National Institute of Environmental Health Sciences
Your Environment. Your Health.

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

Decoding UCMR3: Clear Communication about Drinking Water Contaminants

Christopher P Weis, Ph.D., D.A.B.T.

Office of the Director

National Institute of Environmental Health Science and National Toxicology Program

Bethesda, Maryland USA

October 25, 2013

The National Institute of Environmental Health Sciences

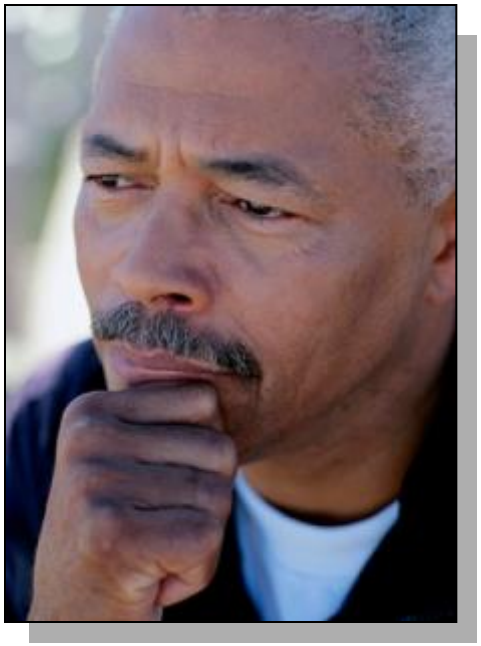
- One of the U.S. National Institutes of Health, but located in Research Triangle Park, North Carolina
- Wide variety of programs supporting our mission of environmental health:
  - -- Intramural laboratories
  - -- Extramural funding programs
  - -- Disease Prevention
  - -- Clinical research program
  - -- National Toxicology Program
  - -- Public Health Focus

New ways of thinking about environmental health sciences…

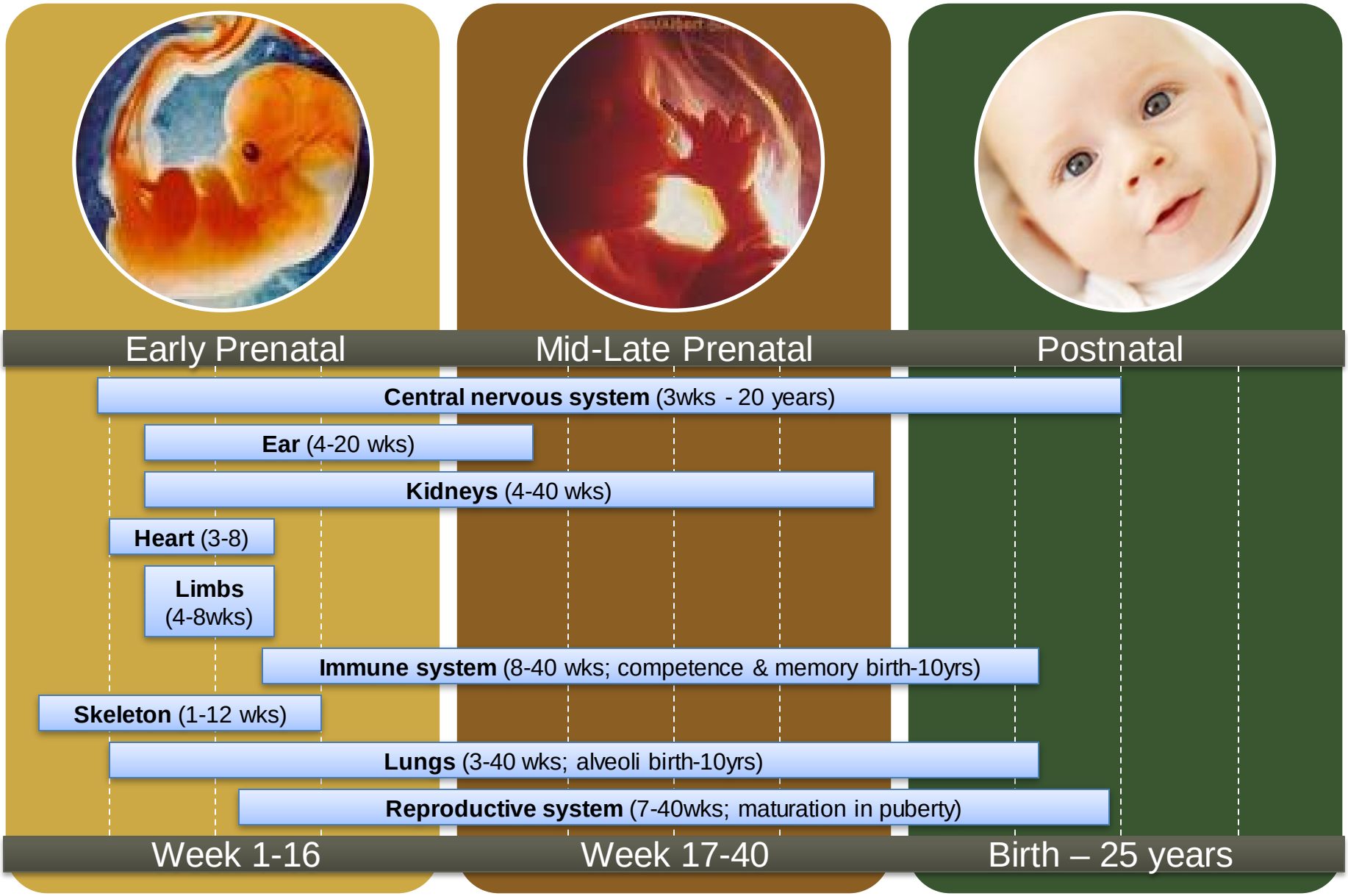
OLD… chemicals act by overwhelming the body's defenses by brute force at very high doses

NEW… chemicals can act like hormones and drugs to disrupt the control of development and function at very low doses to which the average person is exposed

NEW… susceptibility to disease persists long after exposure **(epigenetics)**

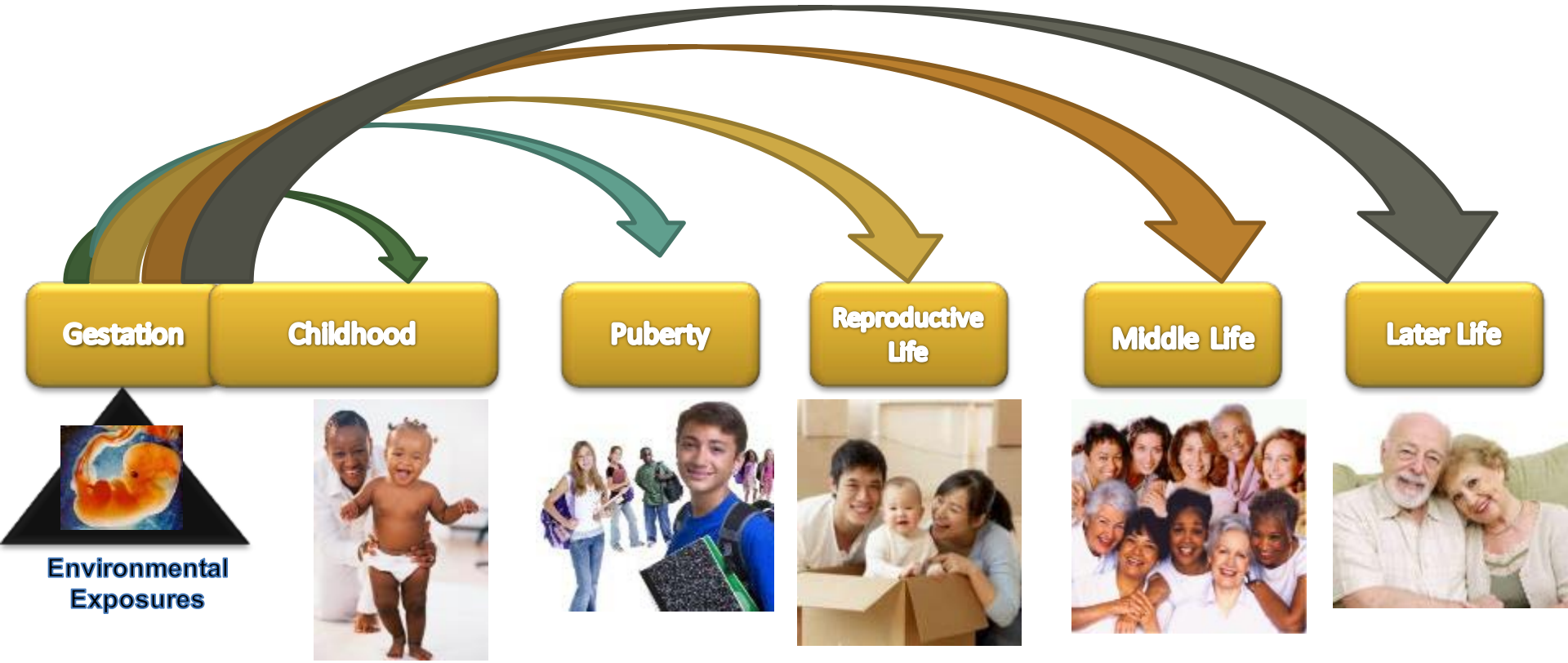


Stages of Prenatal and Postnatal Organ Development

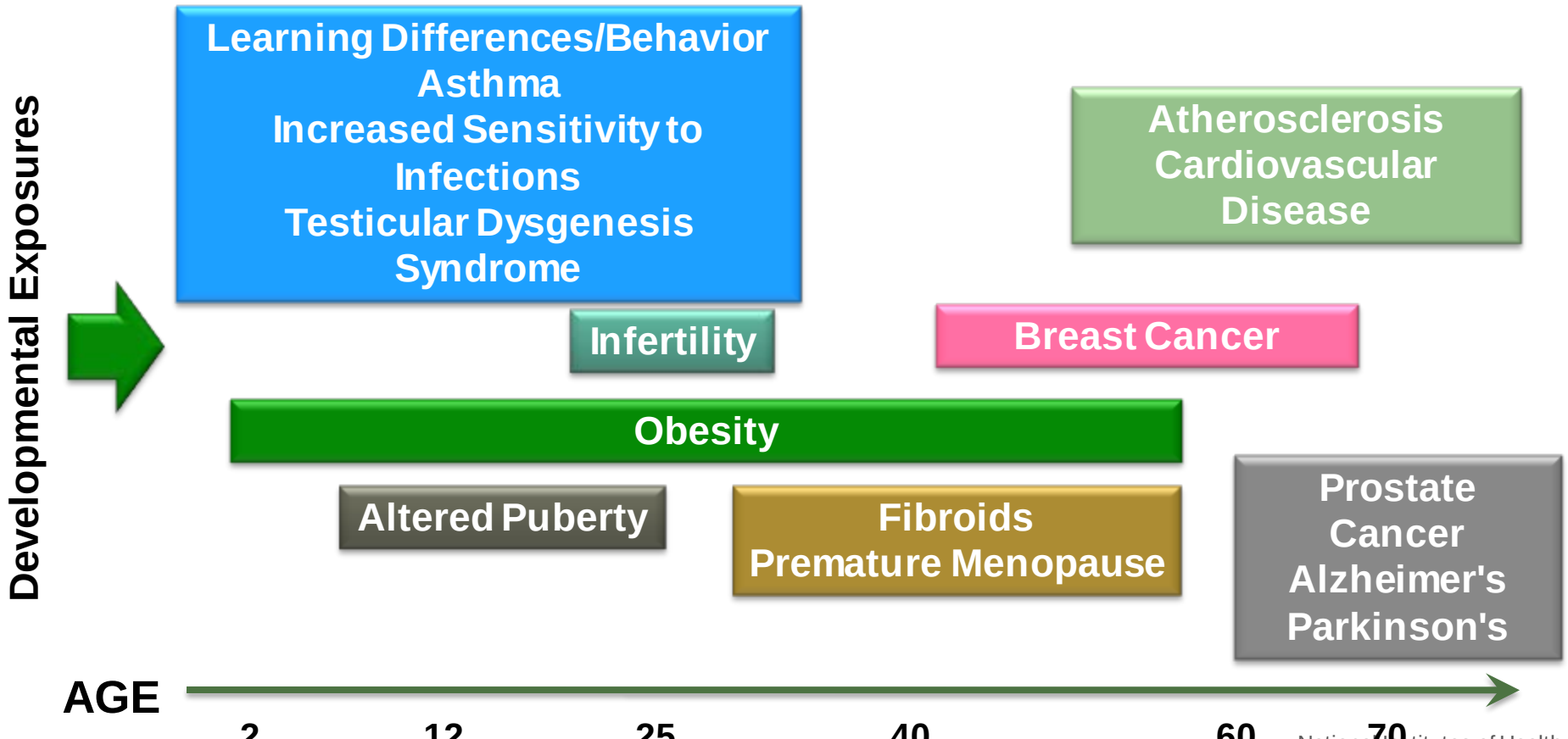


Source: Altshuler, K; Berg, M et al. *Critical Periods in Development,* OCHP Paper Series on Children's Health and the Environment, February 2003.

Windows of Susceptibility: Developmental Exposures Lead to Disease Throughout Life



Examples of Developmental Origins of Health and Disease (DOHAD)



Endocrine Disruptors*

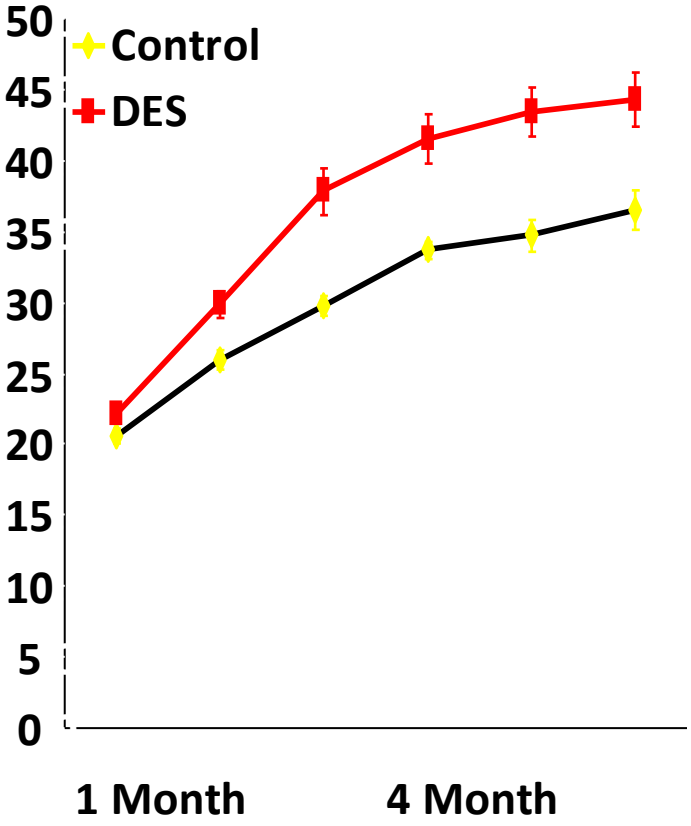
- **There are more than 85,000 chemicals in commerce;**
- **An unknown subset of these are toxic;**
- **A subset of those that are toxic are EDCs.**

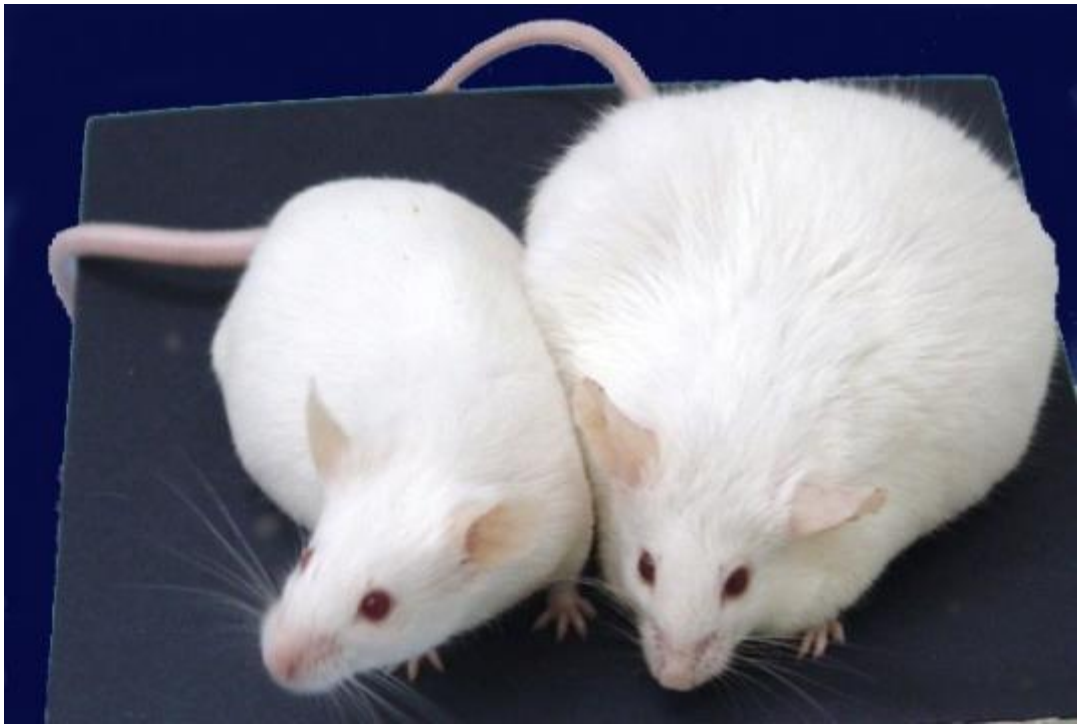
* "An endocrine disruptor (ED) is an exogenous substance or mixture that **alters function(s) of the endocrine system and consequently causes *adverse health effects*** in an intact organism, or its progeny, or (sub) populations (WHO/I 2002)"

Characteristics of EDC Toxicity

- **Low dose effects**
  - High dose effects are different from low dose effects
  - Non-monotonic dose-responses
- **Wide range of effects**
  - Endocrine signaling govern all tissues/organs
  - Nuclear and membrane receptors, neurotransmitters, metabolism
- **Persistent and latent effects**
  - Developmental exposure most sensitive window
  - Trans-generational effects (vinclozolin, dioxin, BPA, phthalates)
- **Ubiquitous exposure**
  - Consumer products
  - Pharmaceuticals
  - Industrial products

Developmental Exposure to DES and Weight Gain Proof of Principle





Exposure of CD-1 mice to DES for 5 days at birth results in increased weight gain starting at puberty in female mice. No change in food intake or exercise. Newbold et al. (2006)

Examples of Endocrine Disruptors

HERBICIDES
2,4,-D
Alachlor
Amitrole
Atrazine
Linuron
Metribuzin
Nitrofen
Trifluralin

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

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

INDUSTRIAL CHEMICALS
Bisphenol - A
Polycarbonates
Butylhydroxyanisole (BHA)
Cadmium
Chloro- & Bromo-diphenyl ether
Dioxin (2,3,7,8-TCDD)
Furans
Lead
Manganese
Methyl mercury
Nonylphenol
Octylphenol
PBDEs
PCBs ★
Pentachlorophenol
Penta- to Nonylphenols
p-tert-Pentylphenol
Phthalates
Styrene

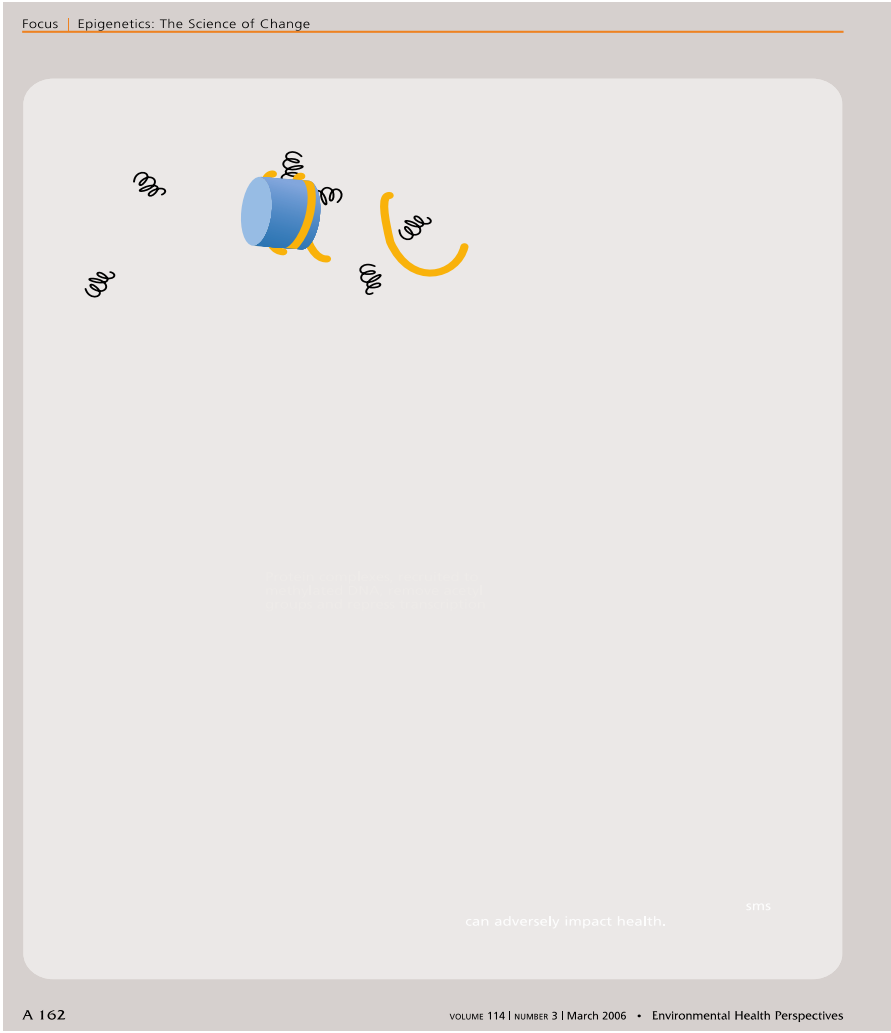
RED= Found in water

One mechanism for epigenetic changes

- **Histone Acetylation by transferases causes expansion of chromatin architecture allowing transcription to occur;**

- **Transcription can be blocked by addition of methyl groups by methyl transferases.**

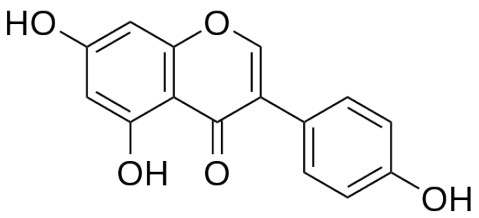
- **Epigenetic changes that occur during sensitive life stages can cause heritable disease.**



B. Weinhold, Environ Health Perspect. 2006 March; 114(3): A160–A167.

Epigenetics: Maternal chemical exposures can cause heritable changes in offspring.

Maternal ingestion of Genstein causes coat color changes in offspring that are traced to heritable changes in methylation patters on DNA.



Genstein

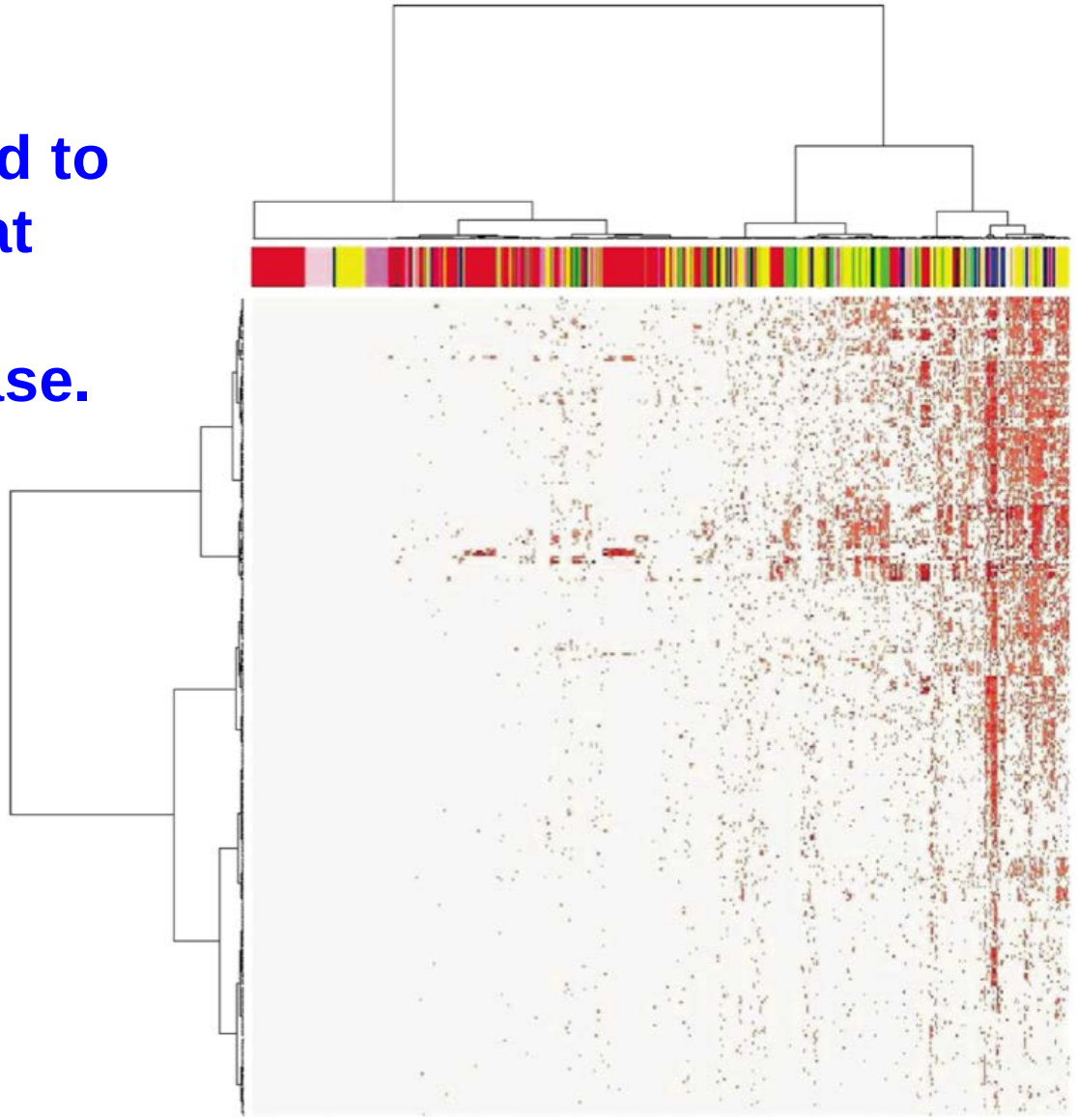
A pup of a different color. Supplementation of maternal diet with genistein and other compounds induced alterations in DNA methylation that were reflected in offspring coat color changes.

Jirtle, EHP, April 2006

Toxicology for the 21st Century Goals….

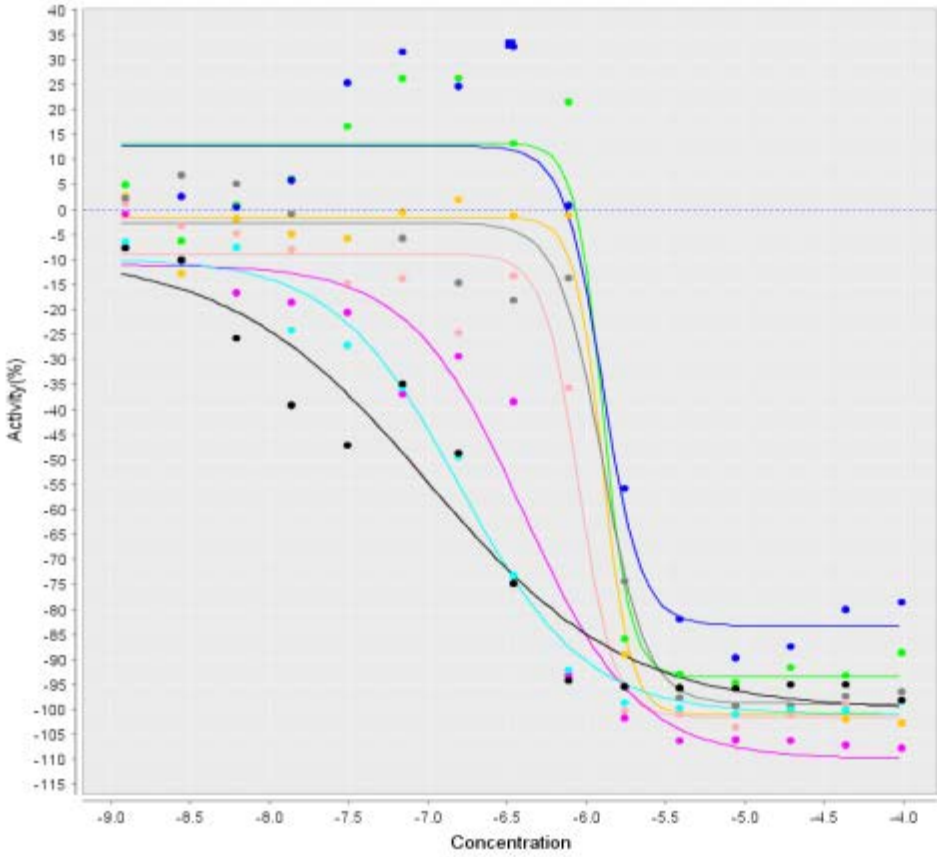
- **Identify patterns of compound-induced biological response in order to:**
  - *characterize toxicity/disease pathways*
  - *facilitate cross-species extrapolation*
  - *model low-dose extrapolation*
- **Prioritize compounds for more extensive toxicological evaluation**
- **Develop predictive models for biological response in humans**

High throughput screening can be used to identify chemicals that activate pathways associated with disease.



The NCGC

- **conducts quantitative high-throughput screening (qHTS)**
  - >300,000 profiles/week
- **qHTS profile**
  - 1536-well plate format
  - 14-point concentration-response curve
  - DMSO soluble
  - 5 nM to 92 μM typical
  - ~5 μL assay volume
  - ~1000 cells/well



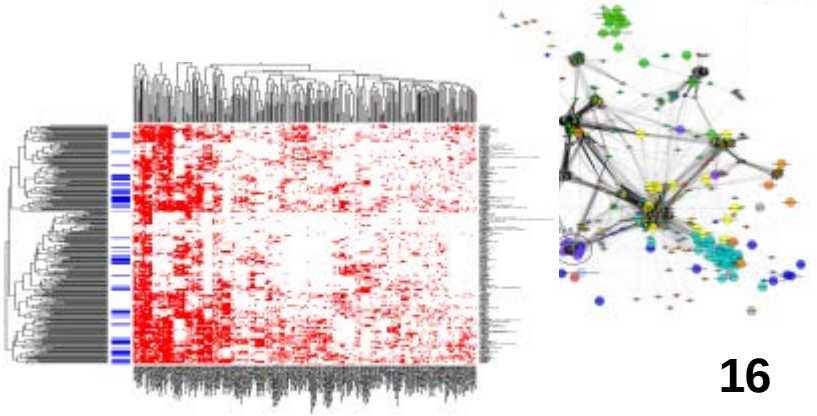
Differential cytotoxicity (measured as levels of ATP) in 7 chicken DT40

New ways of addressing environmental health problems…

Toxicology for the 21st Century Goals….

- **Identify patterns of compound-induced biological response in order to:**
  - characterize toxicity/disease pathways
  - facilitate cross-species extrapolation
  - model low-dose extrapolation
- **Prioritize compounds for more extensive toxicological evaluation**
- **Develop predictive models for biological response in humans**

Tox21



Tox21 Phase II

- **EPA's ToxCast™ Phase II: ~1000 compounds in ~650 assays.**
  - **NCGC qHTS Phase II: >10K compounds 3x at 15 conc for:**
    - **nuclear receptor activation or inhibition (AR, AhR, ER, FXR, GR, LXR, PPAR, PXR, RXR, TR, VDR, ROR)**
    - **induction of stress response pathways (e.g., DNA damage, heat shock, hypoxia, inflammation, mitochondria membrane potential)**
  - **Assay selection based on**
    - **Information from *in vivo* toxicological investigations**
    - **Phase I experience, advice of basic researchers, and nominated assays**
    - **Maps of disease-associated cellular pathways**
  - ***Future focus on disease-associated pathways (e.g., obesity/diabetes, autism) using stem cells/differentiated cells and high throughput gene array assays***

Questions?