

Endocrine Disrupting
Chemicals:
New considerations in the
'toxics space'
TURI Annual Meeting

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Disclosure statement

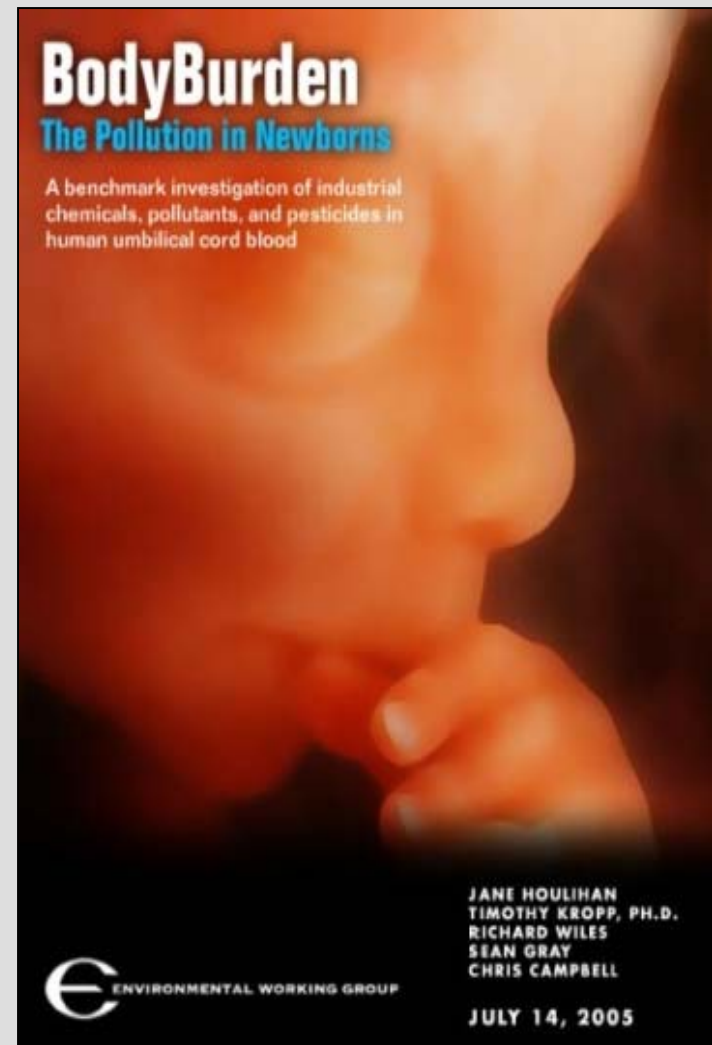
- I am funded by the National Institutes of Health.
- I have received travel support from numerous organizations to give research seminars.
- My spouse is employed by CVS Health.

Goals

- The ‘toxics space’: We all come from different backgrounds, and thus bring different knowledge to the table
- My perspective: Endocrinologists have been working to understand how hormones act in our bodies (and how environmental chemicals disrupt these actions)
- Ultimate goal: It is possible to avoid exposures, at least in some contexts. How should we think about replacing these chemicals?

Chemical Body Burden in Babies (only a few hundred are tested)

- 287 chemicals in cord blood
- 47 chemicals in every pregnant woman tested
- Many chemicals detected in breast milk (PCBs, dioxins, pesticides, mercury, flame retardants & others)



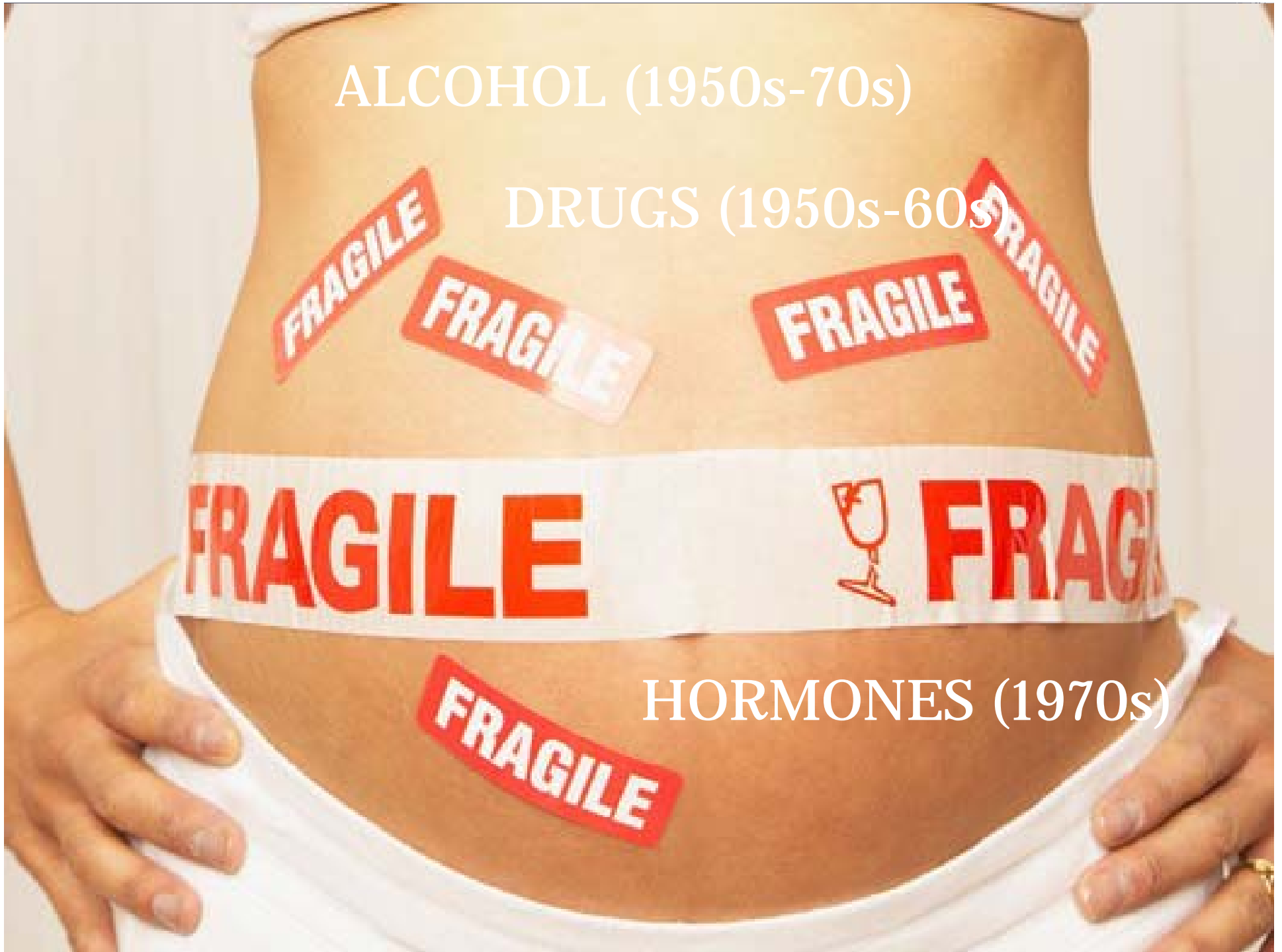


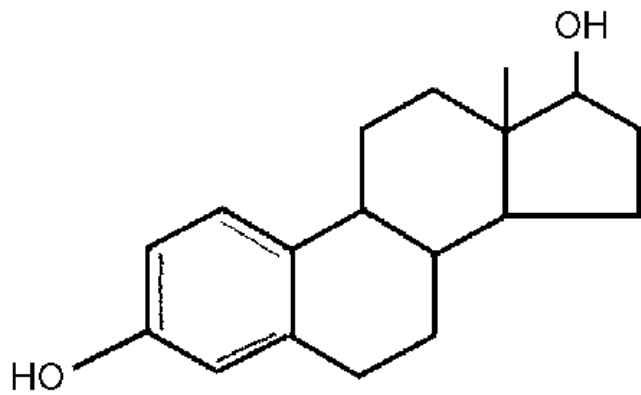
The womb was thought to be a
protected place,
a fortress

ALCOHOL (1950s-70s)

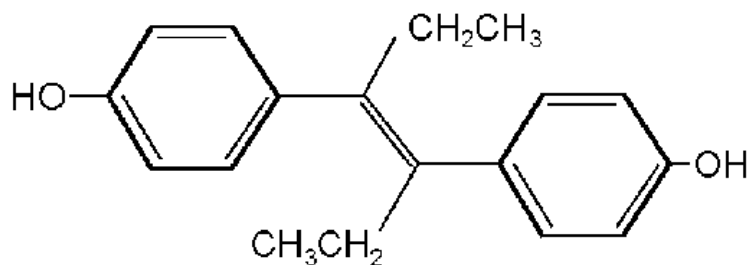
DRUGS (1950s-60s)

HORMONES (1970s)

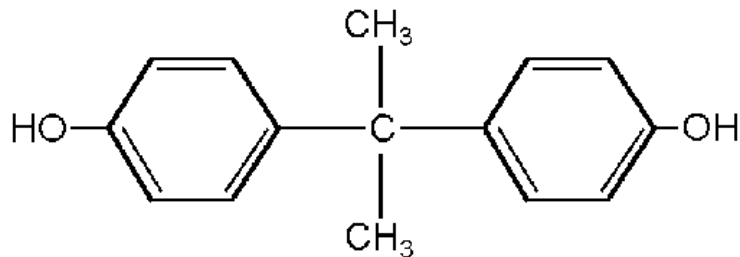




Estradiol



Diethylstilbestrol (DES)



Bisphenol A

The 1940's
led to a push
for synthetic
hormones



TREATMENT OF
Menopausal Disorders

Diethylstilbestrol, Lilly, fulfills all requirements for the prompt and thorough treatment of menopausal disorders. An estrogenic response which quickly eliminates the effects of ovarian inactivity immediately follows the administration of Diethylstilbestrol. A variety of forms and dosage sizes is available through your regular source of medical supplies.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.


Diethylstilbestrol (DES):

Prescribed for:

- treatment of menopause symptoms
- to stop lactation
- birth control
- to prevent spontaneous abortions & stillbirths

DES and "The Fragile Fetus"

Medscape® www.medscape.com



"Really?"

Yes...
desPLEX®

to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies . . .*

96 per cent live delivery with **desPLEX**
in one series of 1200 patients:
- *bigger and stronger babies, too.*

No gastric or other side effects with **desPLEX**
- in either high or low dosage^{1,4,5}

Source: J Midwifery Womens Health © 2003 Elsevier Science, Inc.

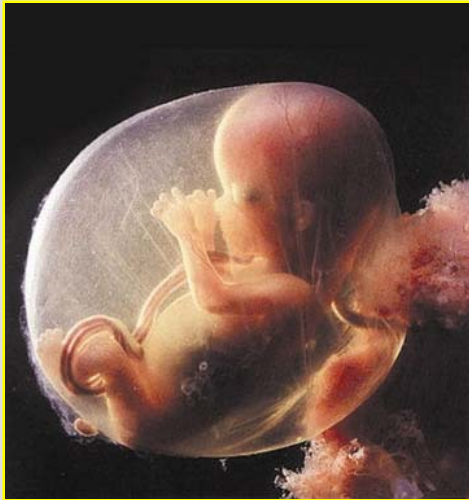
bigger and stronger babies, too.

Diethylstilbestrol (DES):

A potent synthetic estrogen given to between 2 and 10 million pregnant women in the US between the years of 1948 and 1971.

DES treatment was banned in the US in 1971, but continued to be used in other countries until the 1980s.

Developmental Origins of Health and Disease (DOHaD)



HEALTHY



DISEASE

DOHaD: The Dutch Famine

prenatal cues $\xrightarrow[\text{prepare for}]{\text{predict}}$ postnatal environment

famine



thrive in a limited environment

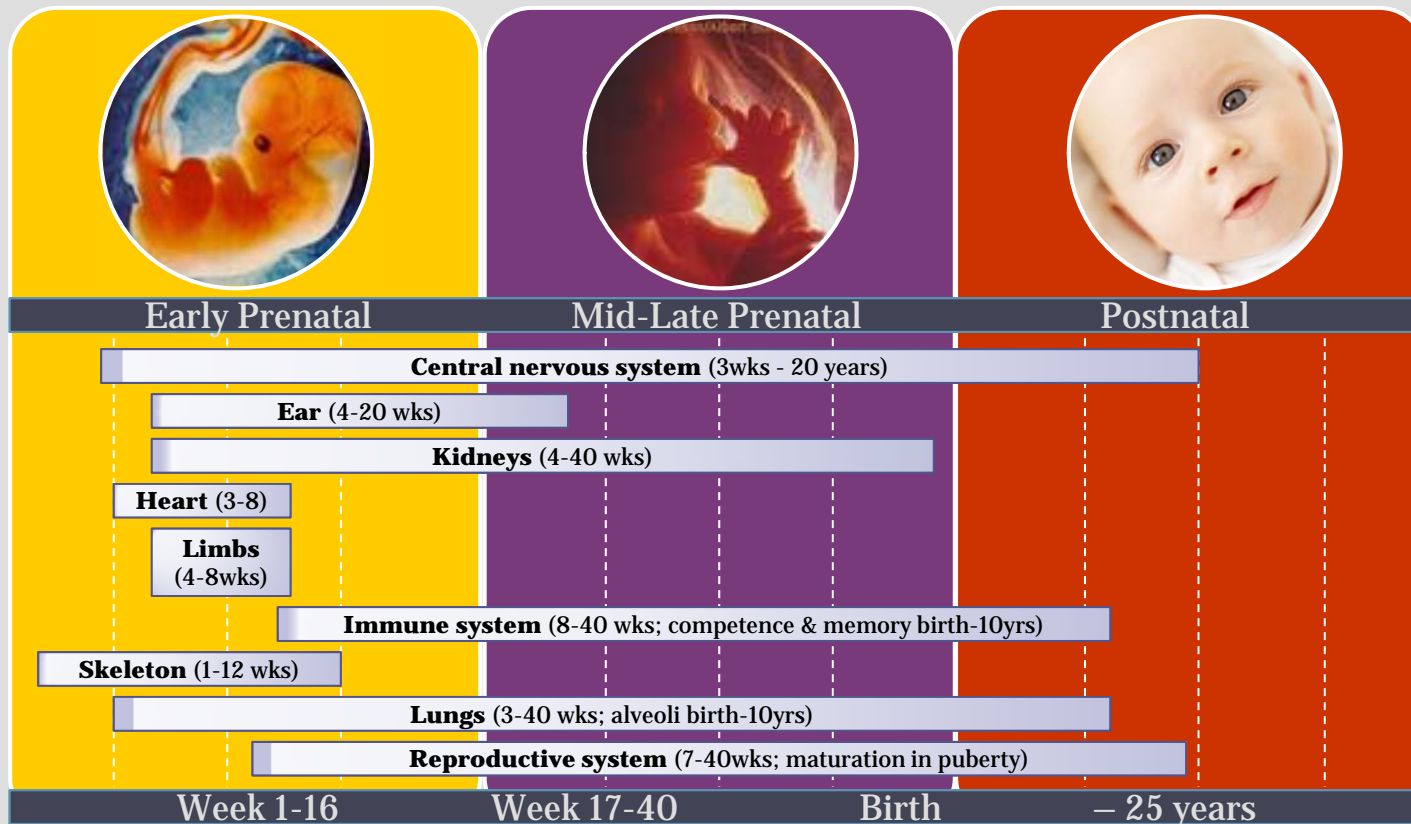
????? in a plentiful environment

"The Fragile Fetus"



In addition to malnutrition, other prime examples of the **fragile fetus** include exposure to thalidomide, alcohol, or other drugs during gestation.

Critical windows of development differ by organ



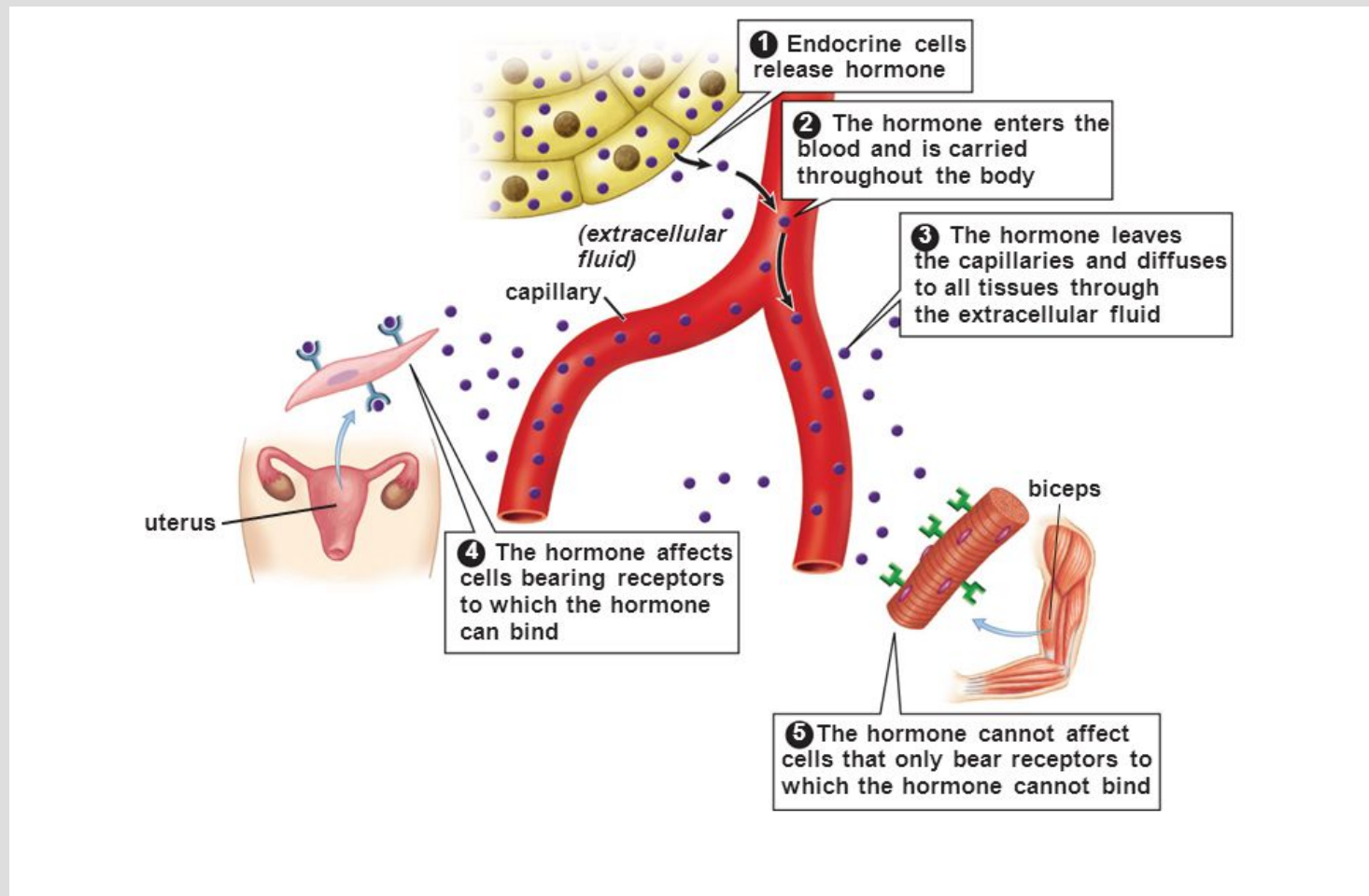


THE
ENDOCRINE
SOCIETY

Endocrine Disrupting Chemicals (EDCs)

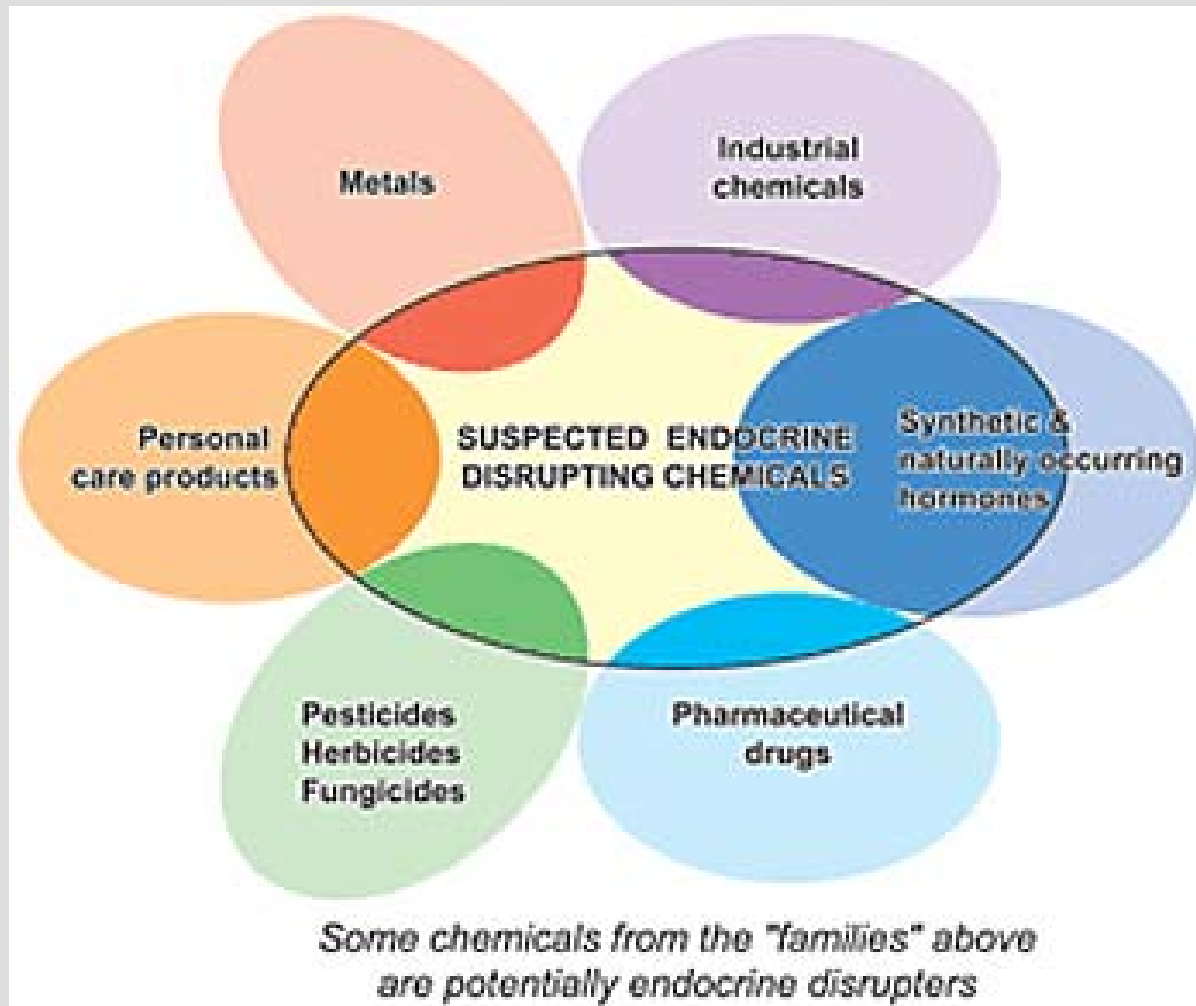
EDCs are exogenous chemicals or chemical mixtures that interfere in some way with hormone action.

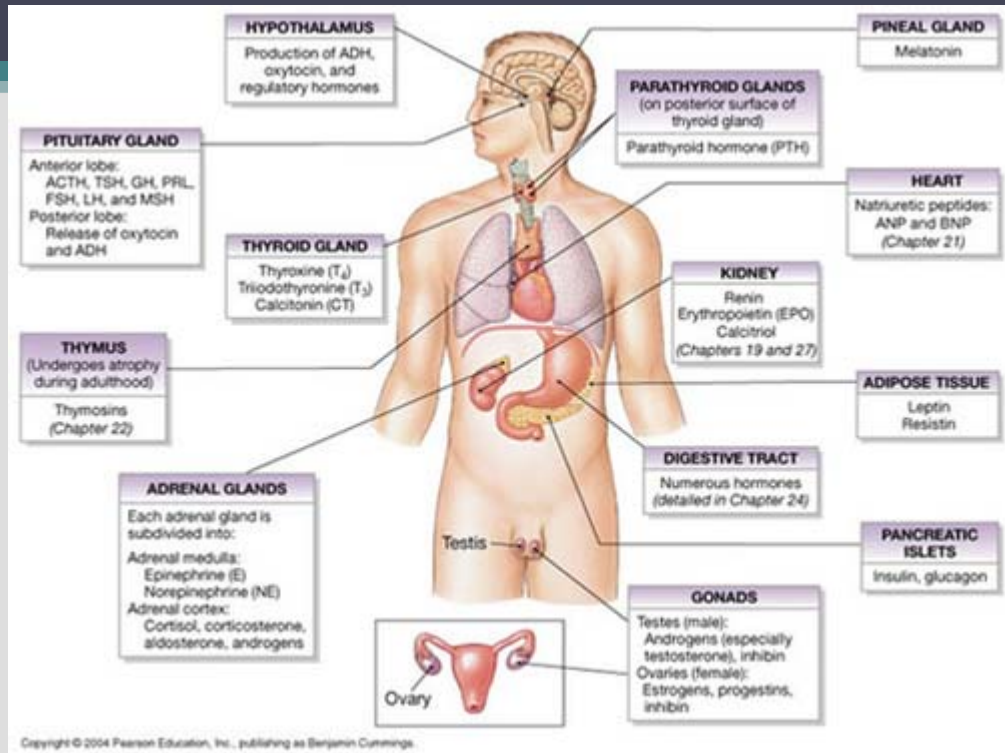
Hormone action



EDCs and regulatory agencies

- EPA: “An endocrine disruptor is an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.”





The Endocrine System: What doesn't it control?



Low doses of hormones can induce permanent alterations in development

“From the day of conception until an individual is born or hatched, the development of each stage of life is fully under the control of hormones.

Changes that happen during development are far less reversible [than those occurring in an adult]; you can't go back and rewire the brain”.

-Theo Colborn, zoologist, writer



The Low Dose Hypothesis

- 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

In 2002, the NTP agreed that there were “low dose effects” for 4 EDCs

- DES (adult prostate weight)
- Genistein (brain sexual dimorphisms, male mammary gland development, immune responses)
- Methoxychlor (immune responses)
- Nonylphenol (brain sexual dimorphisms, immune response, estrus cyclicity)

- *BPA (adult prostate weight)*

- *Octylphenol*

Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

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For decades, studies of endocrine-disrupting chemicals (EDCs) have challenged traditional concepts in toxicology, in particular the dogma of “the dose makes the poison,” because EDCs can have effects at low doses that are not predicted by effects at higher doses. Here, we review two major concepts in EDC studies: low dose and nonmonotonicity. Low-dose effects were defined by the National Toxicology Program as those that occur in the range of human exposures or effects observed at doses below those used for traditional toxicological studies. We review the mechanistic data for low-dose effects and use a weight-of-evidence approach to analyze five examples from the EDC literature. Additionally, we explore nonmonotonic dose-response curves, defined as a nonlinear relationship between dose and effect where the slope of the curve changes sign somewhere within the range of doses examined. We provide a detailed discussion of the mechanisms responsible for generating these phenomena, plus hundreds of examples from the cell culture, animal, and epidemiology literature. We illustrate that nonmonotonic responses and low-dose effects are remarkably common in studies of natural hormones and EDCs. Whether low doses of EDCs influence certain human disorders is no longer conjecture, because epidemiological studies show that environmental exposures to EDCs are associated with human diseases and disabilities. We conclude that when nonmonotonic dose-response curves occur, the effects of low doses cannot be predicted by the effects observed at high doses. Thus, fundamental changes in chemical testing and safety determination are needed to protect human health. (*Endocrine Reviews* 33: 378–455, 2012)

I. Introduction

- A. Background: low-dose exposure
- B. Background: NMDRCs
- C. Low-dose studies: a decade after the NTP panel’s assessment
- D. Why examine low-dose studies now?
- E. Mechanisms for low-dose effects
- F. Intrauterine position and human twins: examples of natural low-dose effects

II. Demonstrating Low-Dose Effects Using a WoE Approach

- A. Use of a WoE approach in low-dose EDC studies
- B. Refuting low-dose studies: criteria required for acceptance of studies that find no effect
- C. BPA and the prostate: contested effects at low doses?
- D. BPA and the mammary gland: undisputed evidence for low-dose effects

Abbreviations: A4, Androstenedione; AhR, aryl hydrocarbon receptor; BPA, bisphenol A; CDC, Centers for Disease Control and Prevention; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DES, diethylstilbestrol; EDC, endocrine-disrupting chemical; EPA, Environmental Protection Agency; ER, estrogen receptor; FDA, Food and Drug Administration; GLP, good laboratory practices; LOAEL, lowest observed adverse effect level; mER, membrane-associated ER; NHANES, National Health and Nutrition Examination Survey;NIS, sodium/iodide symporter; NMDRC, nonmonotonic dose-response curve; NOEL, no observed effect level; NOAEL, no observed adverse effect level; NTP, National Toxicology Program; PIN, prostatic intraepithelial neoplasia; POP, persistent organic pollutants; ppb, parts per billion; SERM, selective ER modulator; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; WoE, weight of evidence.

Why did we revisit the 'low dose hypothesis'?

Epidemiology studies continue to suggest associations between EDC exposures and human disease

- Phthalates: neurobehavior, adult fertility, metabolic syndrome, anogenital distance
- Dioxin: metabolic syndrome, male infertility, age of pubertal onset (males)
- DDT: body weight, cancer, neurodevelopment, oxidative stress
- Atrazine: size at birth, pre-term birth, abdominal defects, cancer, sperm quality
- Heptachlor: diabetes, asthma & chronic bronchitis, male reproductive tract defects
- PBDEs: thyroid hormone levels, neurodevelopment, autism
- BPA: metabolic syndrome, infertility, neurodevelopment
- Dieldrin: neurotoxicity, cancer, diabetes, infertility
- Toluene: bronchitis & asthma
- Simazine: cancer
- Chlorpyrifos: neurodevelopment, behavior, asthma

Evidence Linking EDCs to Human Disease



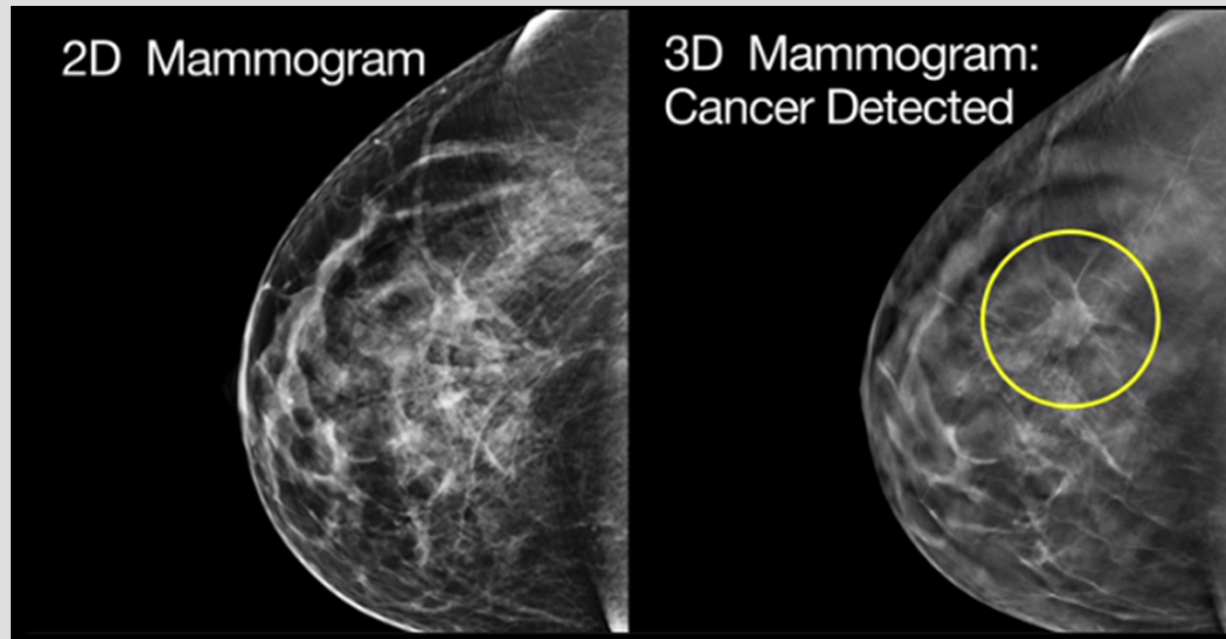
Addressing some common misperceptions



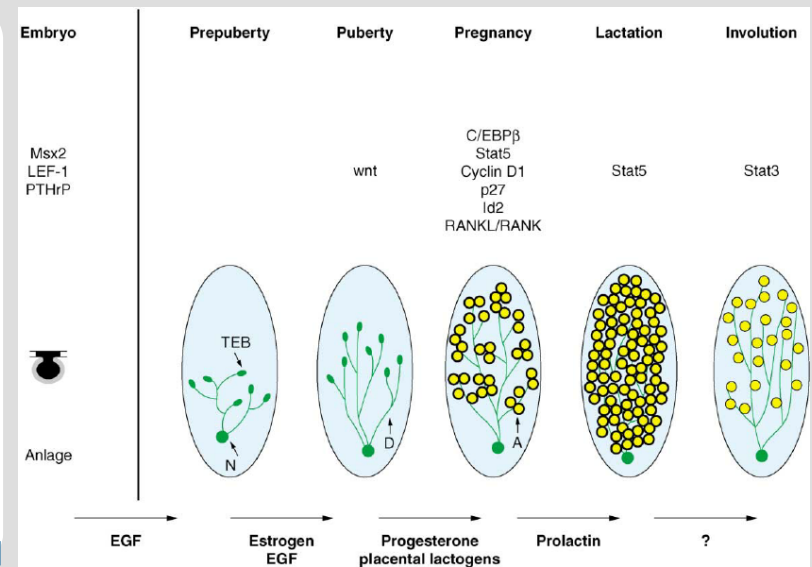
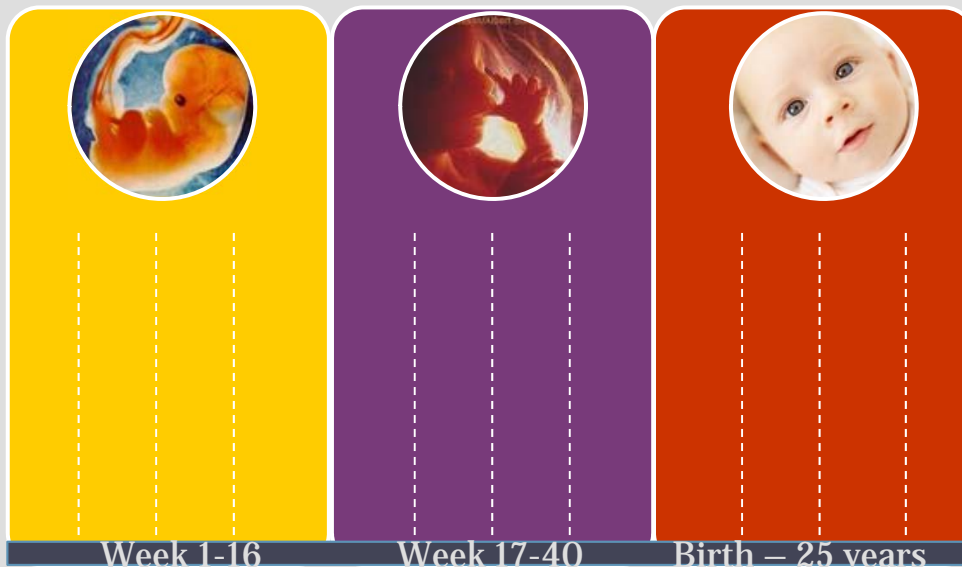
Animals aren't people. How much do these studies really tell us?

Animals are an essential component of drug testing (FDA)

Rodents were excellent predictors of the DES syndrome



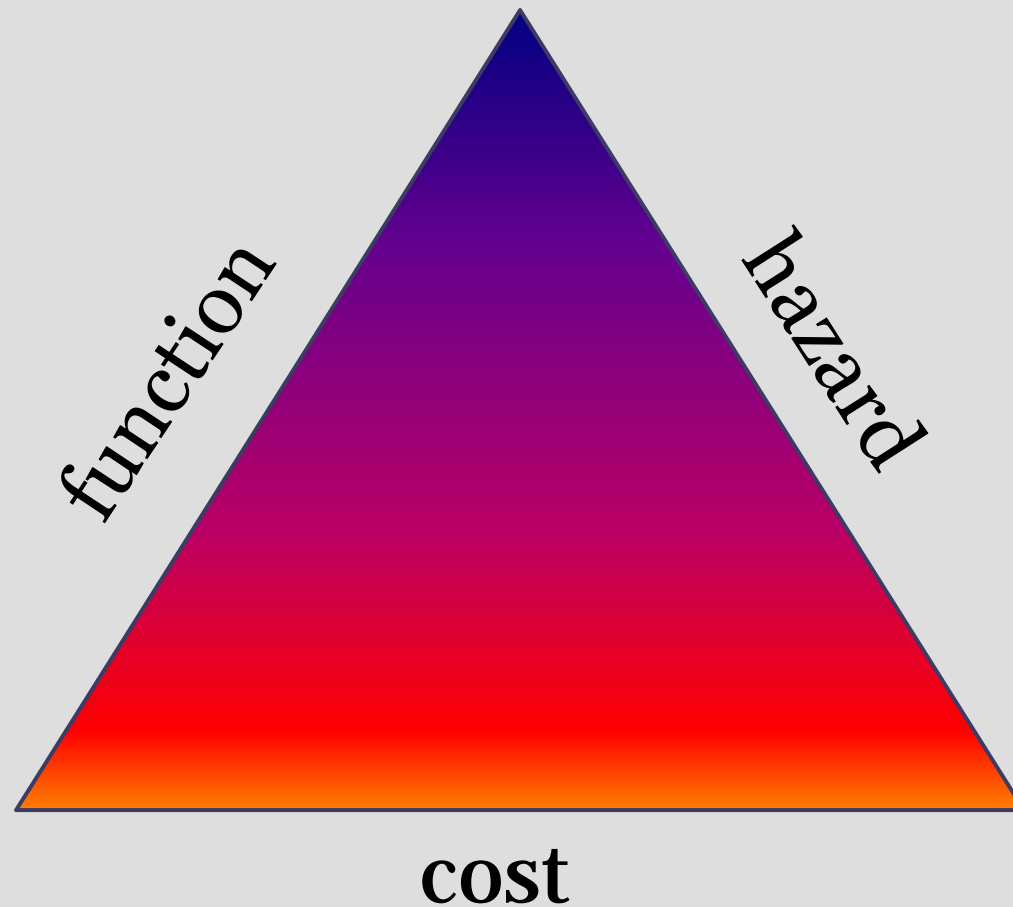
Critical windows of development: the adult is unaffected



The “natural” versus “unnatural” debate



BPA costs “pennies per pound” ... we will never find a cheaper replacement



Eliminating these chemicals means
living in the dark ages



Exposures are so low that they can't cause harm



“But we’ve all been exposed and we’re all fine!”

Hormone associated diseases/disorders on the rise:

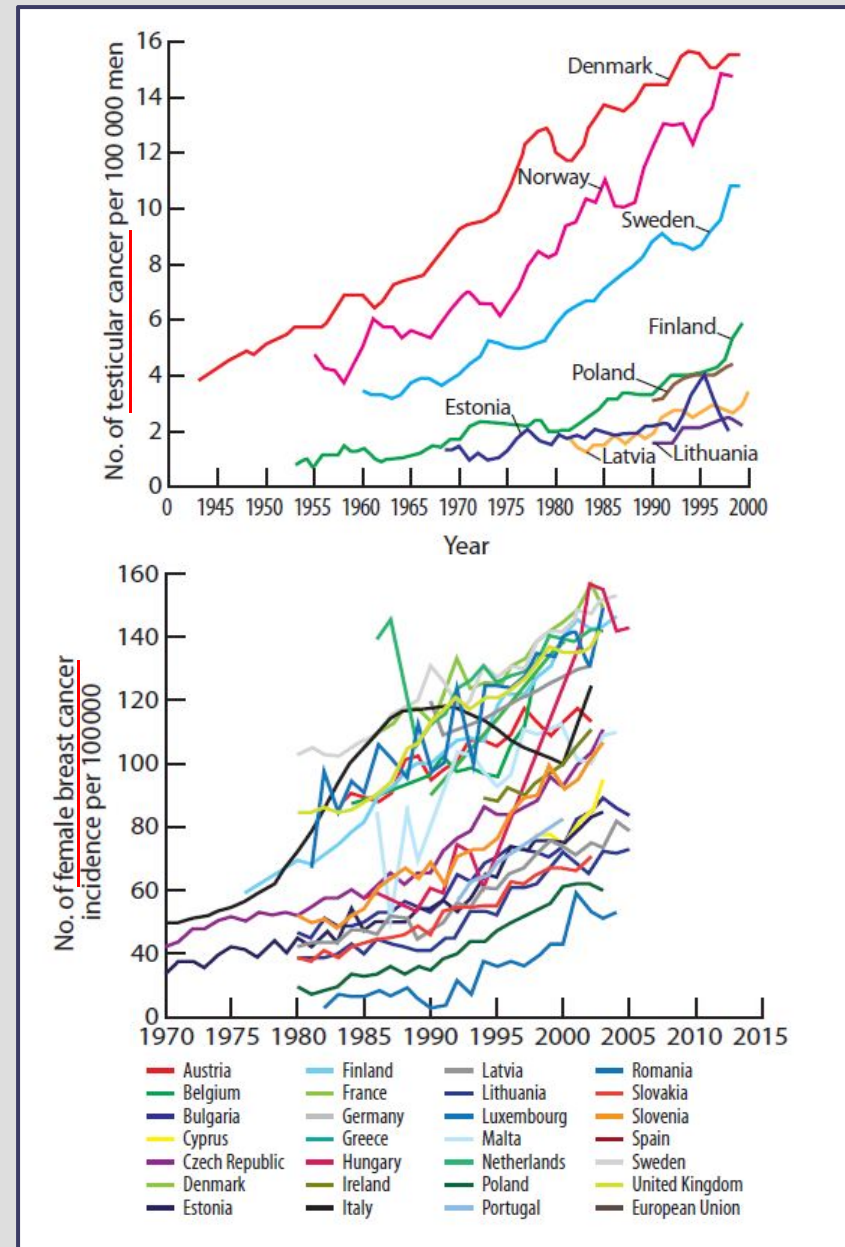
- * Testicular cancer**
- * Prostate cancer**
- * Breast cancer**
- * Decrease in quantity and quality of sperm**
- * Male genital tract defects (hypospadias, cryptorchidism)**
- * Obesity**
- * Infertility rates: affects at least 11% of American couples of reproductive age (~10 million couples). Causes: 51% female, 49% male-associated**

Are we fine?

Over recent decades there has been:

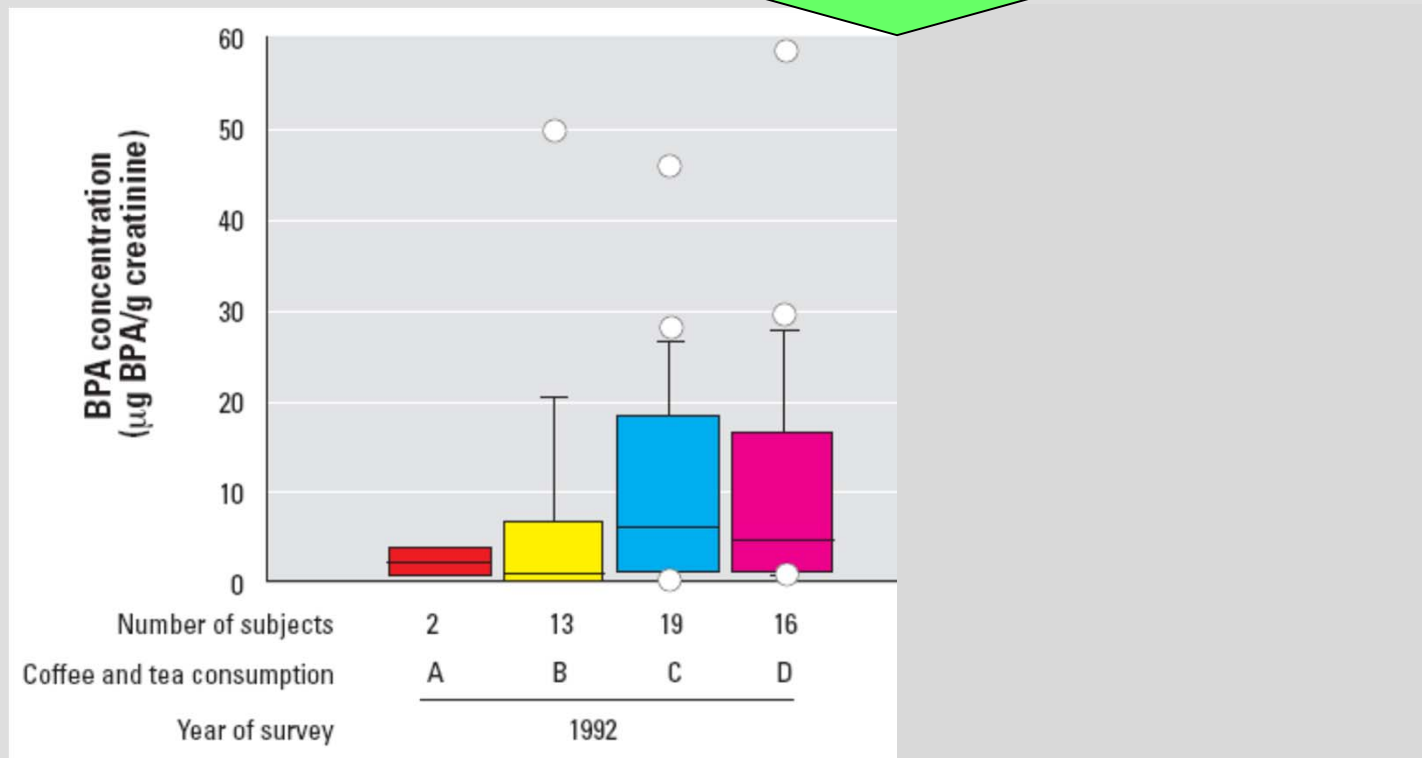
- significant increase in **reproductive problems** in some regions of the world, suggesting a strong role for unidentified environmental factors in disease etiology
- increase in **endocrine cancers**
- significant decrease in **human fertility rates**
- increase in use of assisted reproductive services
- Increases in **neurobehavioral disorders**
- increasing number of chemicals to which all humans in industrialized areas are exposed

Top: Richiardi et al., Cancer Epidem. Biomark. (2004);
Bottom: based on data from <http://data.euro.who.int/hfad/>



Changes at a higher level do make a difference.

Changes in the composition of can coating

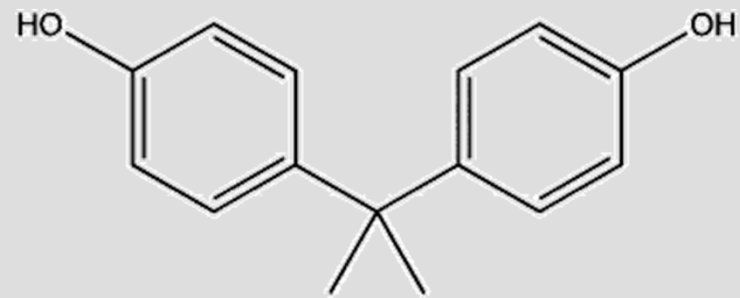
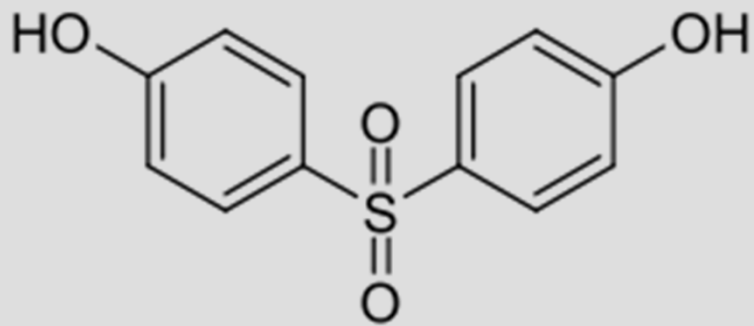


Your (likely) goal: Avoiding Regrettable Replacements

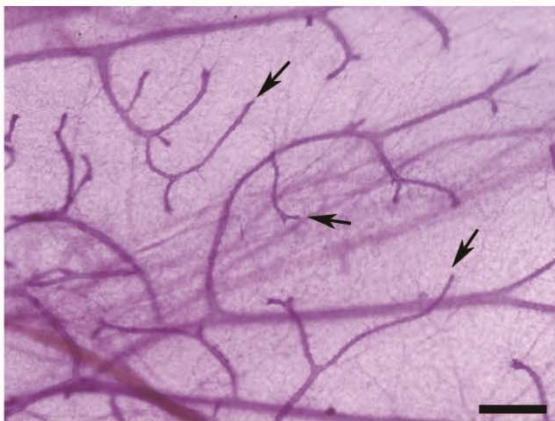
FLAME
SAFE



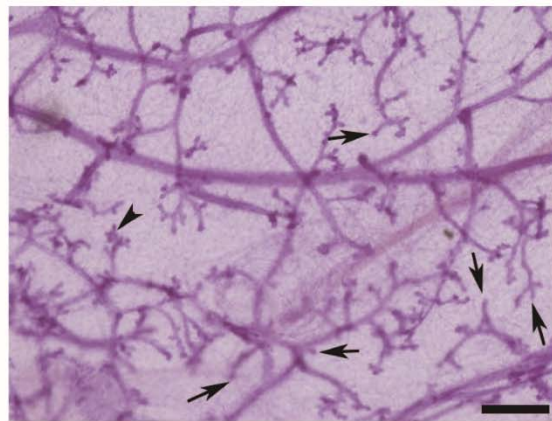
Another Regrettable Replacement: The world of BPA-free products...



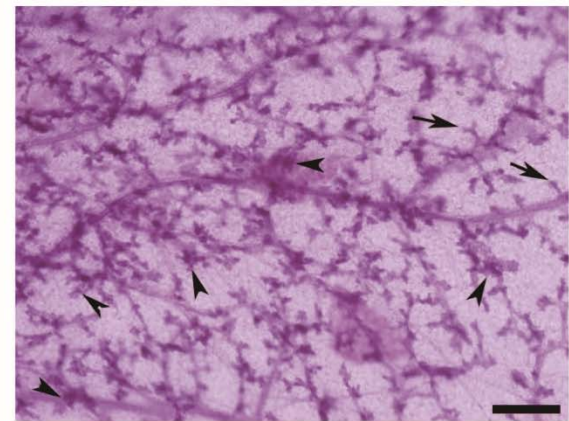
control



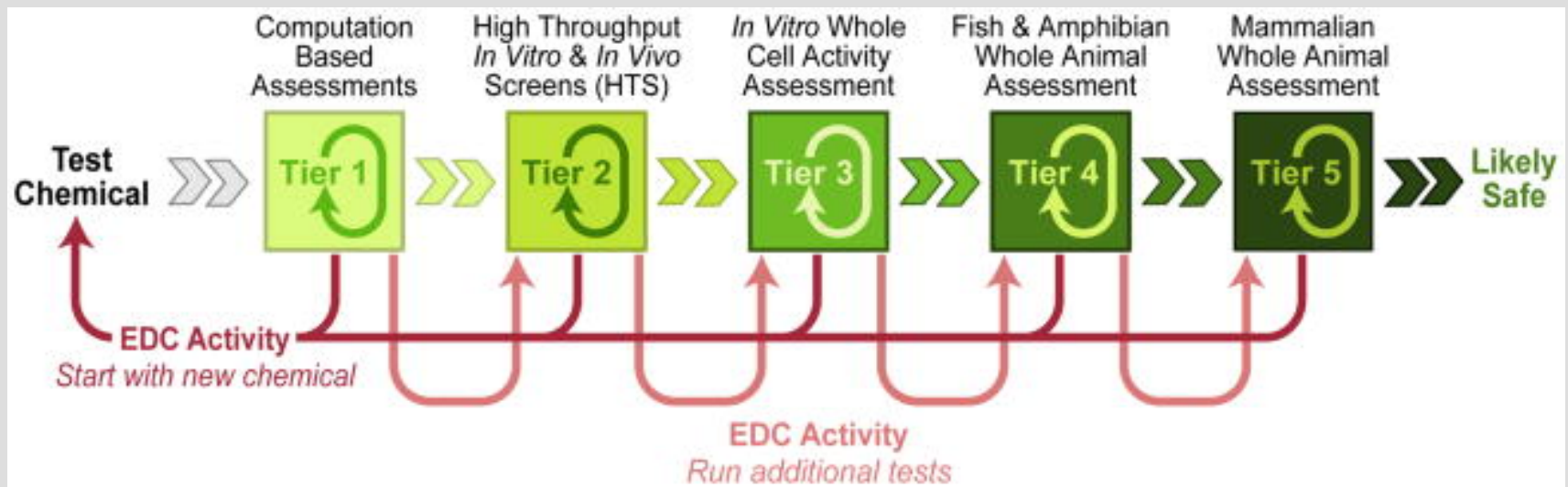
2 μg BPS/kg/day



200 μg BPS/kg/day



Opportunities to change how we test chemicals



- Without appropriate testing, 'safety' should not be assumed
- 'positive' effects should trigger chemical abandonment

Questions?