
      - Development of databases linking genomic signatures with pathologies
      - Development of predictive signatures of pathological and toxicological concerns

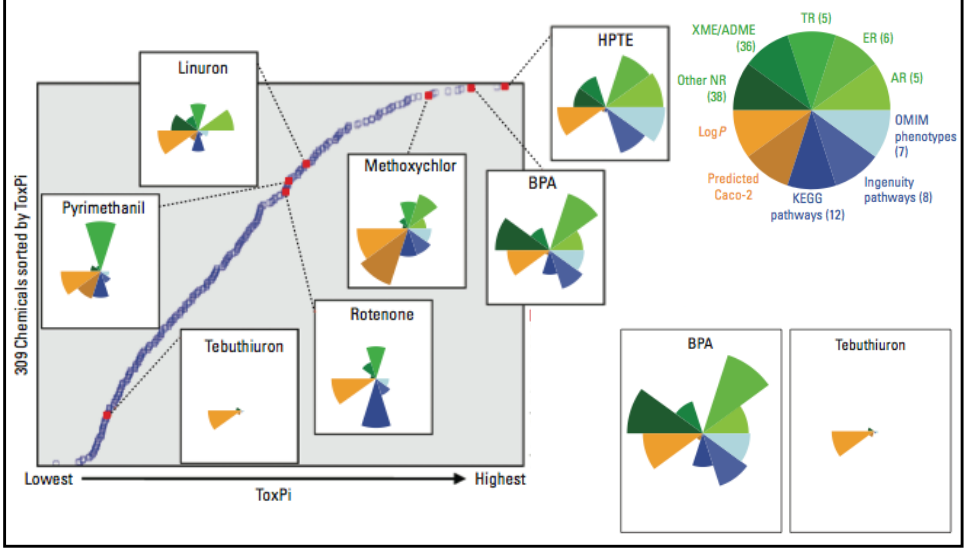
NIEHS
National Institute of Environmental Health Sciences

Relationships Evaluated in Tox 21



NIEHS
National Institute of Environmental Health Sciences

High-Throughput Screening: Bisphenol A



NIEHS
National Institute of Environmental Health Sciences

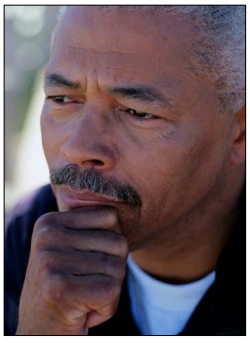
Considerations When Testing for Endocrine Activity

- Low doses
- Non monotonic dose responses
- Modes of action change across dose response
- Strain and species vary in sensitivity
- Development (in utero and neonatal) will be a sensitive window of exposure
- Developmental effects may not show up until later in life
- Assessment of new endocrine related endpoints may be needed
- Expect conservation of receptors and pathways across species

NIEHS
National Institute of Environmental Health Sciences

Summary: Where We Go From Here

- Endocrine Disruptors are cause for concern
- Need to better characterize:
  - Low dose / nonmonotonic effects
  - Wide range of biological effects
  - Later life effects from early life exposures
  - Effects from mixtures
  - Exposure assessment
- Focus on Public Health impact
- Regulatory issues



NIEHS
National Institute of Environmental Health Sciences

Thank you!