Endocrine Disrupting Chemicals & Their Health Effects

Laura N. Vandenberg

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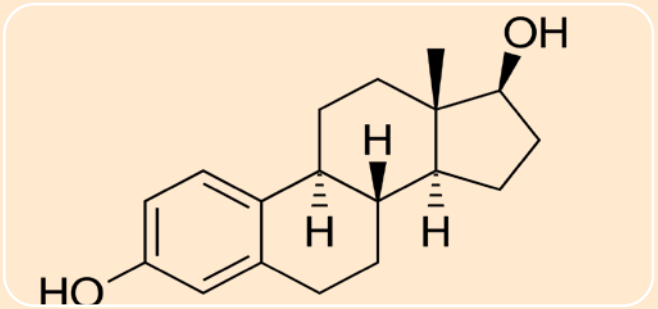
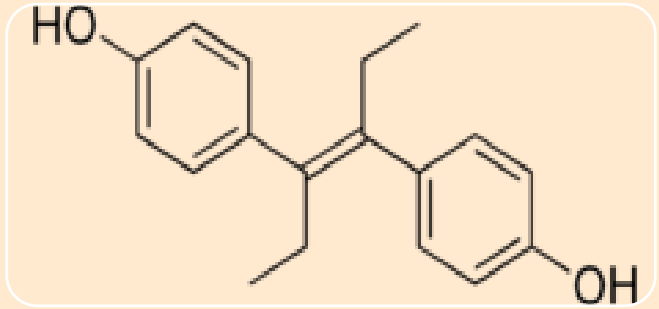
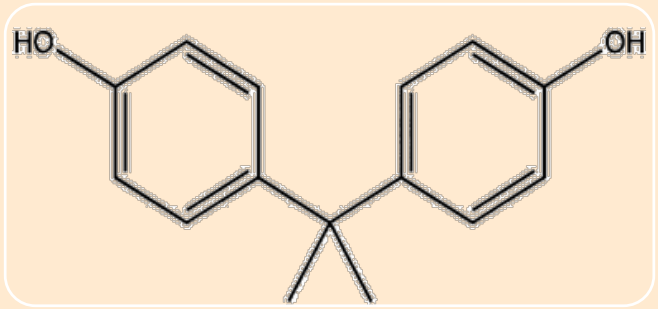
The 1940’s led to a hunt for synthetic hormones



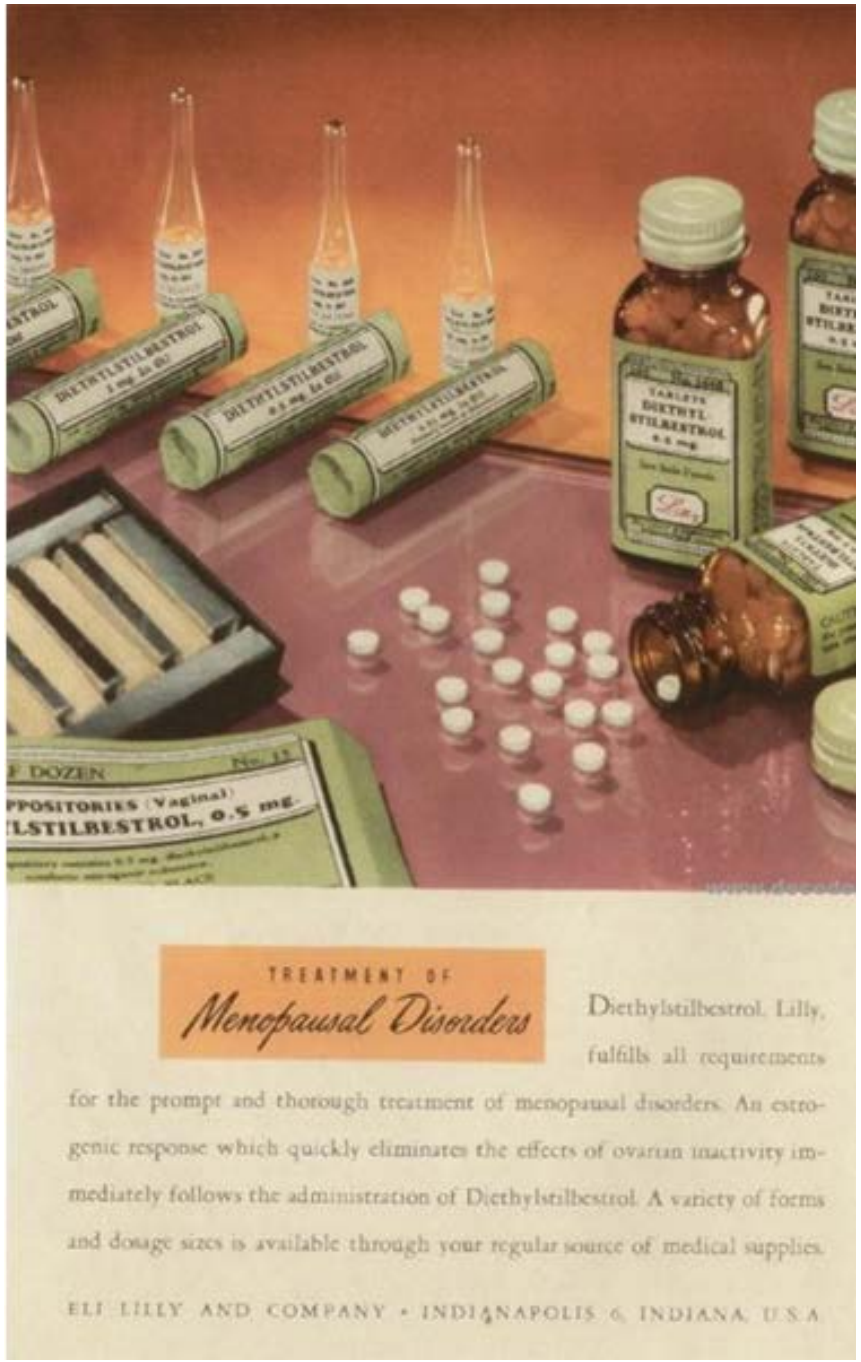
Estradiol



DES



BPA



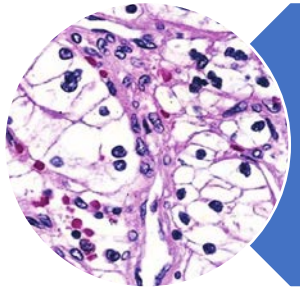
Diethylstilbestrol (DES)

- birth control
- treatment of menopause symptoms
- to stop lactation
- Prevent spontaneous miscarriage

The tragedy of diethylstilbestrol

bigger and stronger babies, too.

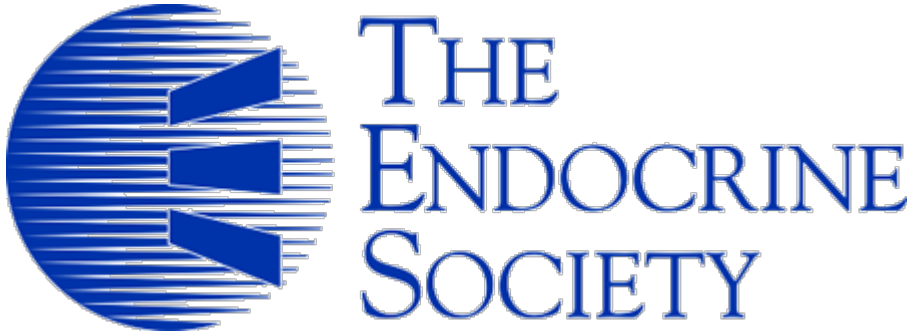
Given to between 2 and 10 million pregnant women in the US between the years of 1948 and 1971.



Clear cell adenocarcinoma of the vagina is detected in exposed daughters

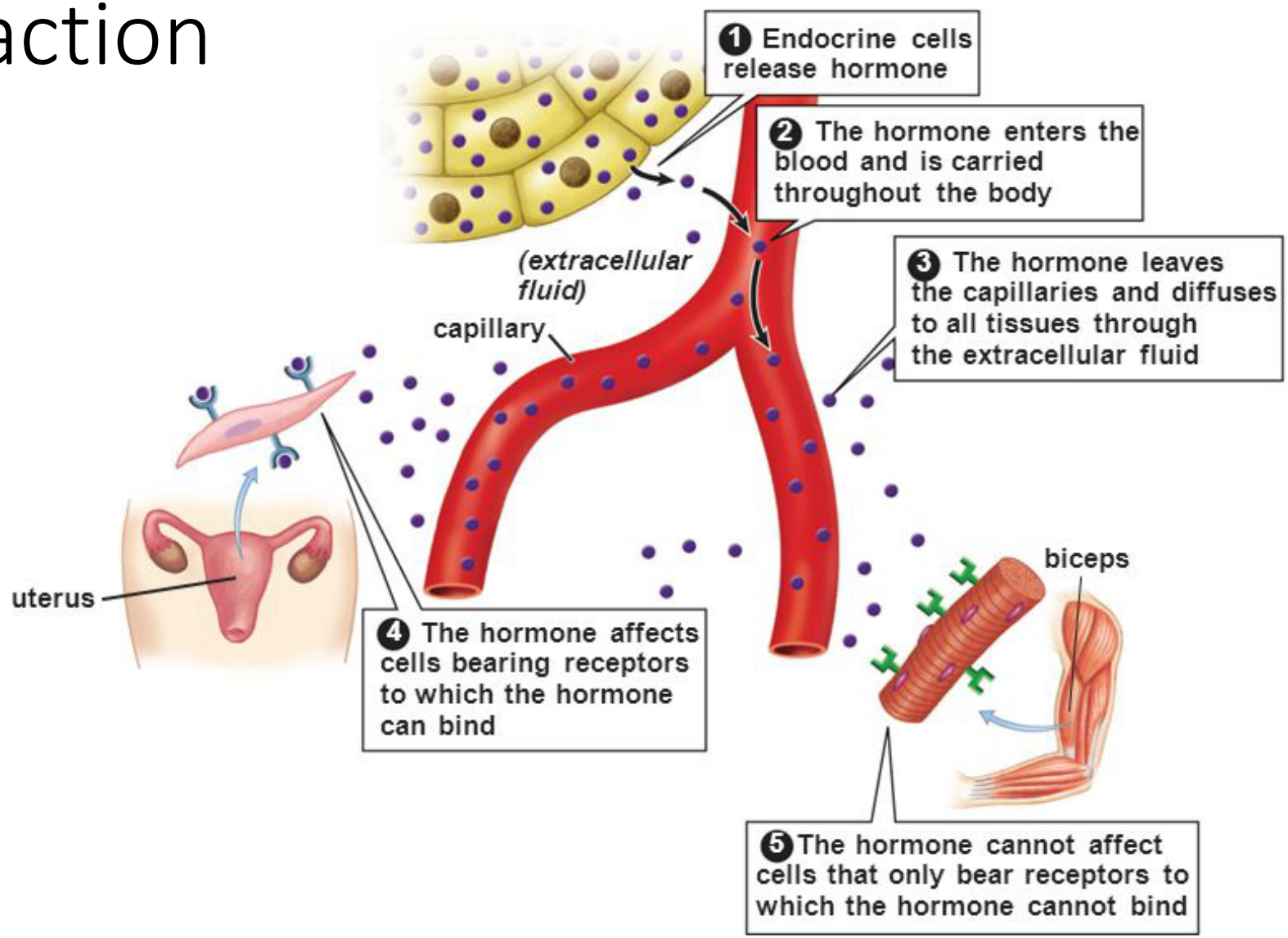
Banned in the US in 1971, but continued to be used in other countries until the 1980s.

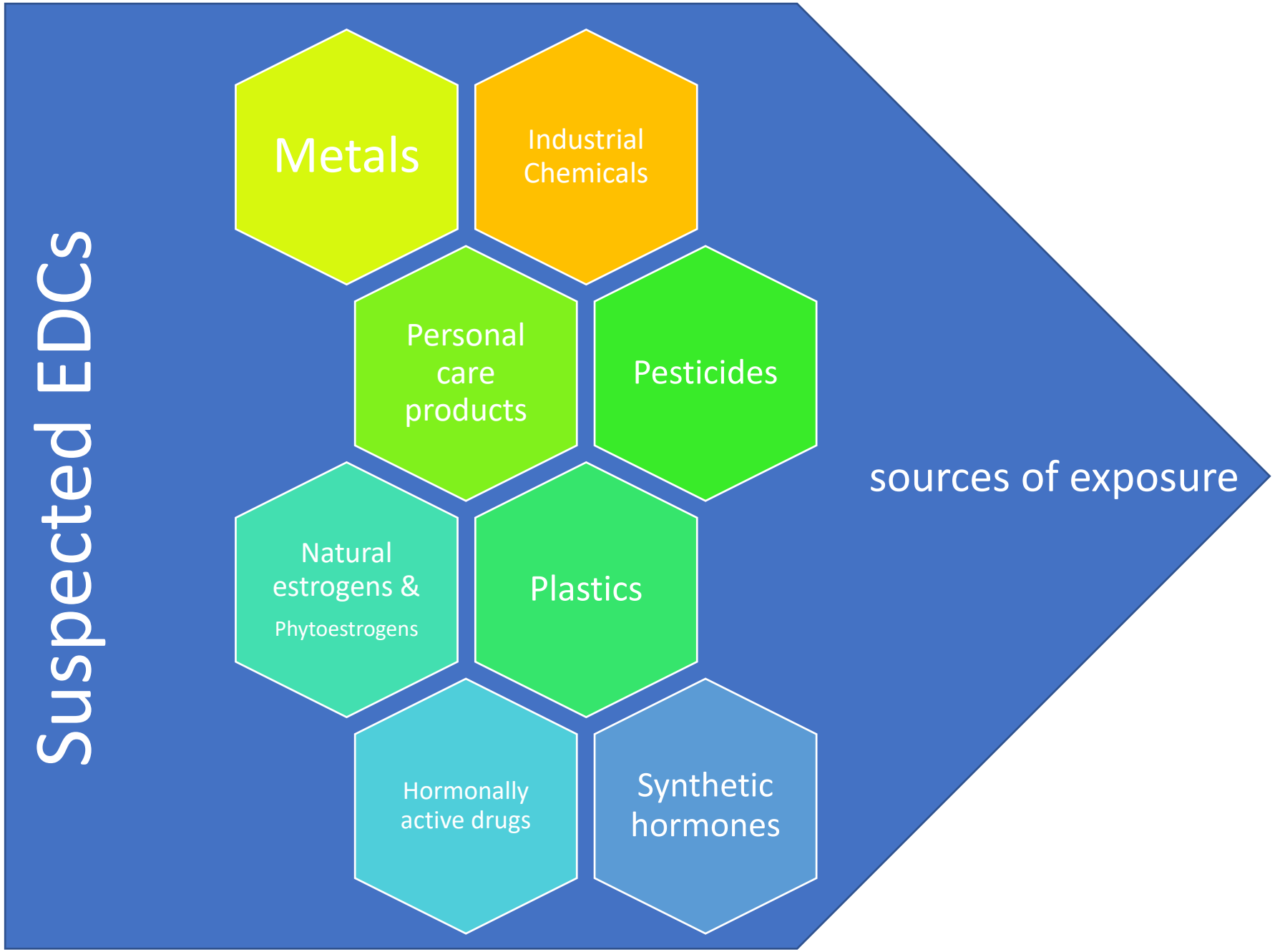
What are Endocrine Disrupting Chemicals (EDCs)?



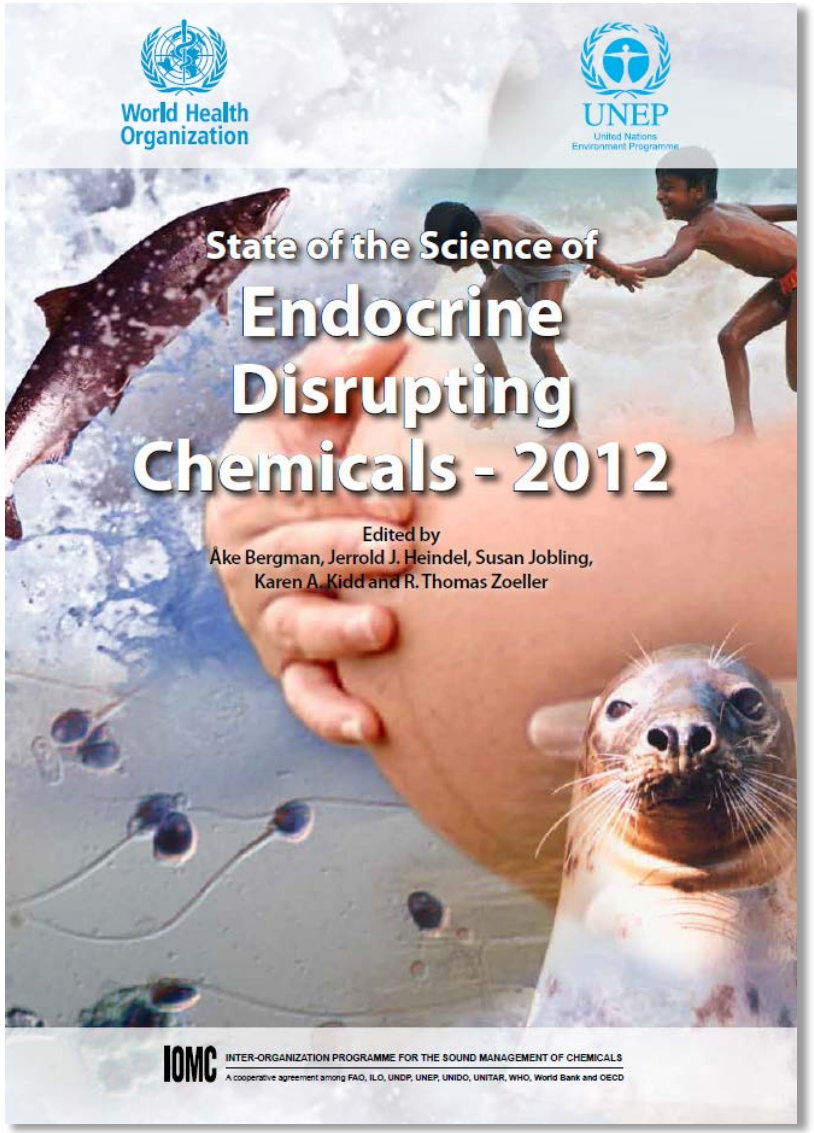
EDCs are exogenous chemicals or chemical mixtures that interfere in some way with hormone action.

Hormone action




Suspected EDCs
Metals
Industrial Chemicals
Personal care products
Pesticides
Natural estrogens & Phytoestrogens
Plastics
Hormonally active drugs
Synthetic hormones
sources of exposure

The UNEP/WHO report (2012)



(1) Data from controlled laboratory studies confirm that chemicals can contribute to endocrine disorders. Many of these diseases have been observed in humans and wildlife populations.

(2) Wildlife populations are affected by EDC exposures with negative effects specifically observed on growth and reproductive endpoints.

(3) The methods that are widely used to identify and evaluate the safety of EDCs examine only limited endpoints, missing a large fraction of the known spectrum of endocrine disrupting effects.

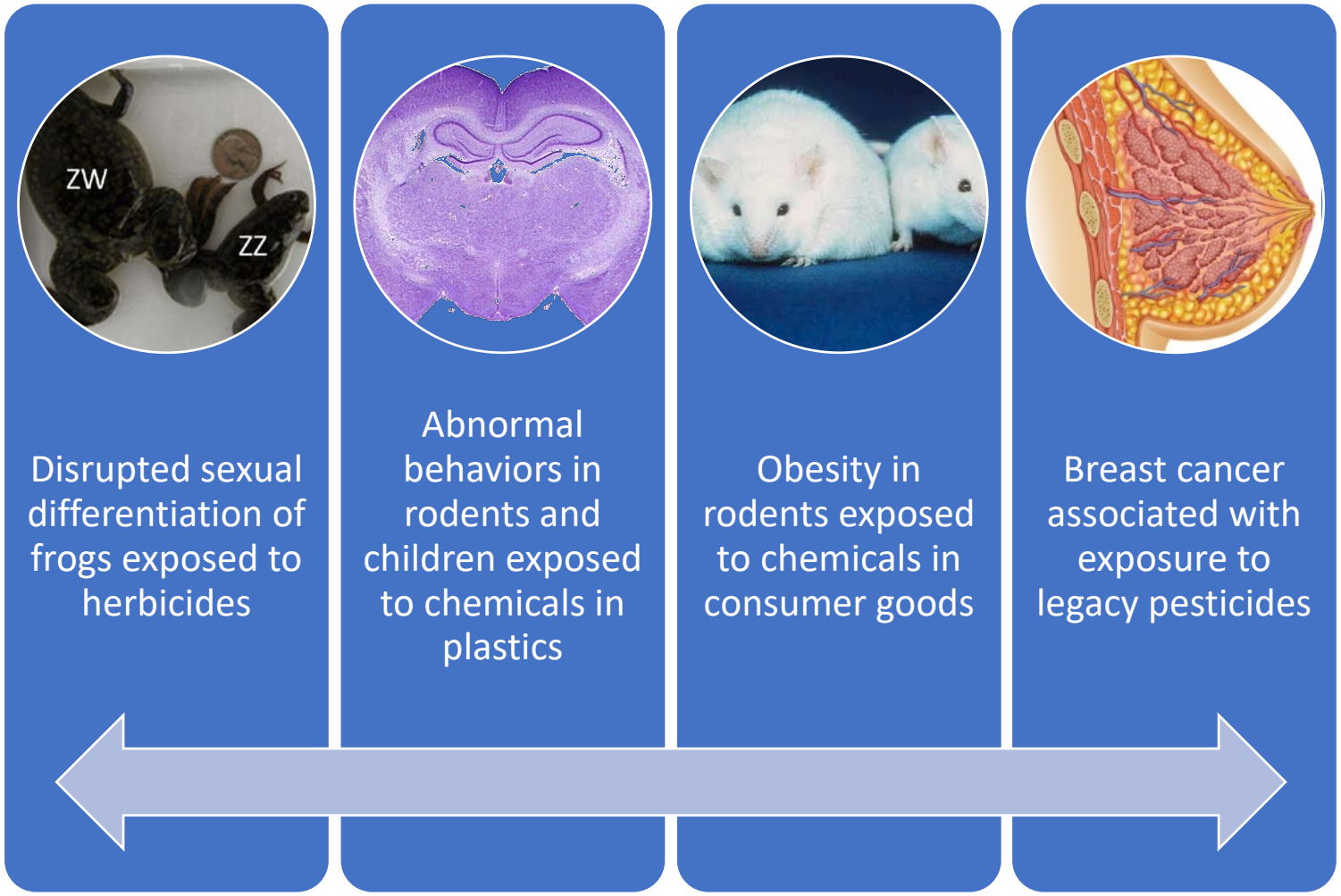
Today, I hope to impress upon you that:

One EDCs are a threat to human and environmental health, even when exposures are "low"

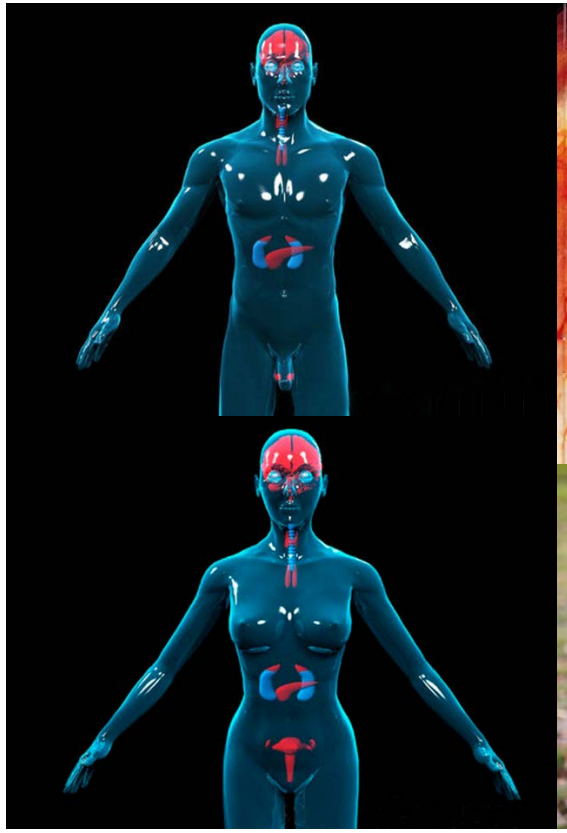
Two Hazards/Risks are not borne evenly across populations

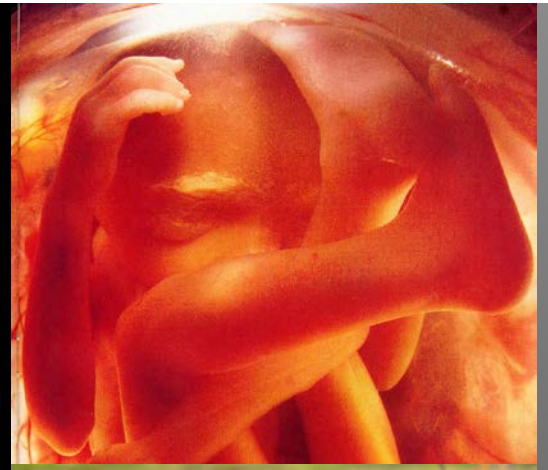
Three The ways we are testing chemicals for safety are insufficient to protect public health

1. EDCs are a threat to human and environmental health, even when exposures are ‘low’



When talking about environmental chemicals, what are low doses?

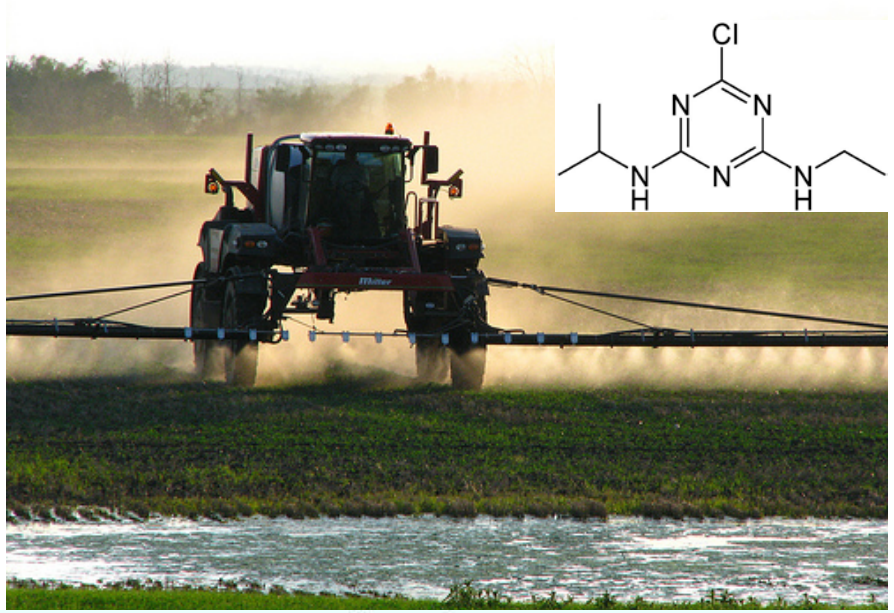


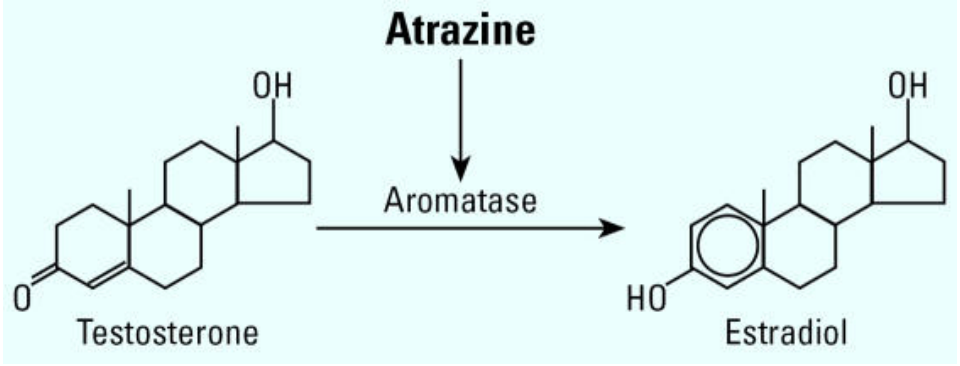


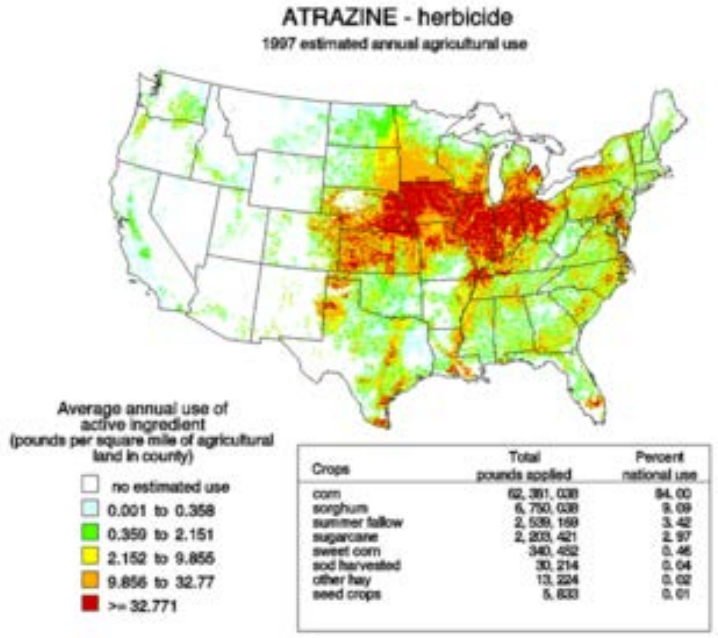
“LOW DOSES” FOR EDCs:

- BELOW AN OVERTLY TOXIC DOSE (KNOWN FROM PRIOR STUDIES)
- IN THE RANGE OF HUMAN EXPOSURES
- REPLICATE HUMAN SERUM LEVELS

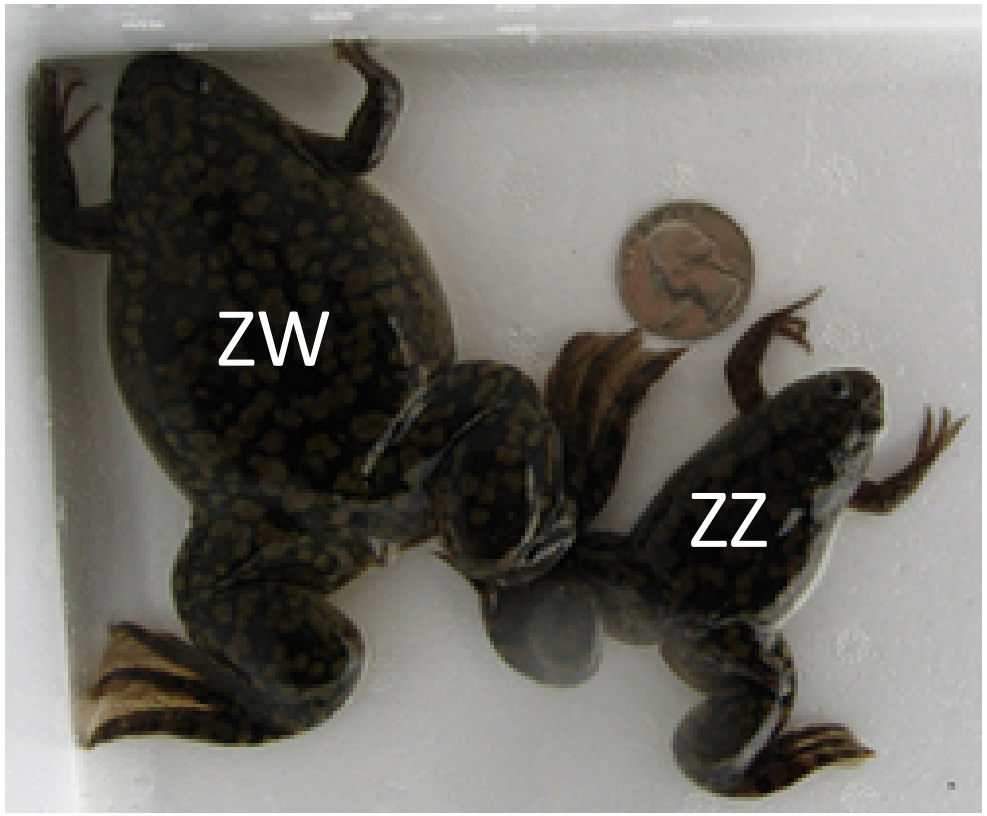
Atrazine & male sexual differentiation, a fascinating example





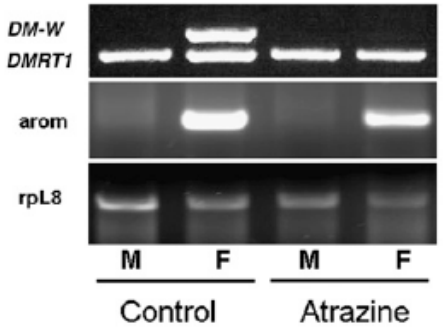


Sexual differentiation in amphibians

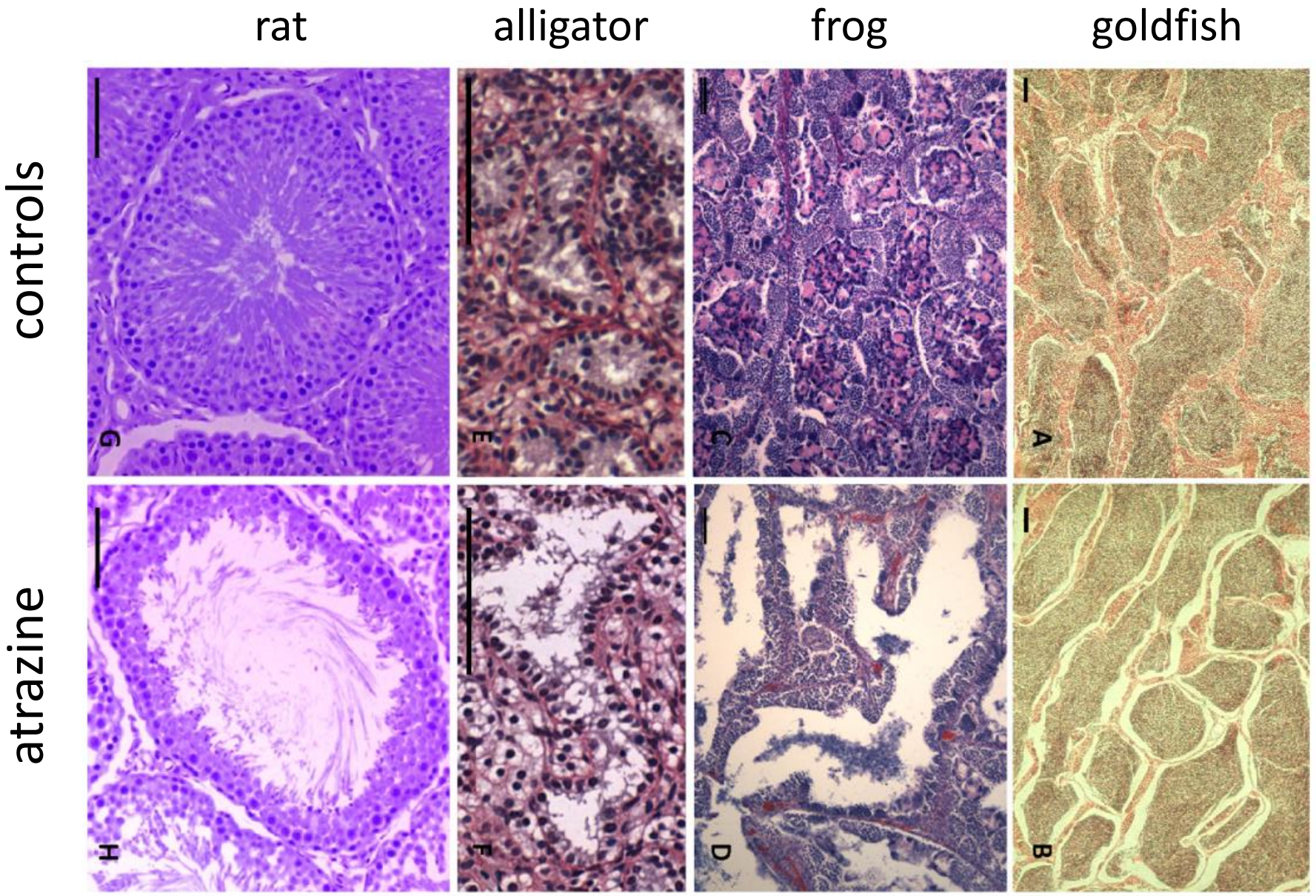


On W chromosome, DM-W gene ⟶ aromatase expression

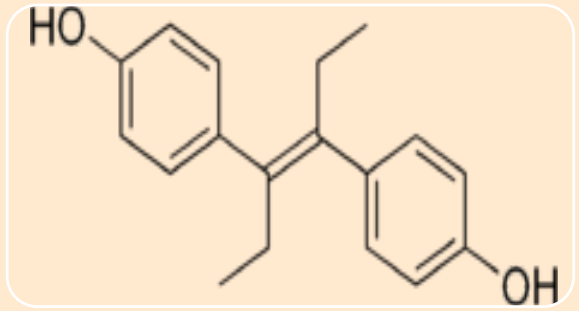
Atrazine: alters sexual differentiation after exposures to 1 ppb

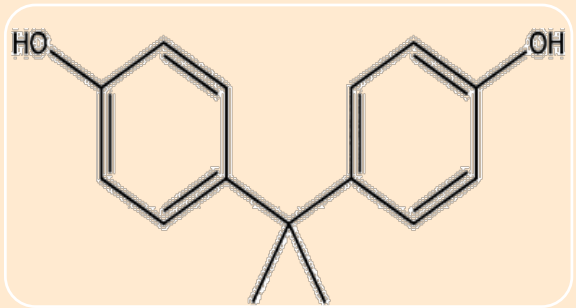


Hayes et al. 2010



Hayes et al.
J Steroid Biochem Molec Biol 2011





DES

BPA

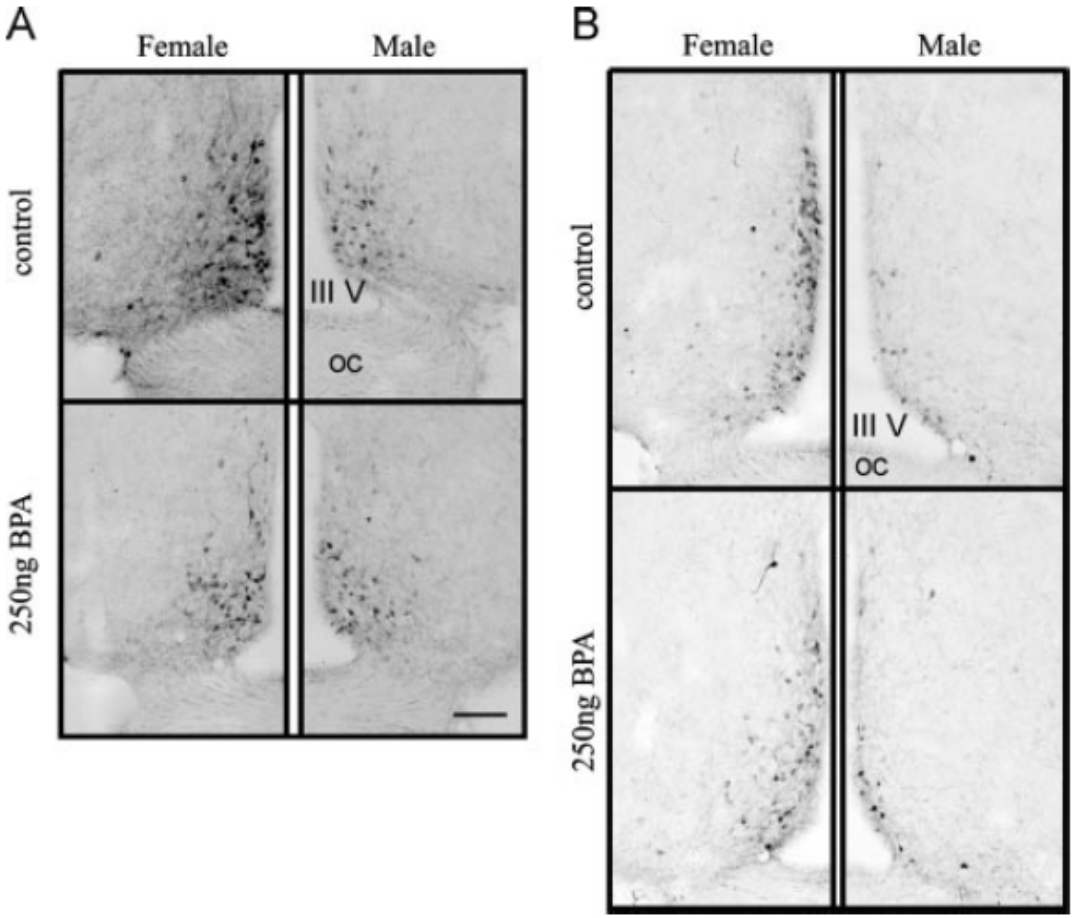
Canned foods & beverages

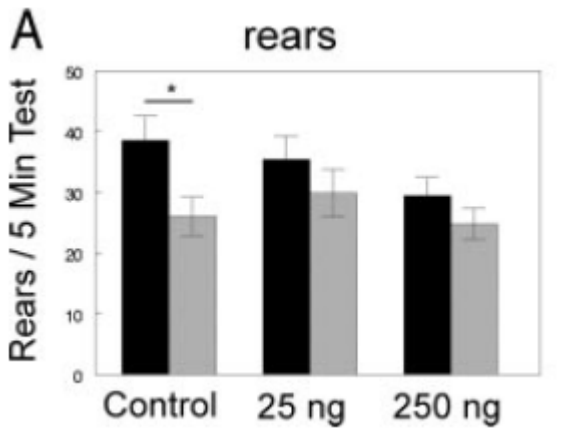
Consumer plastics

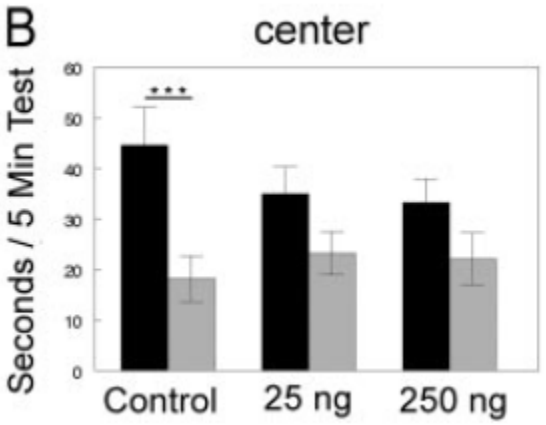
Thermal receipt paper

Sports & medical equipment

BPA alters brain development & behavior in rodents

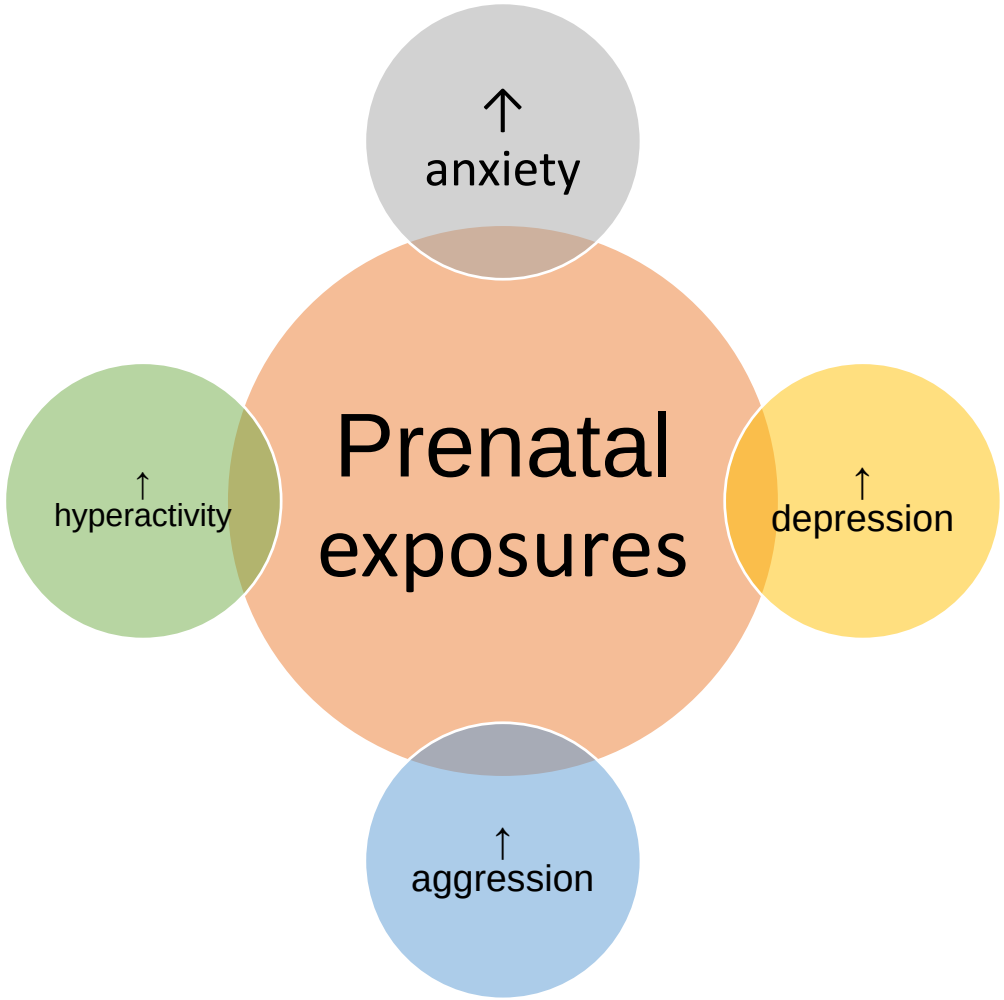


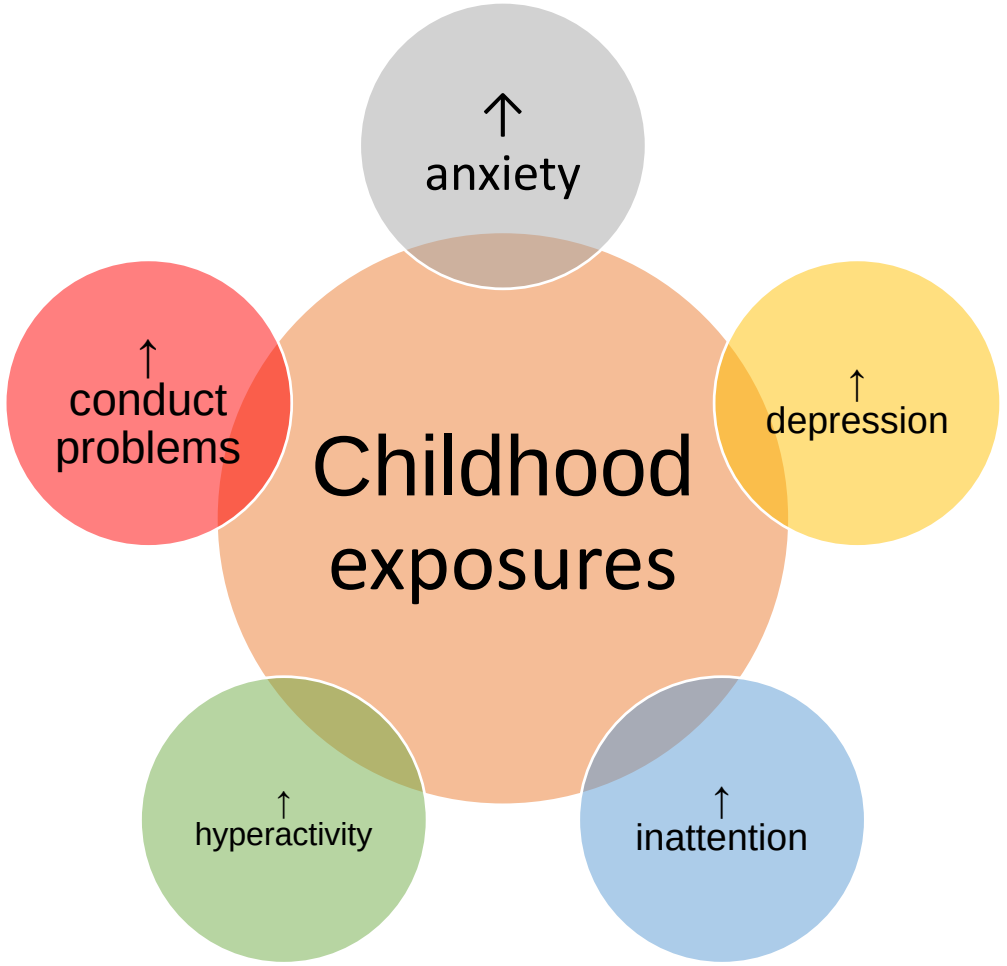




Rubin et al. Endocrinology 2006

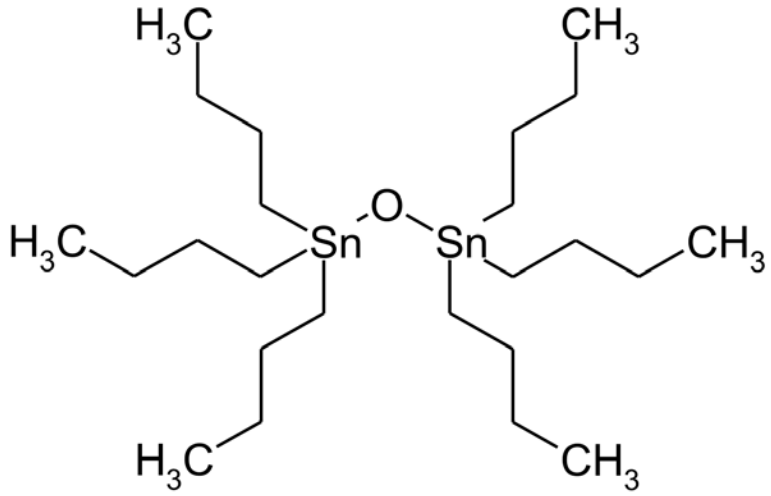
BPA and children's behaviors



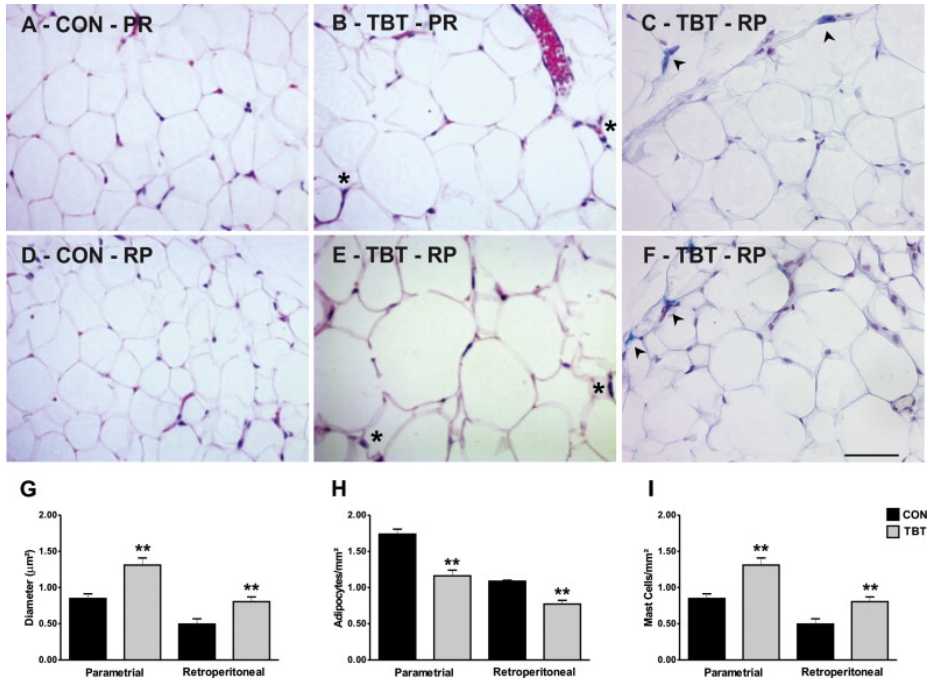


Ejaredar et al. J Exp Sci Environ Epi, 2017.

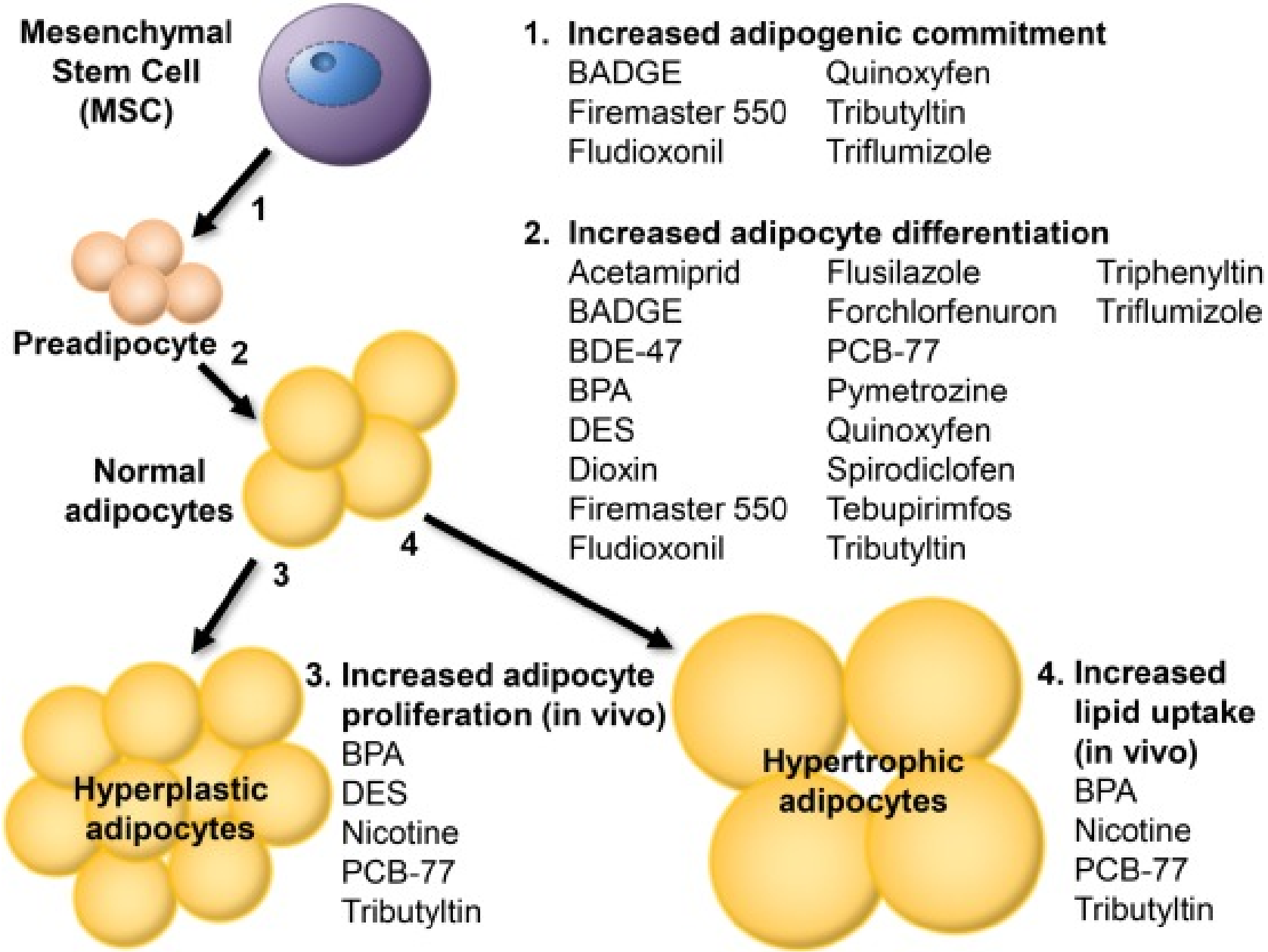
Obesity


H3C
CH3
H3C
Sn
O
Sn
CH3
H3C
CH3

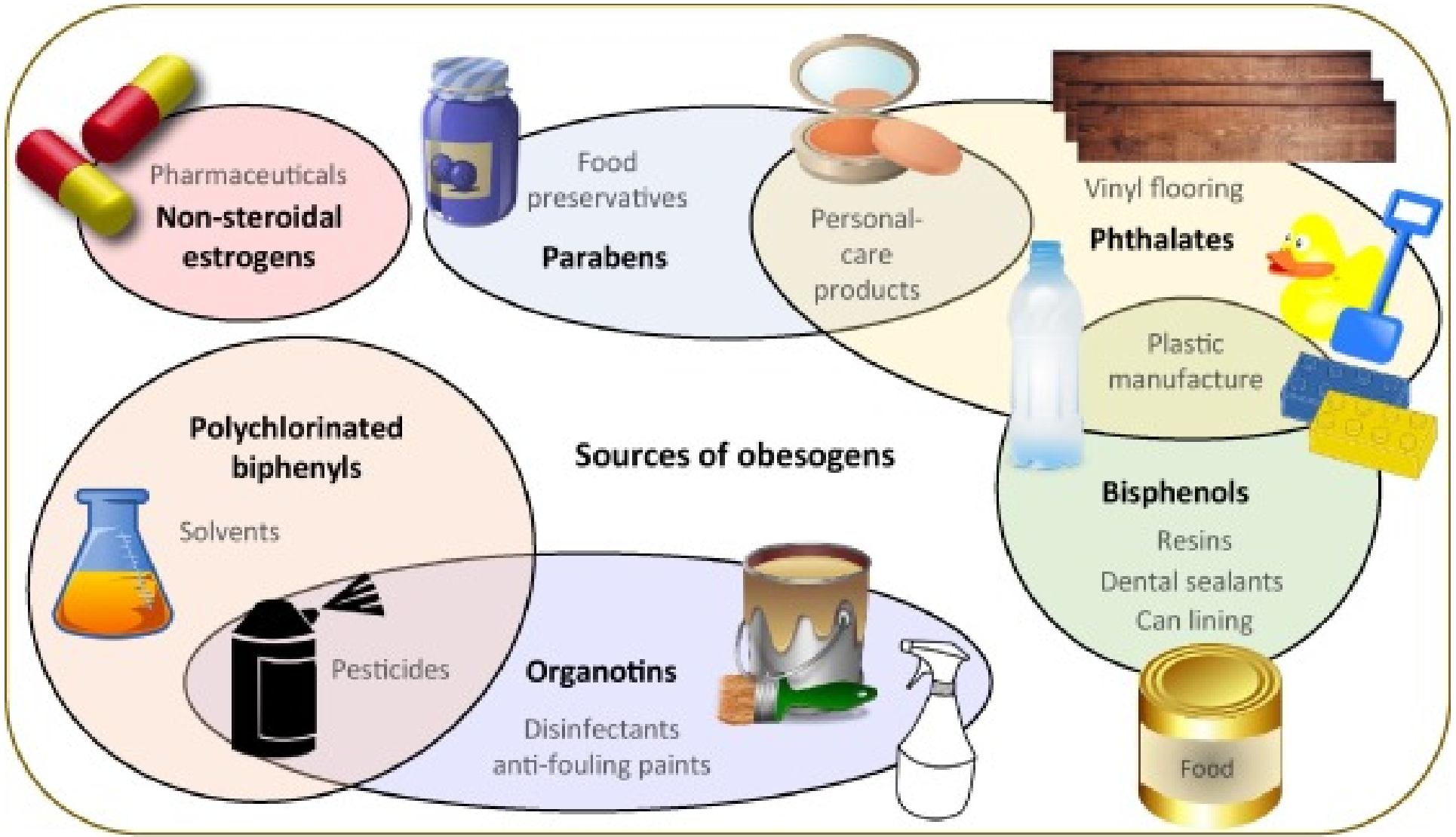

THE BLACK PEARL


A - CON - PR
B - TBT - PR
C - TBT - RP
D - CON - RP
E - TBT - RP
F - TBT - RP
G
Diameter (µm²)
Parametrial
Retroperitoneal
H
Adipocytes/mm²
Parametrial
Retroperitoneal
I
Mast Cells/mm²
CON
TBT
Parametrial
Retroperitoneal

Obesity

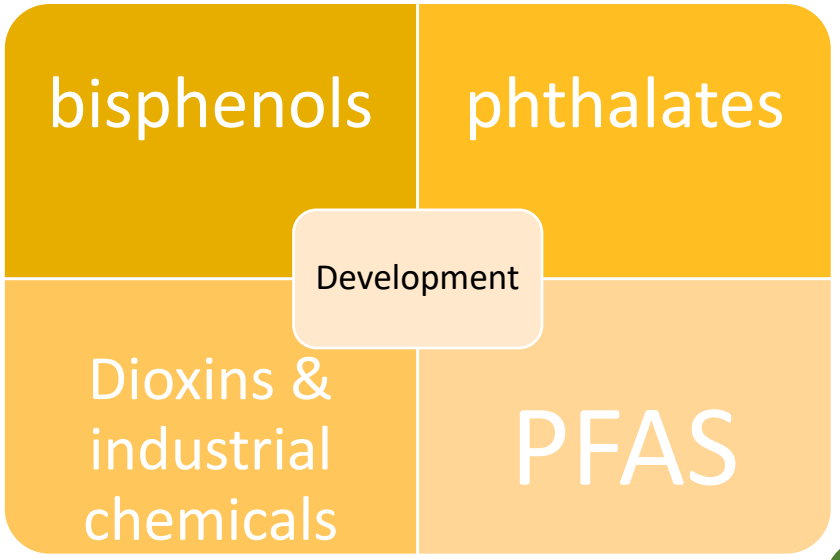

Mesenchymal Stem Cell (MSC)
1
Preadipocyte
2
Normal adipocytes
3
4
Hyperplastic adipocytes
Hypertrophic adipocytes
1. Increased adipogenic commitment
BADGE
Firemaster 550
Fludioxonil
Quinoxyfen
Tributyltin
Triflumizole
2. Increased adipocyte differentiation
Acetamiprid
BADGE
BDE-47
BPA
DES
Dioxin
Firemaster 550
Fludioxonil
Flusilazole
Forchlorfenuron
PCB-77
Pymetrozine
Quinoxyfen
Spirodiclofen
Tebupirimfos
Tributyltin
Triphenyltin
Triflumizole
3. Increased adipocyte proliferation (in vivo)
BPA
DES
Nicotine
PCB-77
Tributyltin
4. Increased lipid uptake (in vivo)
BPA
Nicotine
PCB-77
Tributyltin

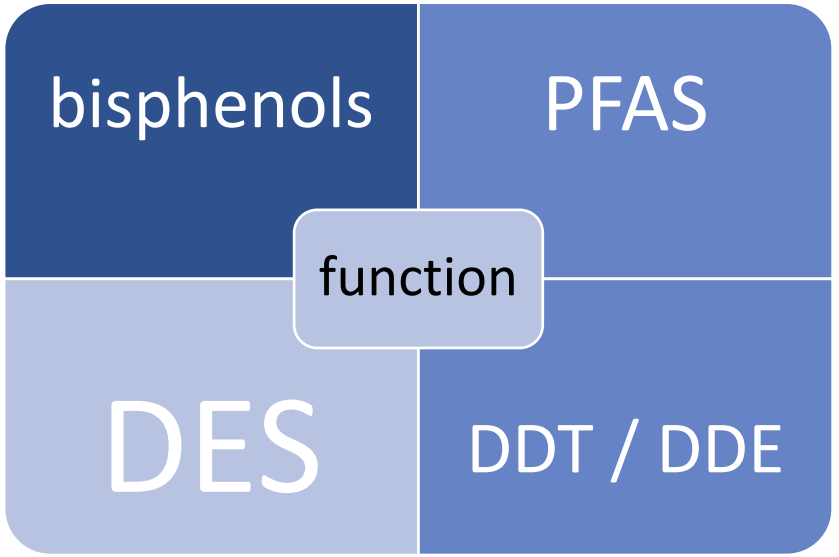
EDCs and obesity in humans

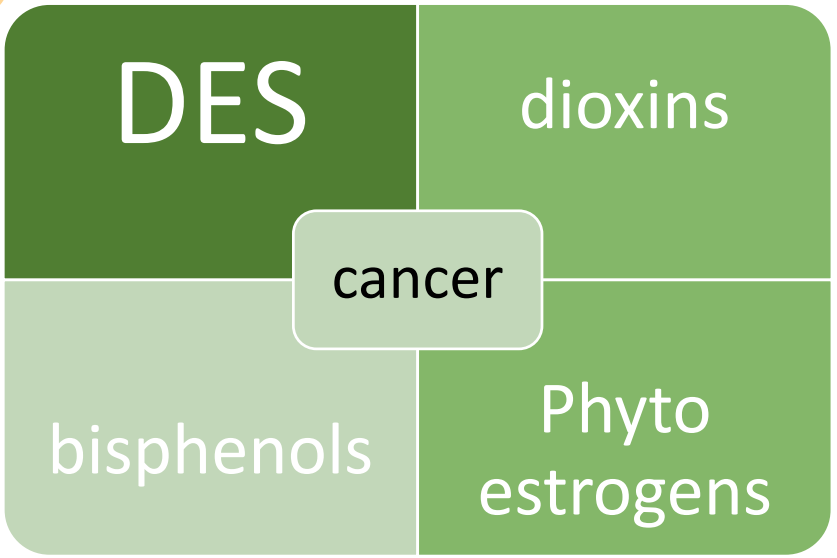


Veiga-Lopez et al., Trends in Endocrinology & Metabolism (2018)

EDCs: Mammary Gland Development, Function & Breast Cancer

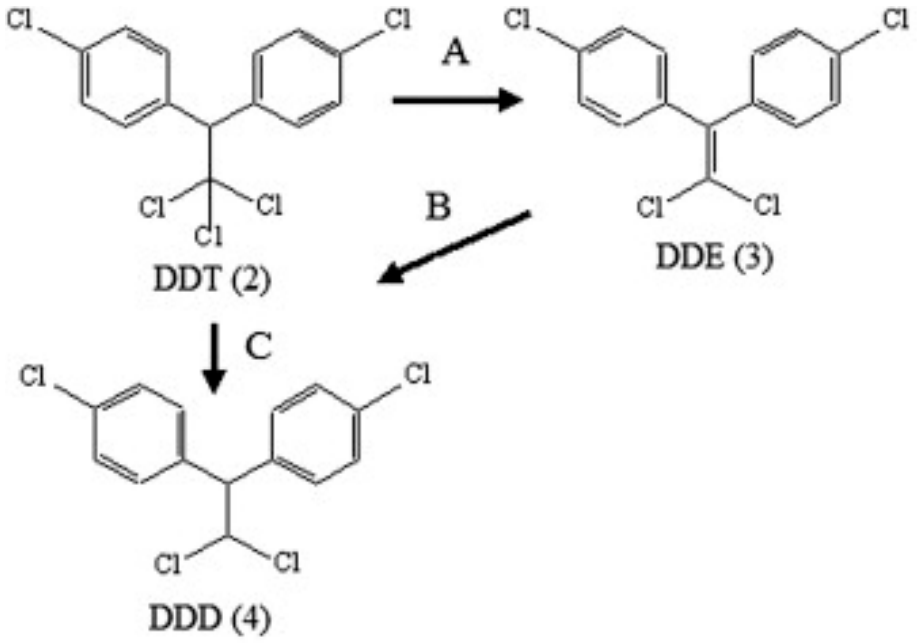


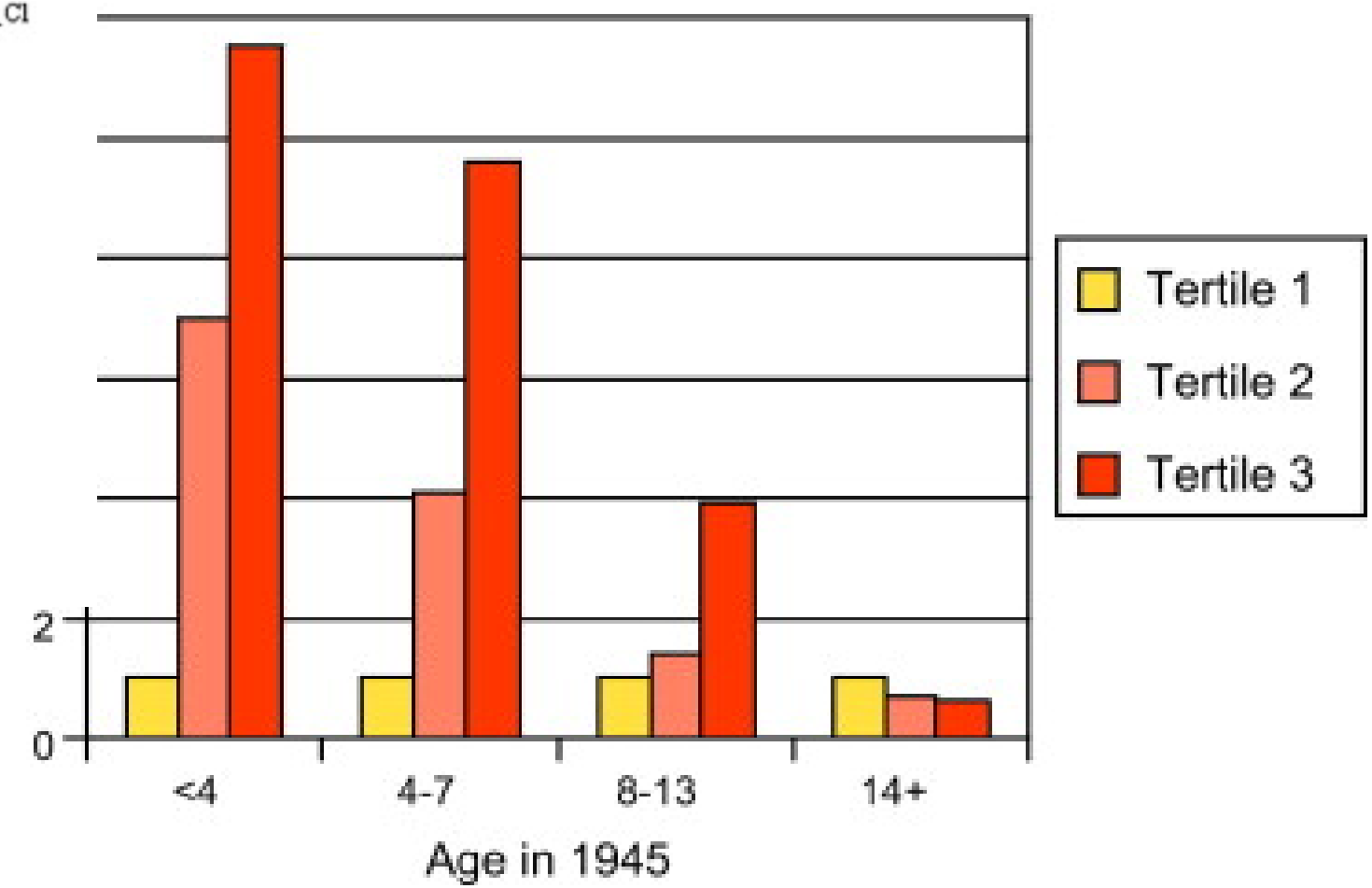




Brody et al. Environ Health Perspect., 2011

Mammary Gland Development, Function & Breast Cancer





Cohn et al. Environ Health Perspect. (2007)

Many, many more examples…

REVIEW

EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

Pharmacology and Toxicology (A.C.G.), College of Pharmacy, The University of Texas at Austin, Austin, Texas 78734; Division of the National Toxicology Program (V.A.C., S.E.F.), National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709; Department of Comparative Biosciences (J.A.F.), University of Illinois at Urbana-Champaign, Urbana, Illinois 61802; Institute of Bioengineering and CIBERDEM (A.N.), Miguel Hernandez University of Elche, 03202 Elche, Alicante, Spain; Departments of Urology, Pathology, and Physiology & Biophysics (G.S.P.), College of Medicine, University of Illinois at Chicago, Chicago, Illinois 60612; Departments of Physiology and Pediatrics (J.T.), University of Turku and Turku University Hospital, 20520 Turku, Finland; and Biology Department (R.T.Z.), University of Massachusetts at Amherst, Amherst, Massachusetts 01003

The Endocrine Society's first Scientific Statement in 2009 provided a wake-up call to the scientific community about how environmental endocrine-disrupting chemicals (EDCs) affect health and disease. Five years later, a substantially larger body of literature has solidified our understanding of plausible mechanisms underlying EDC actions and how exposures in animals and humans—especially during development—may lay the foundations for disease later in life. At this point in history, we have much stronger knowledge about how EDCs alter gene-environment interactions via physiological, cellular, molecular, and epigenetic changes, thereby producing effects in exposed individuals as well as their descendants. Causal links between exposure and manifestation of disease are substantiated by experimental animal models and are consistent with correlative epidemiological data in humans. There are several caveats because differences in how experimental animal work is conducted can lead to difficulties in drawing broad conclusions, and we must continue to be cautious about inferring causality in humans. In this second Scientific Statement, we reviewed the literature on a subset of topics for which the translational evidence is strongest: 1) obesity and diabetes; 2) female reproduction; 3) male reproduction; 4) hormone-sensitive cancers in females; 5) prostate; 6) thyroid; and 7) neurodevelopment and neuroendocrine systems. Our inclusion criteria for studies were those conducted predominantly in the past 5 years deemed to be of high quality based on appropriate negative and positive control groups or populations, adequate sample size and experimental design, and mammalian animal studies with exposure levels in a range that was relevant to humans. We also focused on studies using the developmental origins of health and disease model. No report was excluded based on a positive or negative effect of the EDC exposure. The bulk of the results across the board strengthen the evidence for endocrine health-related actions of EDCs. Based on this much more complete understanding of the endocrine principles by which EDCs act, including nonmonotonic dose-responses, low-dose effects, and developmental vulnerability, these findings can be much better translated to human health. Armed with this information, researchers, physicians, and other healthcare providers can guide regulators and policymakers as they make responsible decisions. (*Endocrine Reviews* 36: E1–E150, 2015)

REVIEW

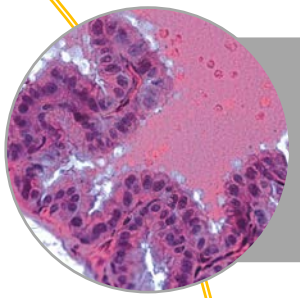
Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers

Center for Regenerative and Developmental Biology and Department of Biology (L.N.V.), Tufts University, Medford, Massachusetts 02155; The Endocrine Disruption Exchange (T.C.), Paonia, Colorado 81428; Laboratory for Integrative Studies in Amphibian Biology (T.B.H.), Molecular Toxicology, Group in Endocrinology, Energy and Resources Group, Museum of Vertebrate Zoology, and Department of Integrative Biology, University of California, Berkeley, California 94720; Division of Extramural Research and Training (J.J.H.), National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina 27709; Division of Epidemiology and Community Health (D.R.J.), School of Public Health, University of Minnesota, Minneapolis, Minnesota 55455; Department of Preventive Medicine (D.-H.L.), School of Medicine, Kyungpook National University, Daegu 702-701, Korea; Molecular Profiling Laboratory (T.S.), Massachusetts General Hospital Center for Cancer Research, Charlestown, Massachusetts 02129; Department of Anatomy and Cellular Biology (A.M.S.), Tufts University School of Medicine, Boston, Massachusetts 02111; Division of Biological Sciences (F.S.v.S.) and Department of Biomedical Sciences (W.V.W.), University of Missouri-Columbia, Columbia, Missouri 65211; Biology Department (T.Z.), University of Massachusetts-Amherst, Amherst, Massachusetts 01003; and Environmental Health Sciences (J.P.M.), Charlottesville, Virginia 22902

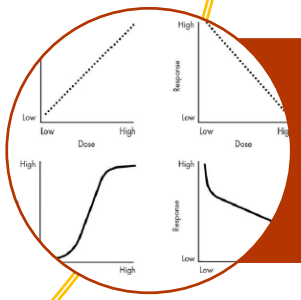
For decades, studies of endocrine-disrupting chemicals (EDCs) have challenged traditional concepts in toxicology, in particular the dogma of "the dose makes the poison," because EDCs can have effects at low doses that are not predicted by effects at higher doses. Here, we review two major concepts in 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)

2. Hazards / Risks are not borne evenly across populations



Hazard assessment

Exposure assessment



Dose response

Lessons from the Dutch Famine

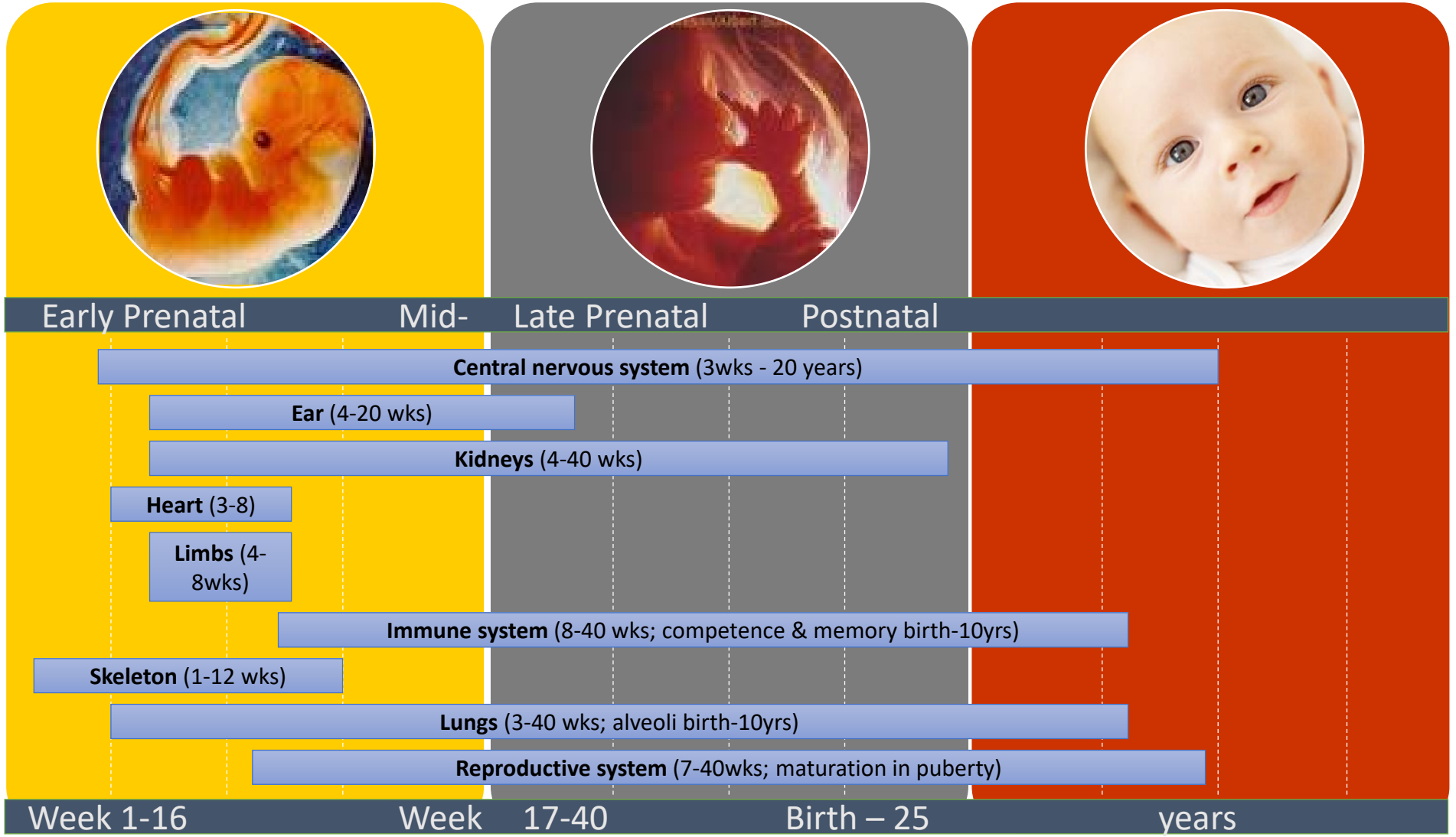
Limited environment

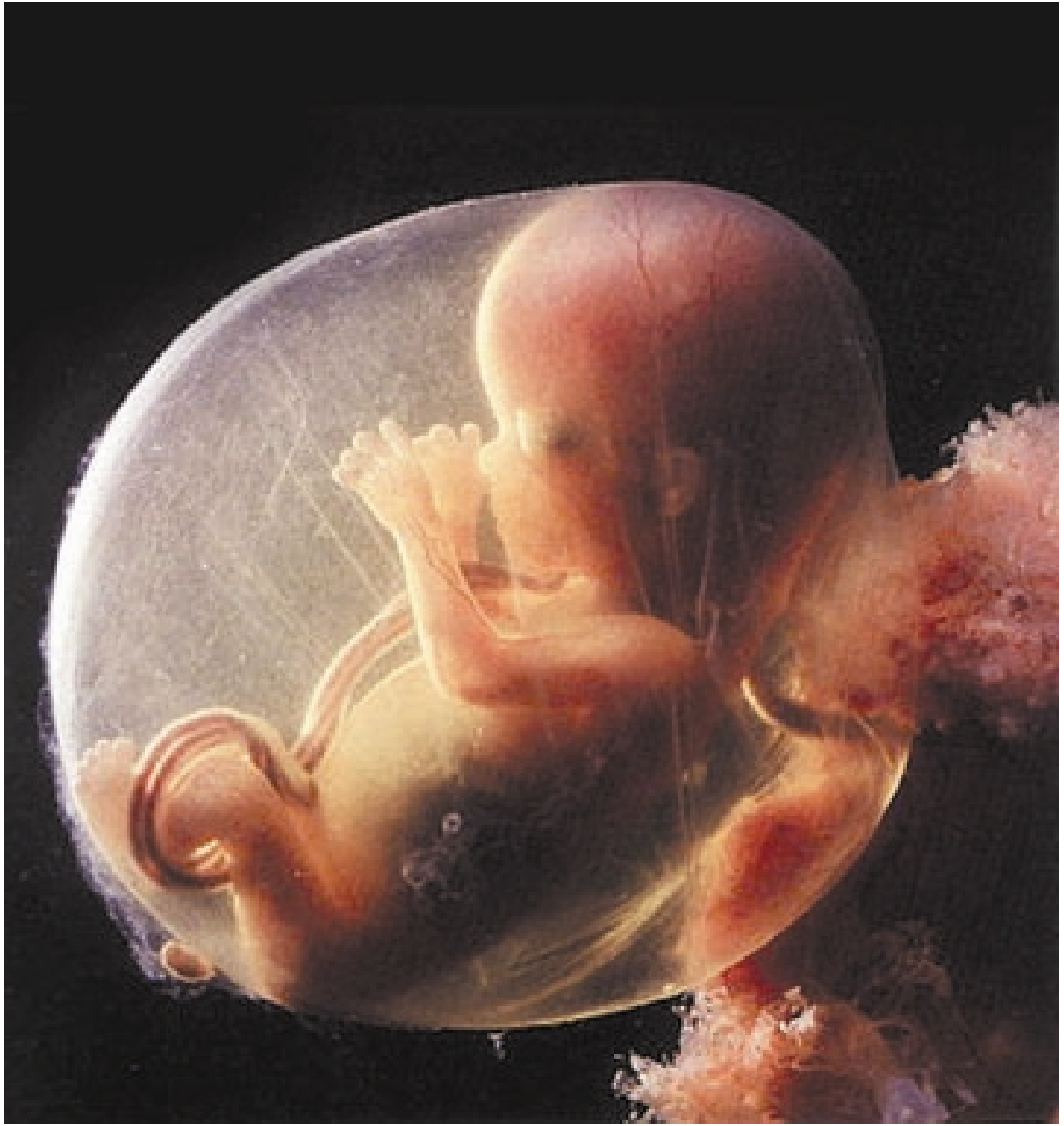
- Survival
- Health

Plentiful environment

- Stroke
- Diabetes
- Cancer

Our developmental stage and physiology predicts if/how we will be affected by EDCs

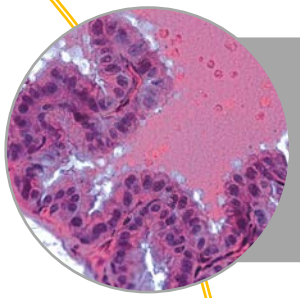




“From the day of conception until an individual is born or hatched, the development of each stage of life is fully under the control of hormones.

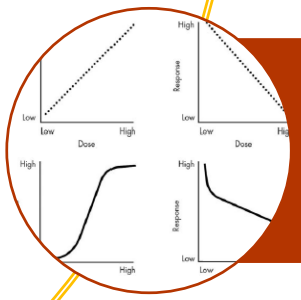
Changes that happen during development are far less reversible [than those occurring in an adult]; you can't go back and rewire the brain”.
-Theo Colborn, zoologist, writer

Exposures to EDCs vary widely across populations



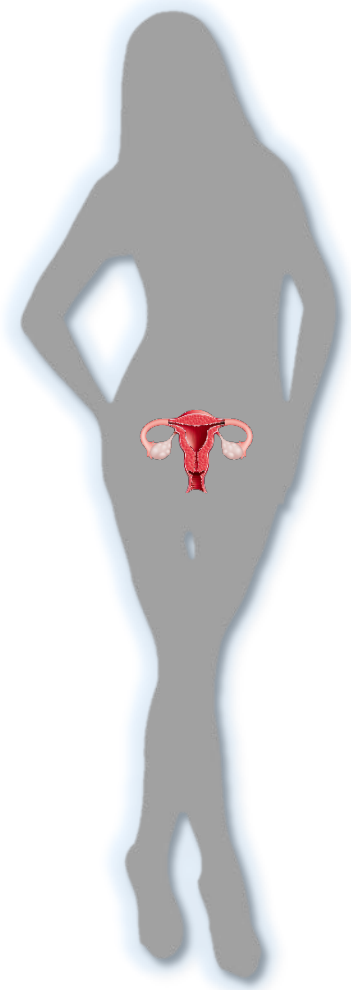
Hazard assessment

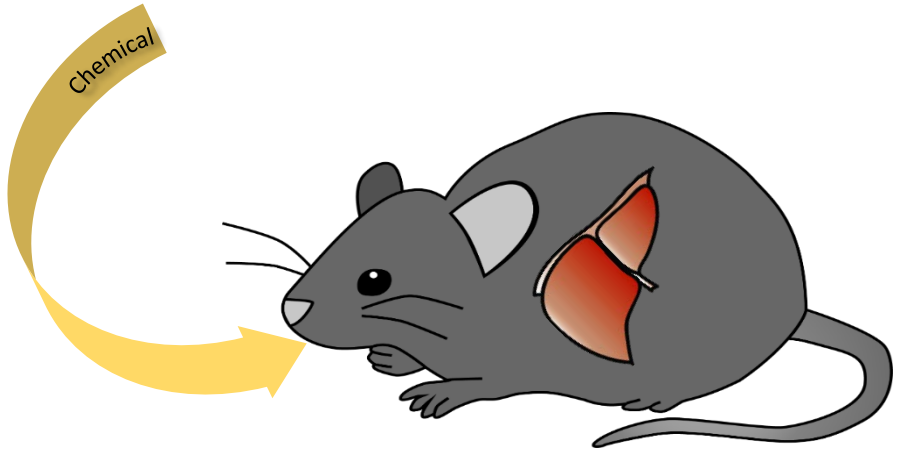
Exposure assessment



Dose response

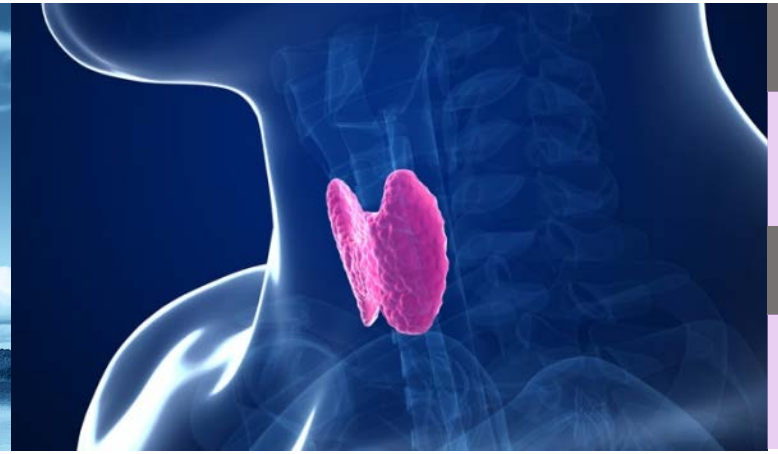
3. The ways we are testing chemicals for safety are insufficient to protect public health





- IDENTIFY LD50, MTD, LOAEL, NOAEL
- CALCULATE **RFD** (NOAEL/10, 100 OR 1,000)
- COMPARE THE **RFD** TO HUMAN EXPOSURE LEVELS

An illustration: perchlorate



NOAEL
0.007 mg/kg/day
RfD
0.0007 mg/kg/day (0.7 µg/kg/day)

NHANES 95th percentile: 0.234 µg/kg/day

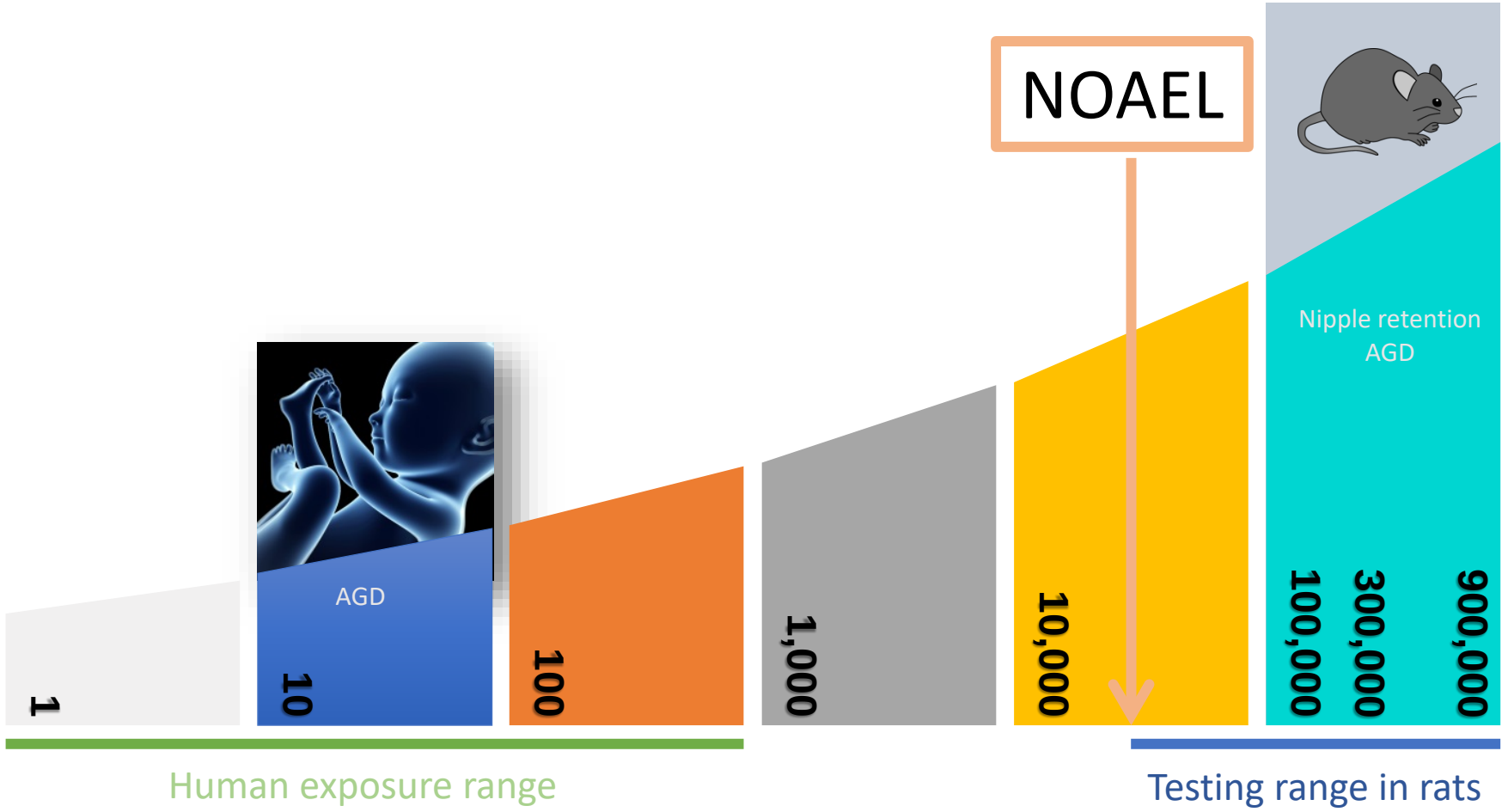
An illustration: perchlorate

NHANES

MATERNAL PERCHLORATE IN TOP 10%

OFFSPRING IQ IN LOWEST 10% AT AGE 3

Another illustration: Diisononyl Phthalate (DINP)



So, what are we doing wrong?

Conflicts

- Most of the data used in regulatory decision-making were generated by groups with vested interests, and academic studies are ignored because of the regulatory framework
- The regulatory structure can prevent new data from being collected

Endpoints

- We might be good at evaluating toxicity, but these outcomes aren't relevant to human diseases
- We can't even agree on what is "adverse"

Doses

- EDCs, like hormones, have effects at low doses but these are rarely included in toxicity testing. Even if they are, the endpoints aren't sensitive enough to detect adverse outcomes
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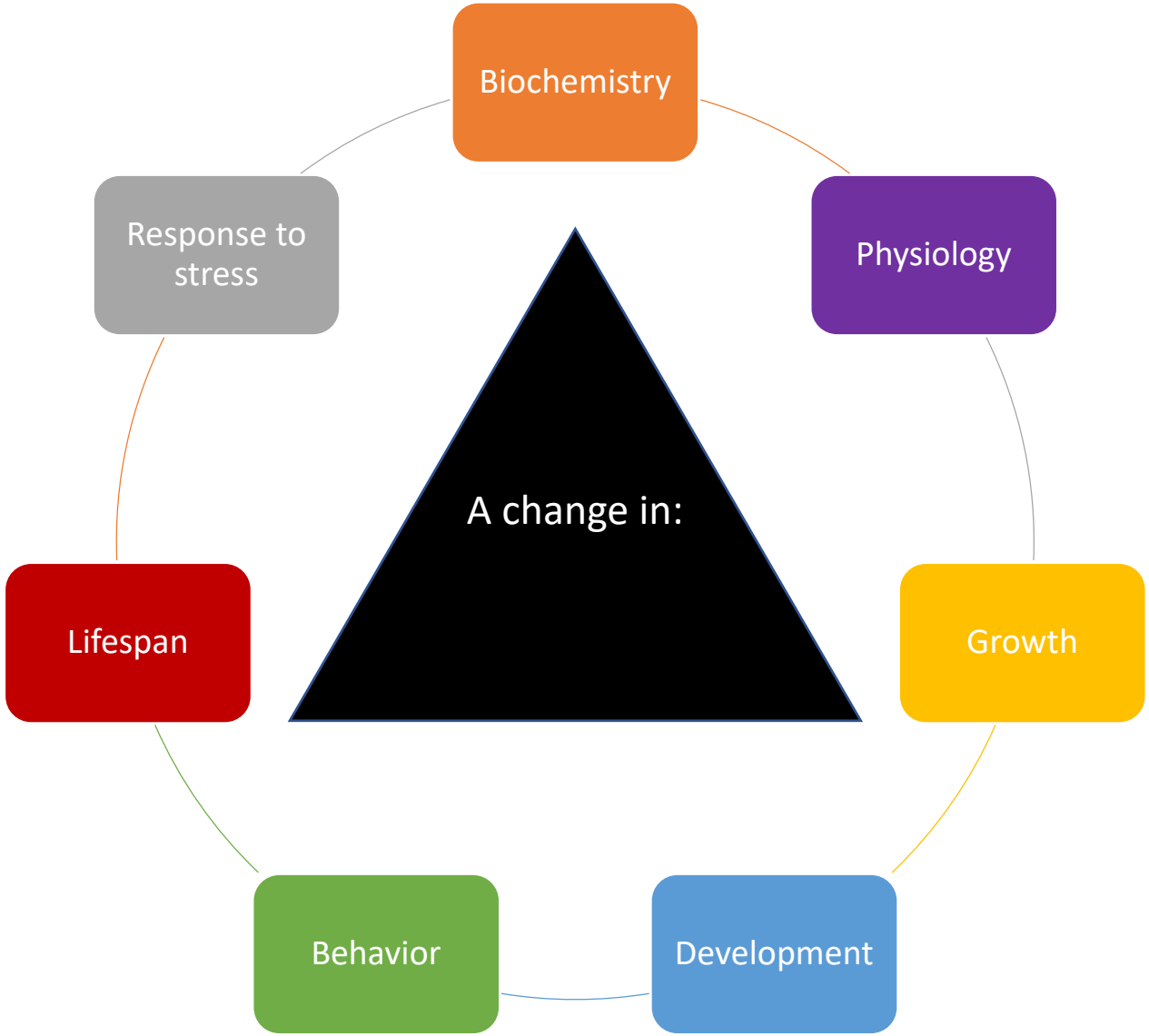
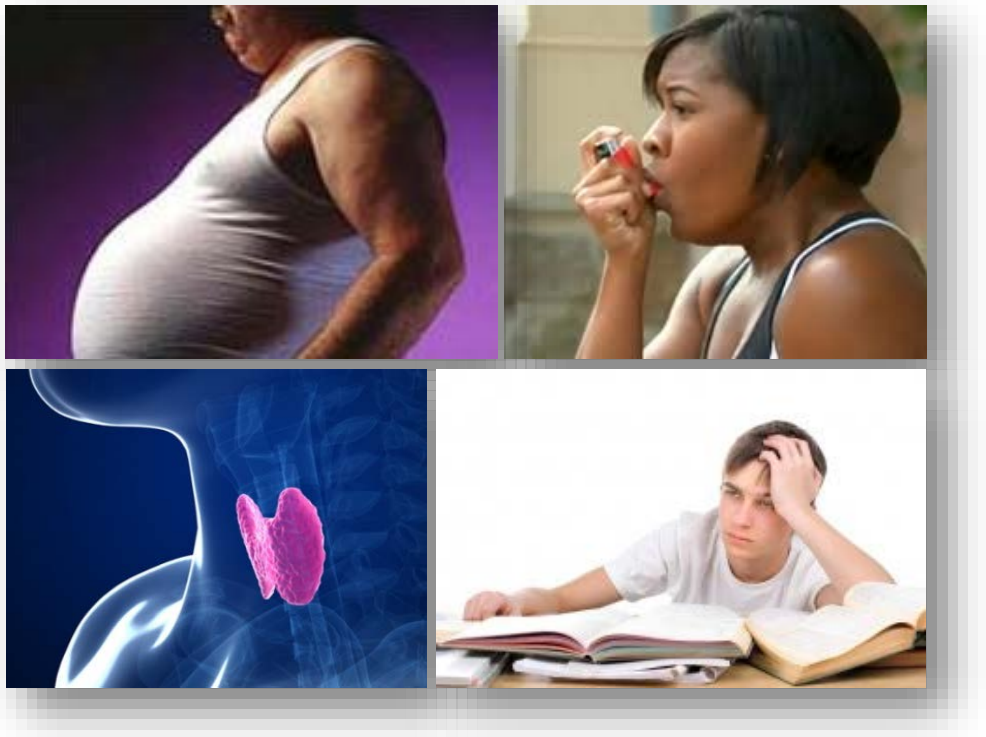
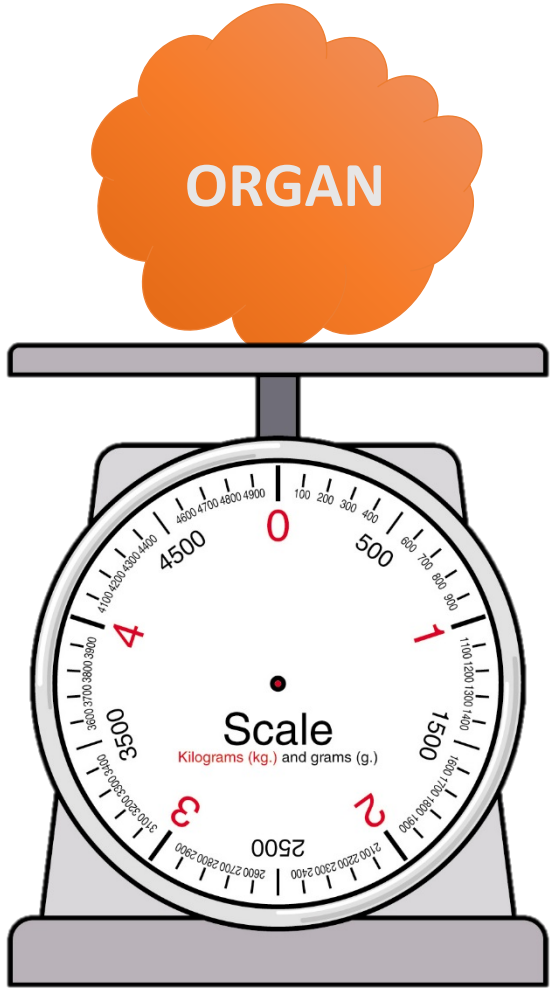
What is an adverse outcome?

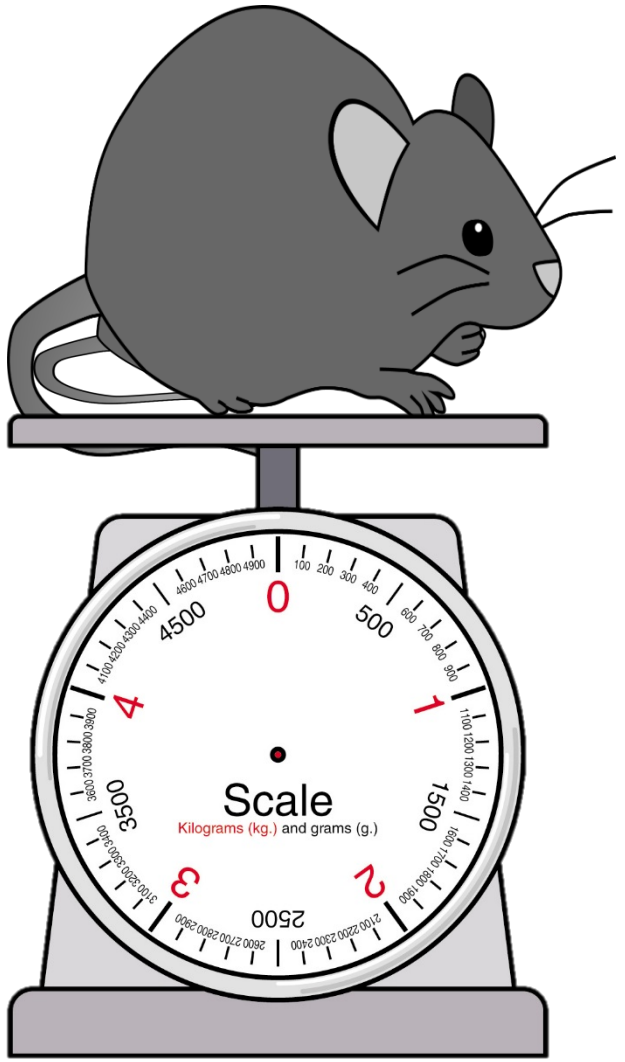


Standard Assays to evaluate Hazard

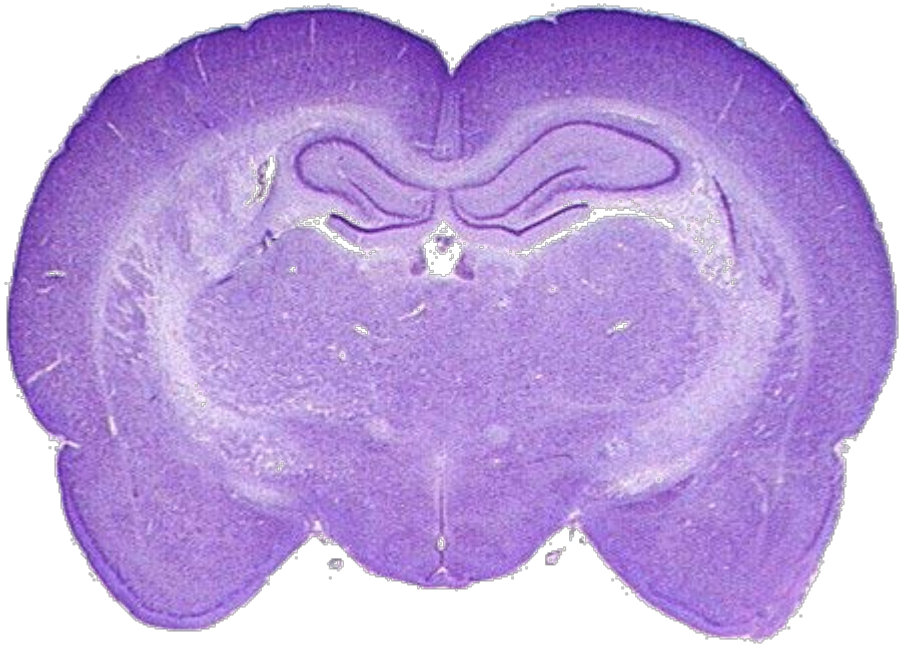


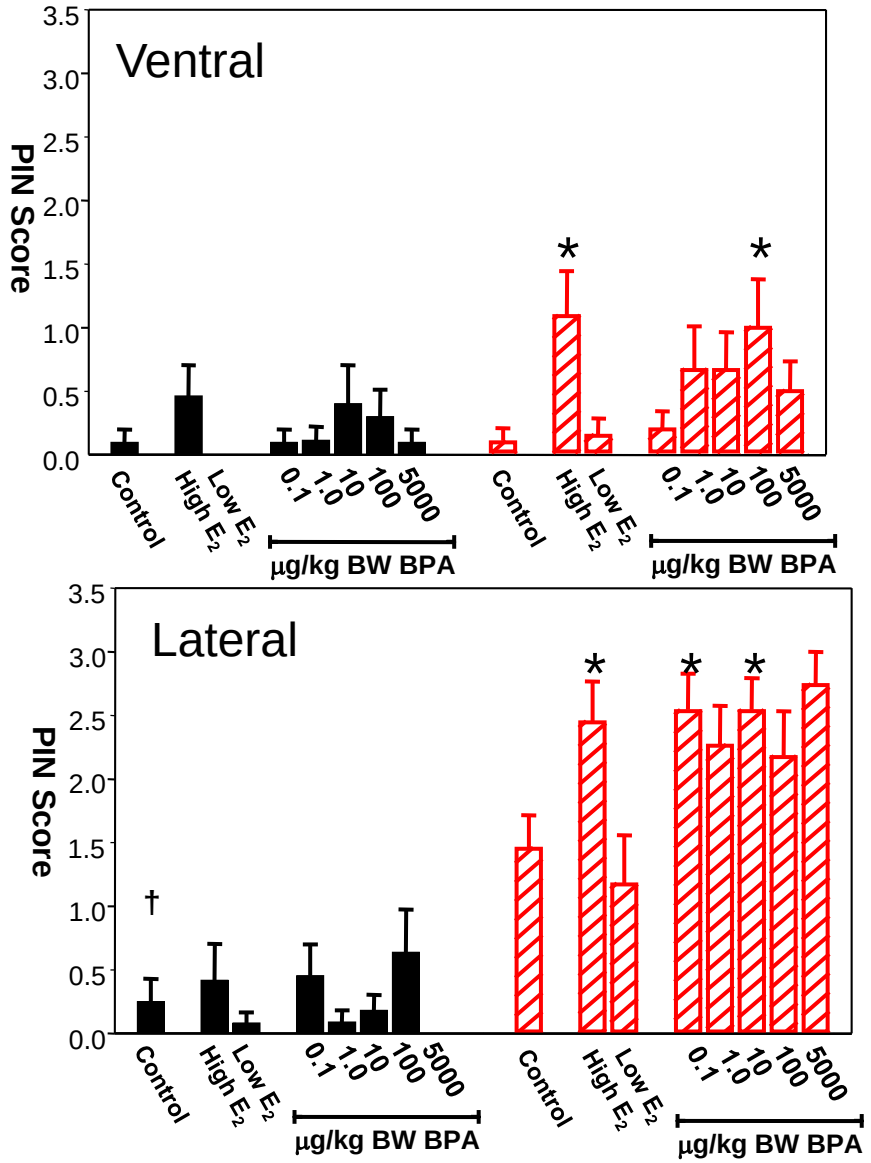


Conditions that are treated by the pharmaceutical industry are not considered “hazards” when induced by chemicals…

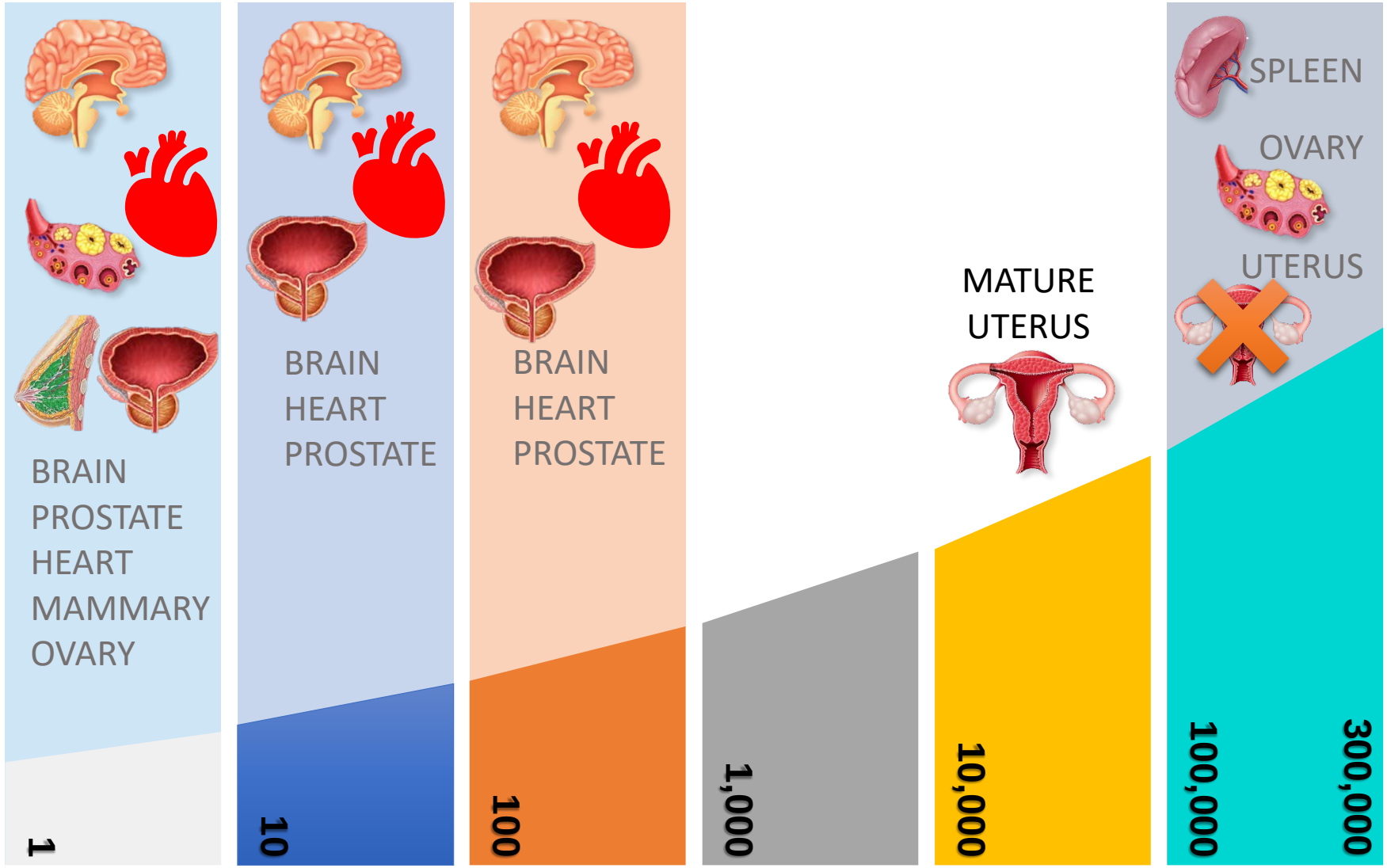


How we address uncertainties matters: experimental design in low dose studies





Incorporating more doses and more endpoints: revealing effects of BPA



Prins et al. BCPT 2018; Vandenberg et al. Nat Reviews Endo 2019

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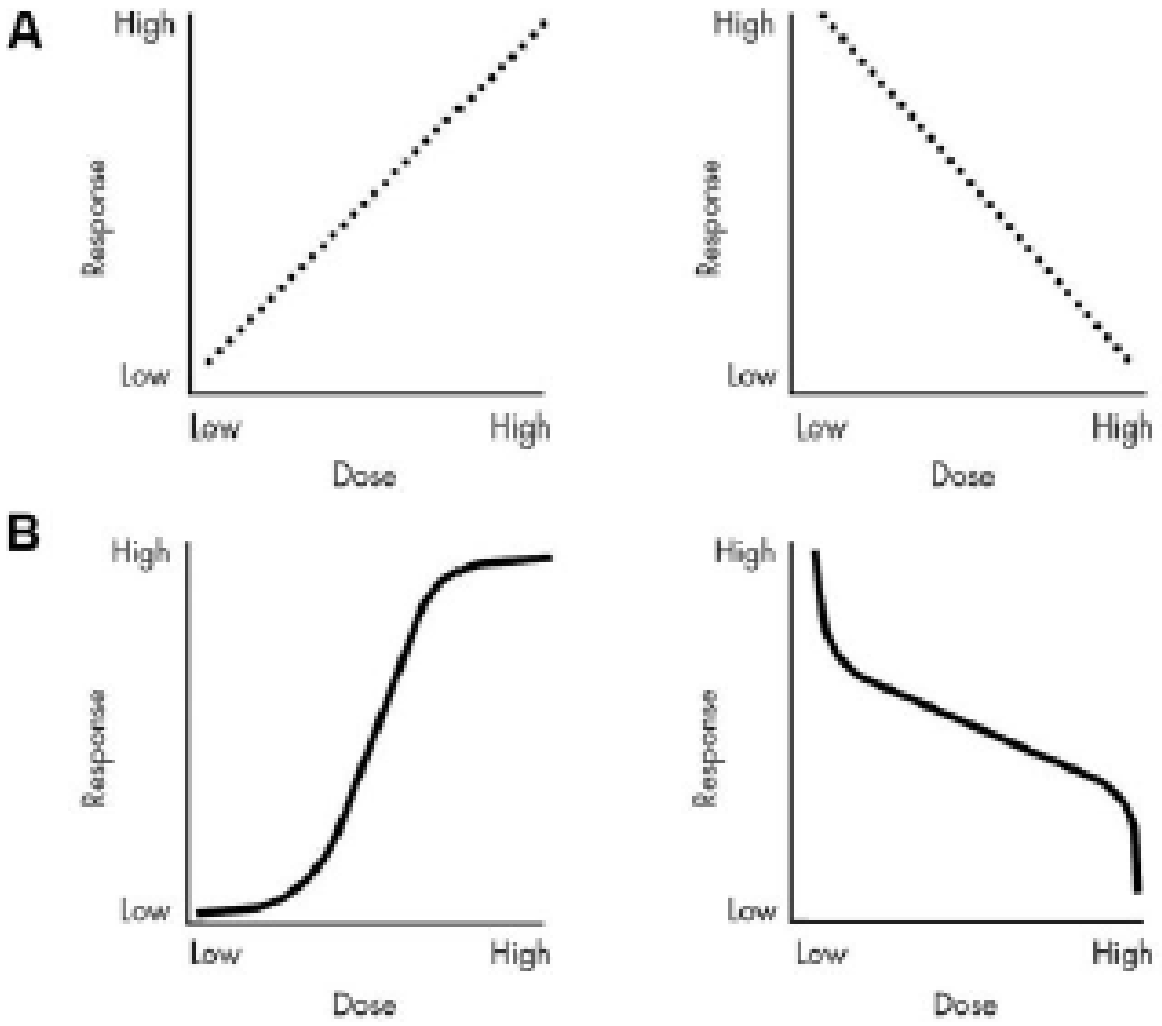
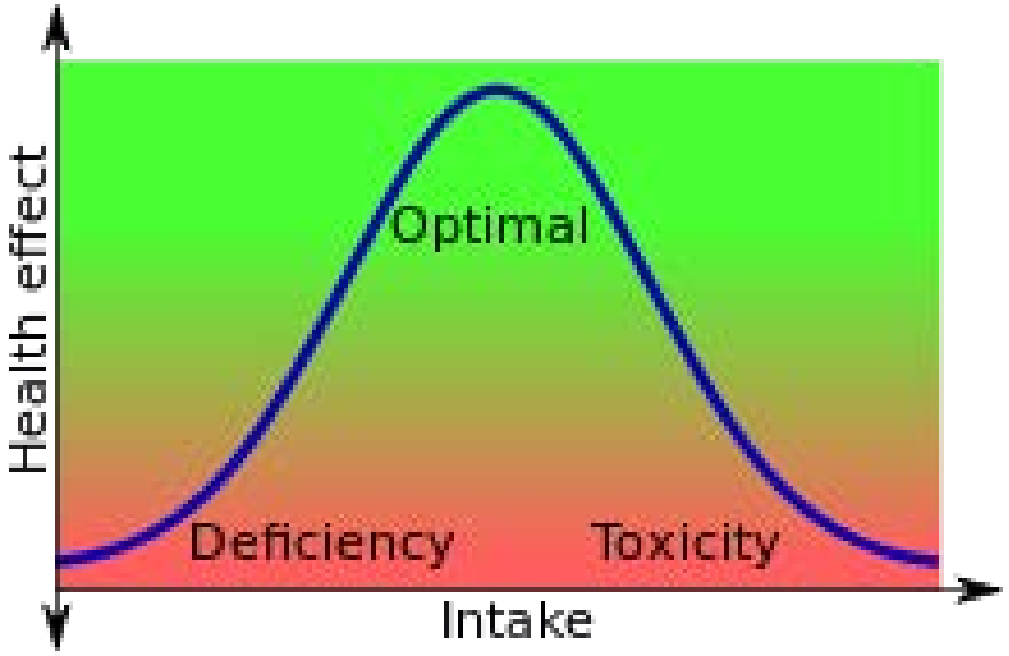
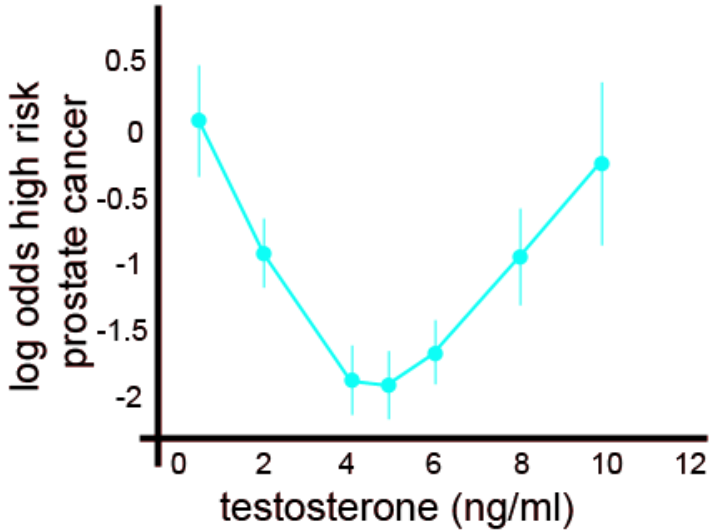
The expectation is that “the dose makes the poison”



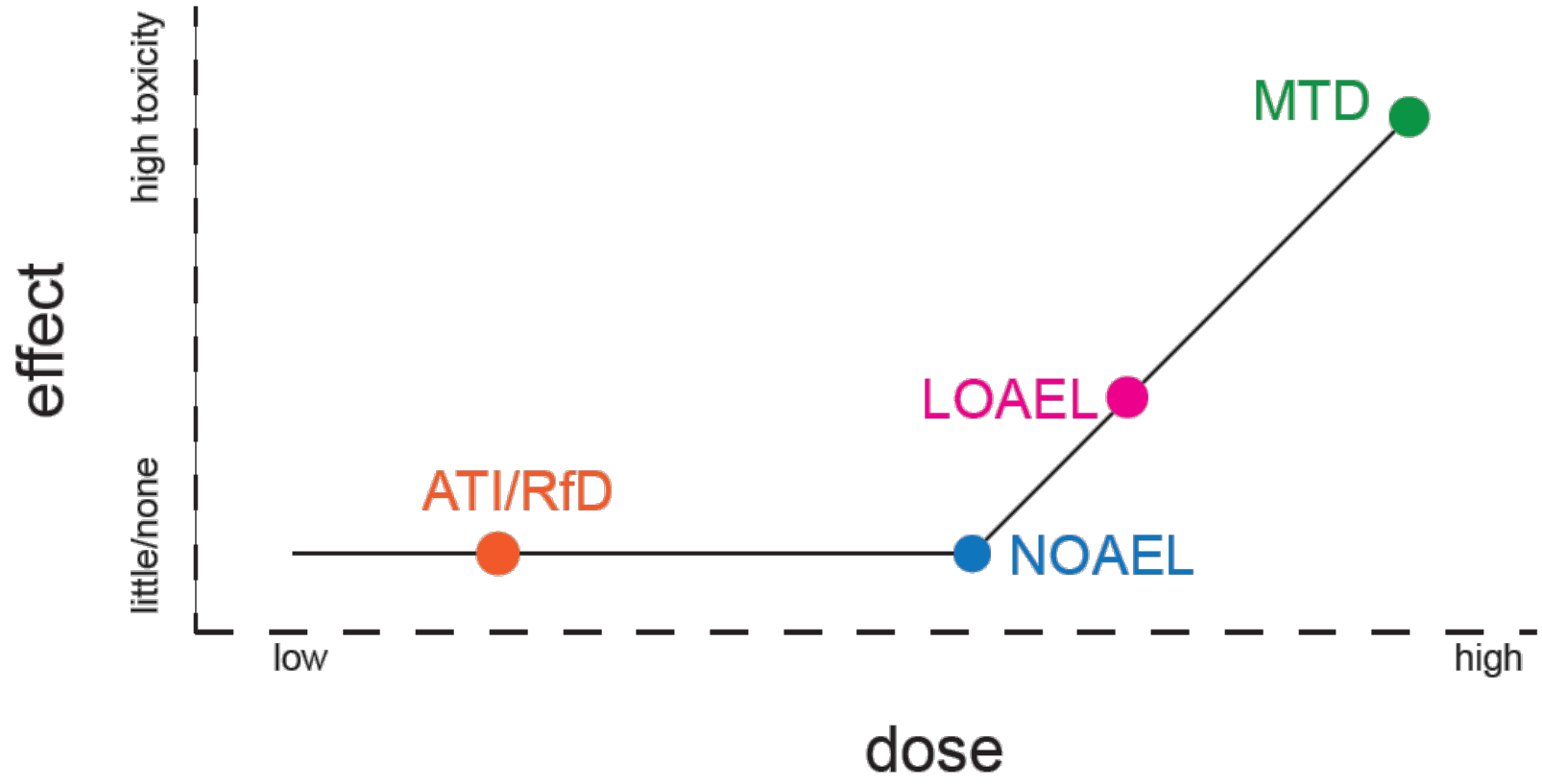
Yet non-monotonic curves are common in medicine, pharmacology & endocrinology



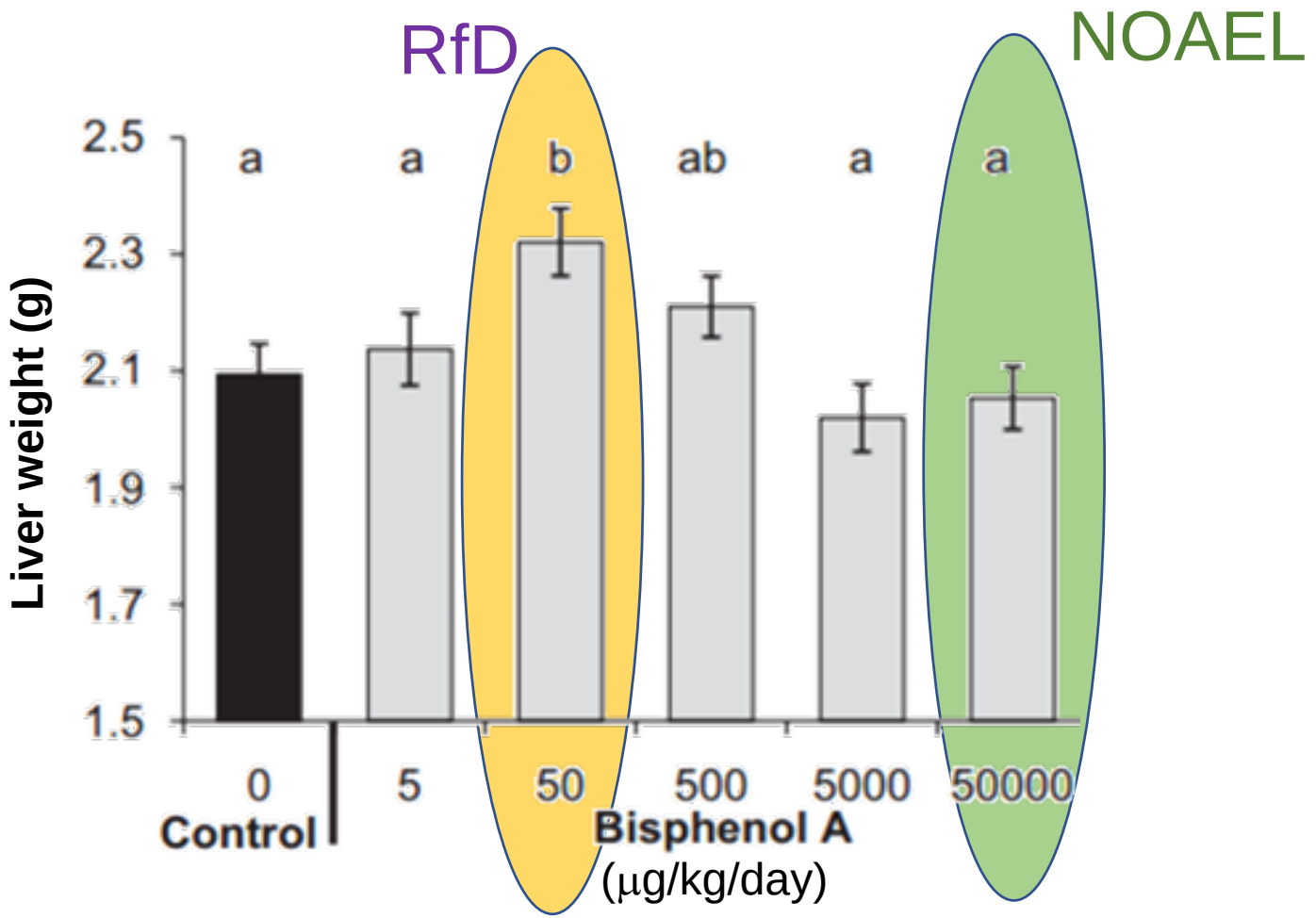


Houshmand et al. 2009

Why this matters: ATI/RFD “safe” doses are calculated from NOAELs with an assumption of linearity

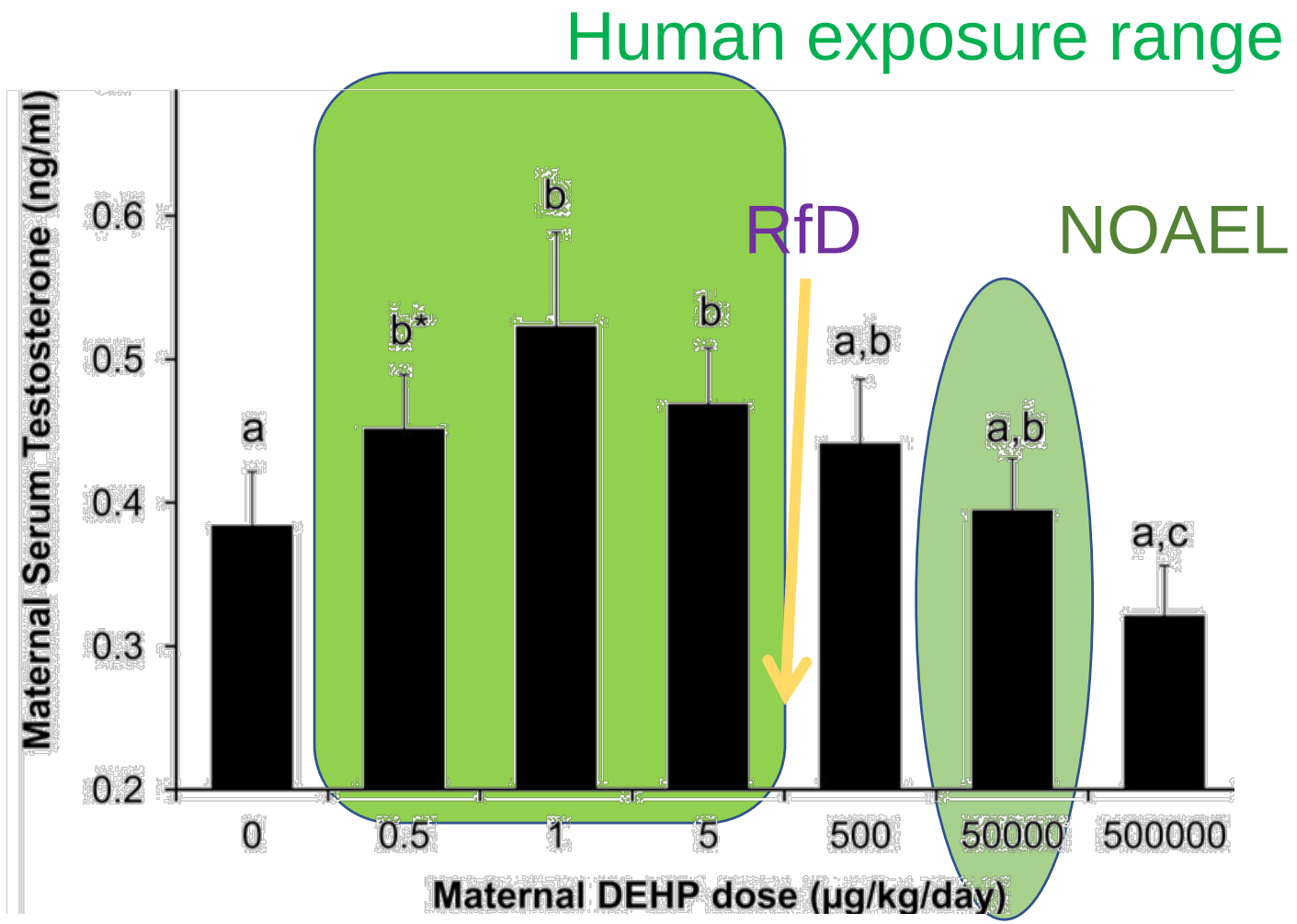


Examples in the context of the NOAEL and RFD



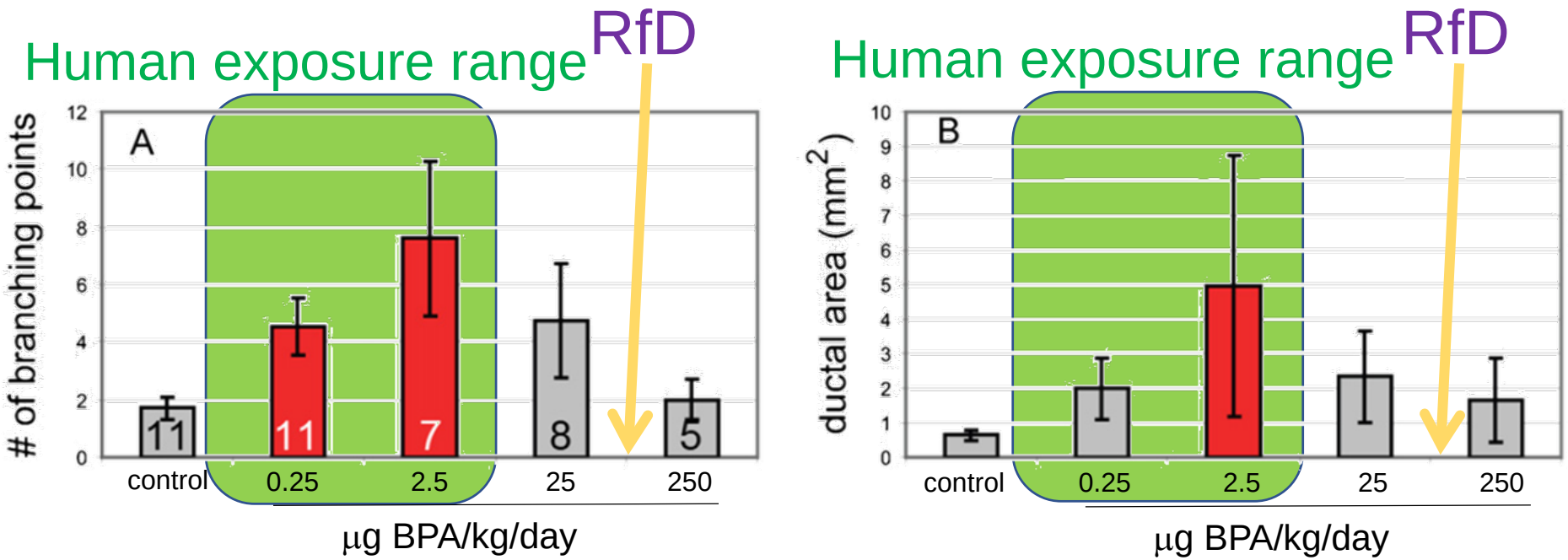
Angle et al. 2013

Examples in the context of the NOAEL, RFD and human exposures



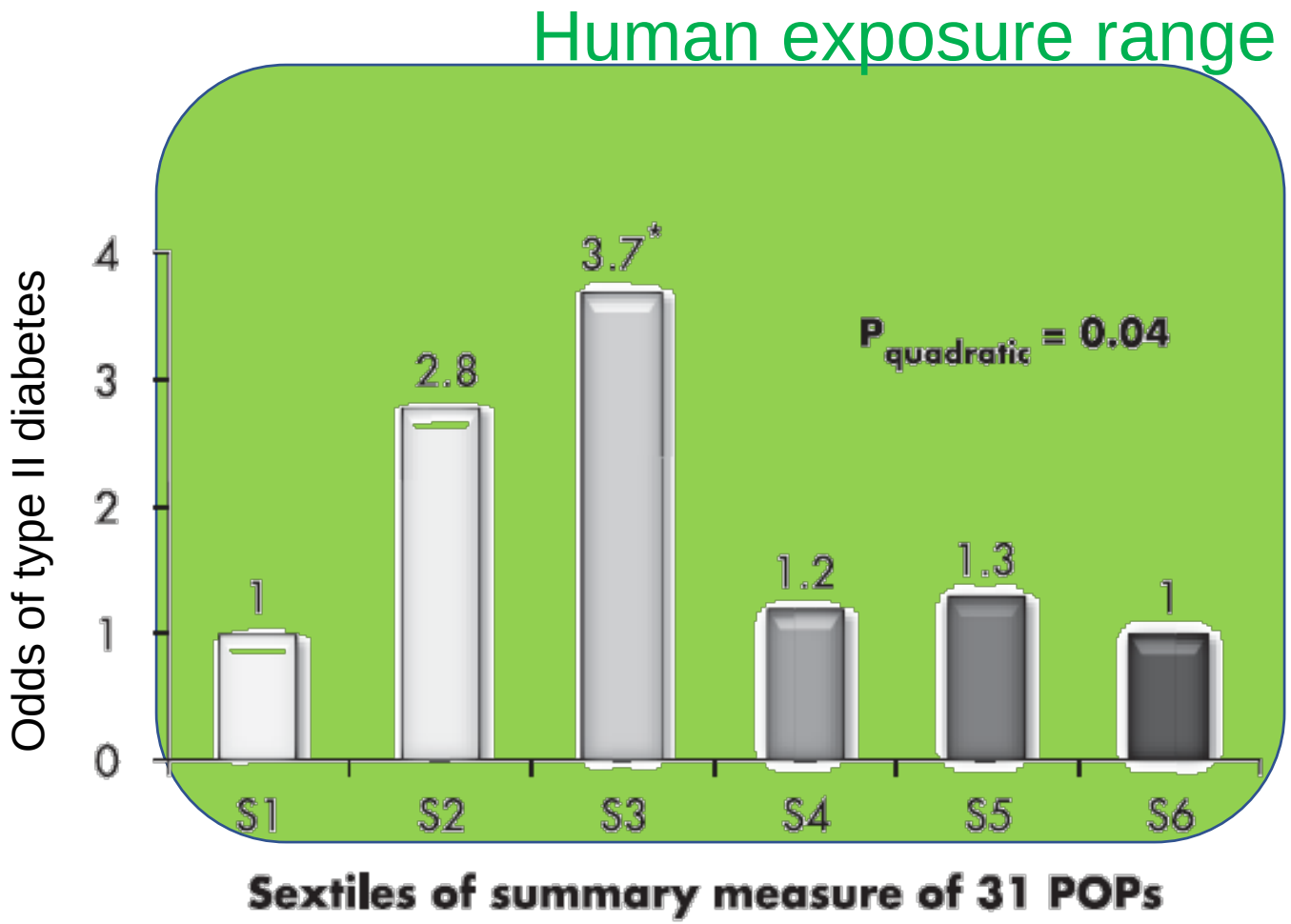
Do et al. 2013

Examples in the context of the RFD and human exposures



Vandenberg et al. 2013

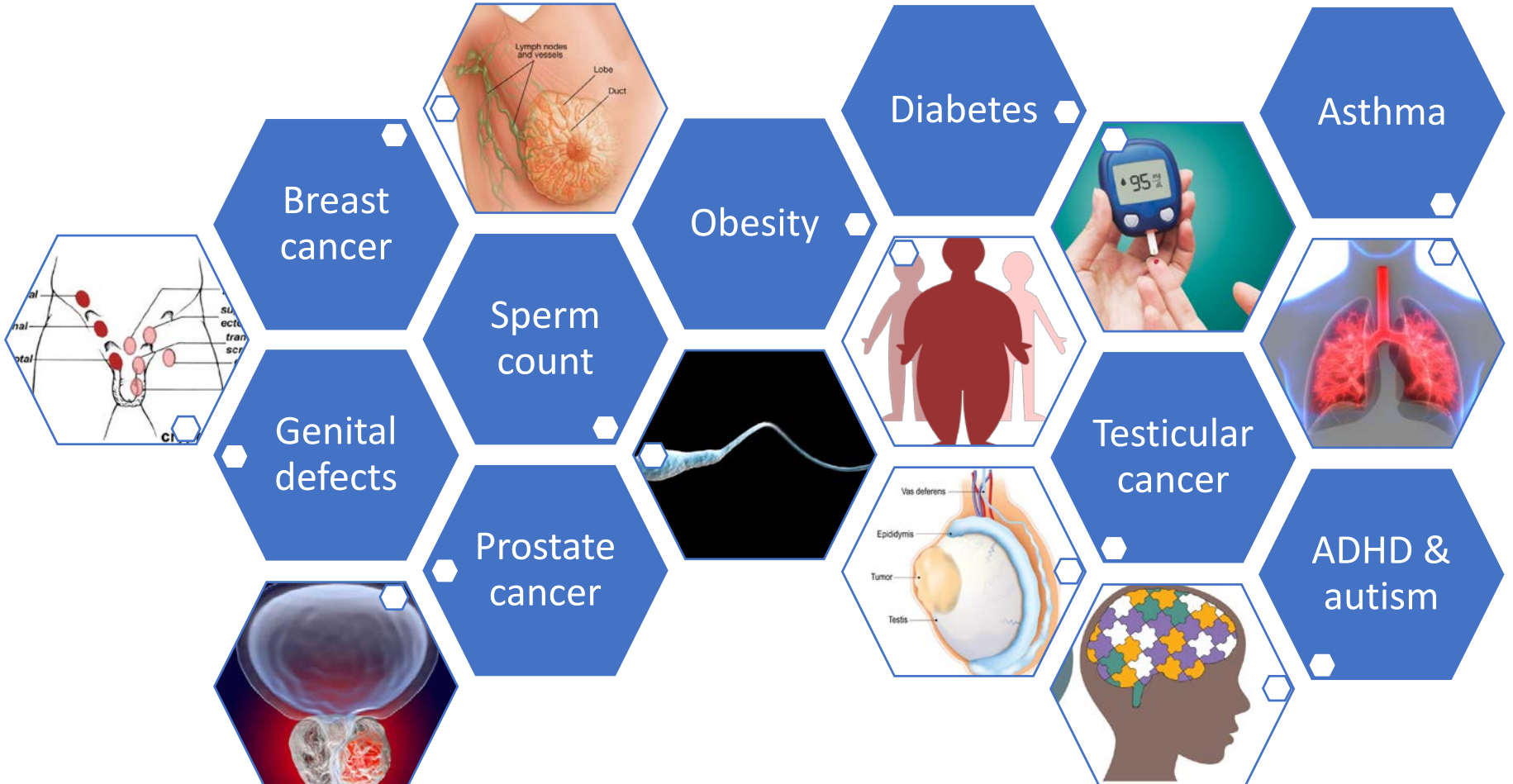
Dozens of epidemiology studies reveal non-monotonic responses (presumably all below the RfD)



Lee et al. 2014

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

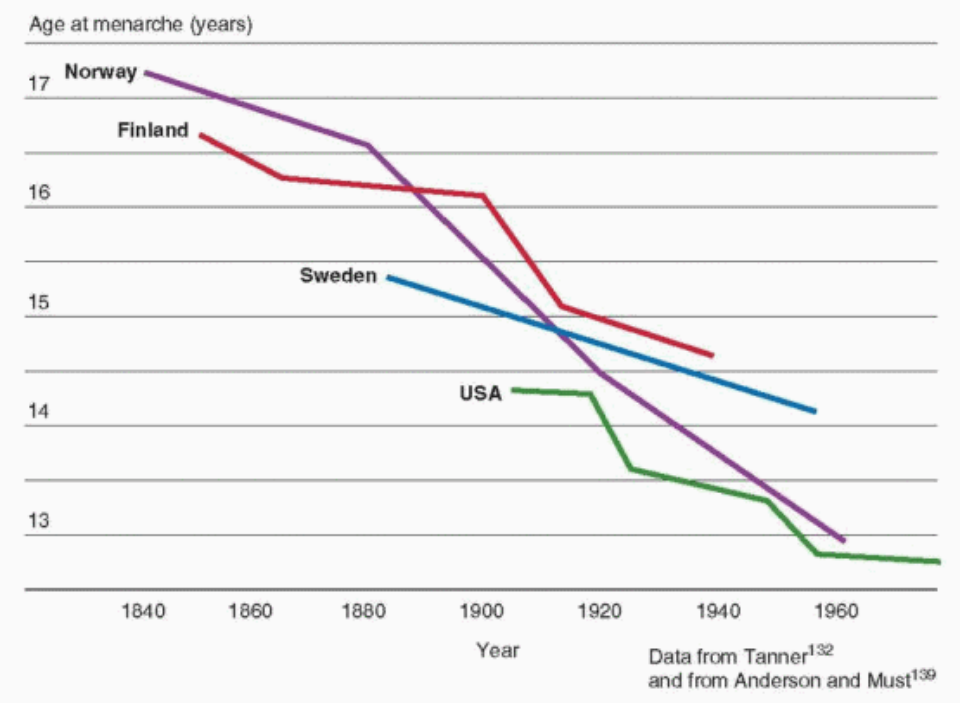
Hormone associated diseases/disorders on the rise:

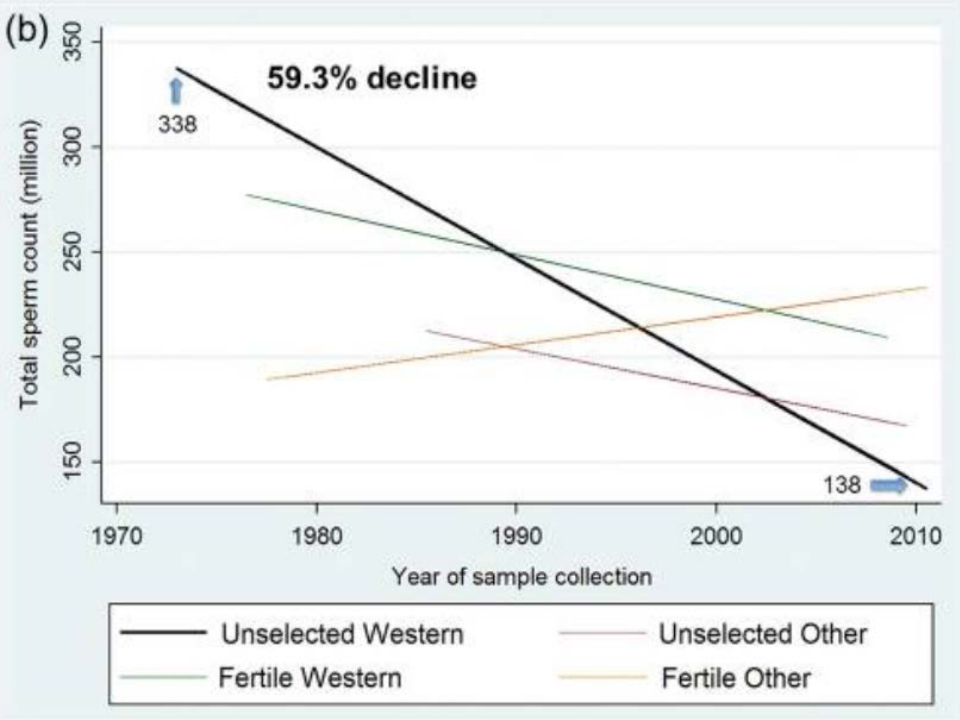


Are we fine?

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: Tanner, Anderson & Must
Bottom: Levine et al., Hum Reprod Update. (2017)

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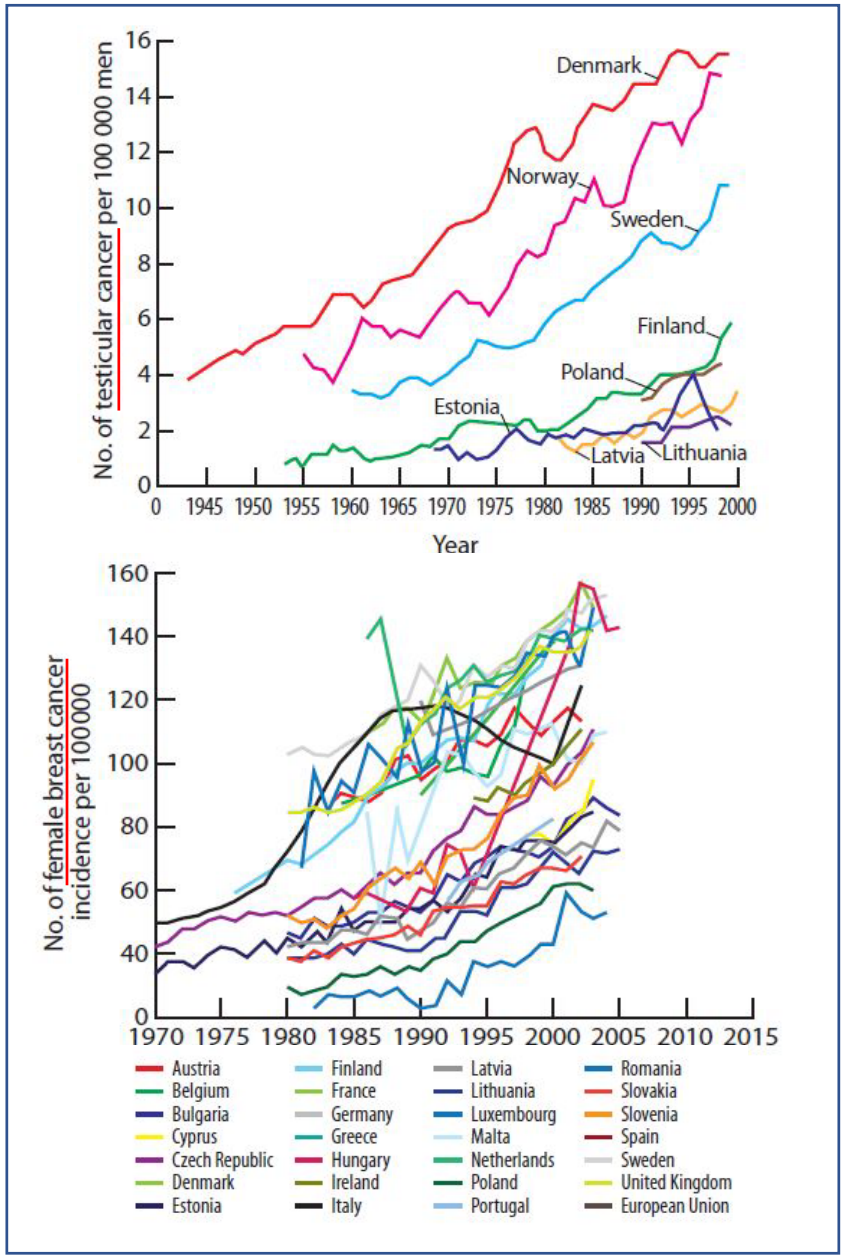

Top: Richiardi et al., Cancer Epidem. Biomark. (2004);
Bottom: based on data from http://data.euro.who.int/hfadb/

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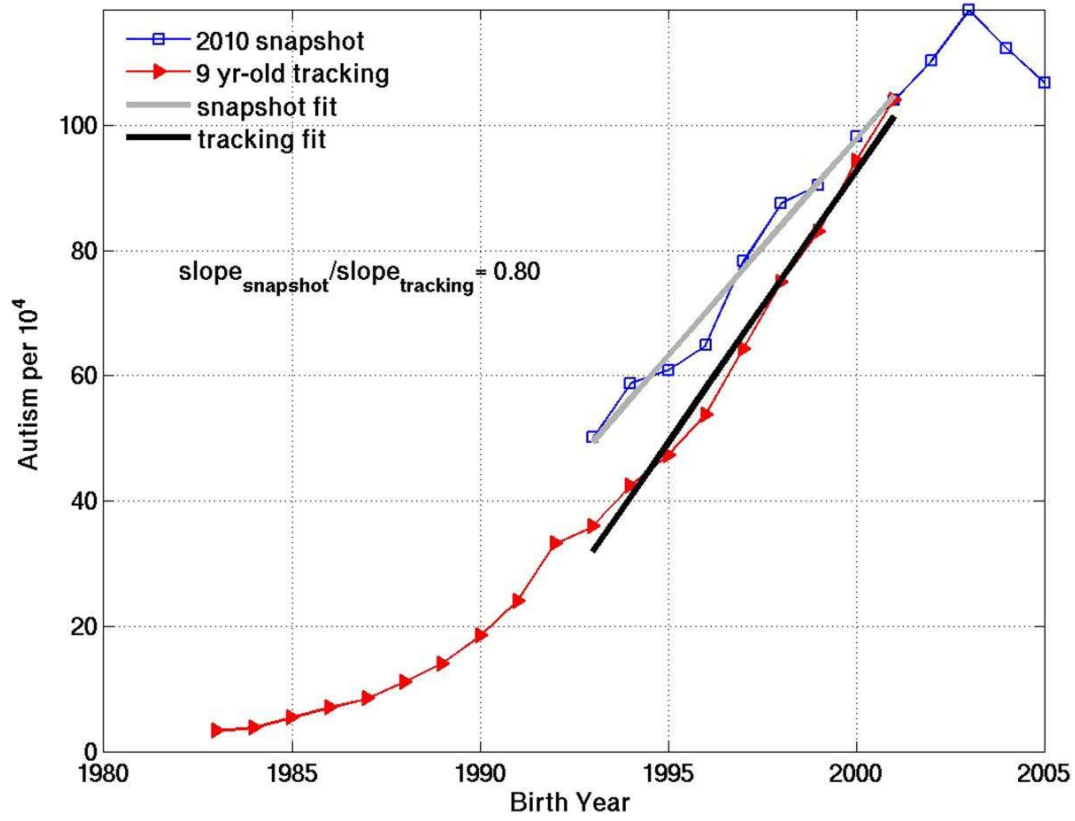

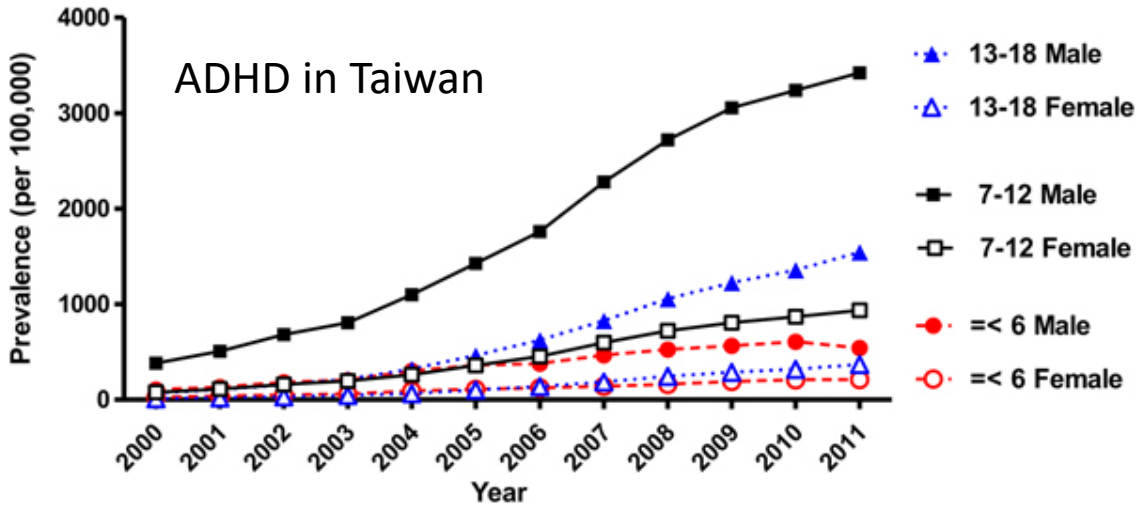

Top: Nevison, Environ Health (2014);
Bottom: Wang et al., Epidemiol & Psychiatry (2017)

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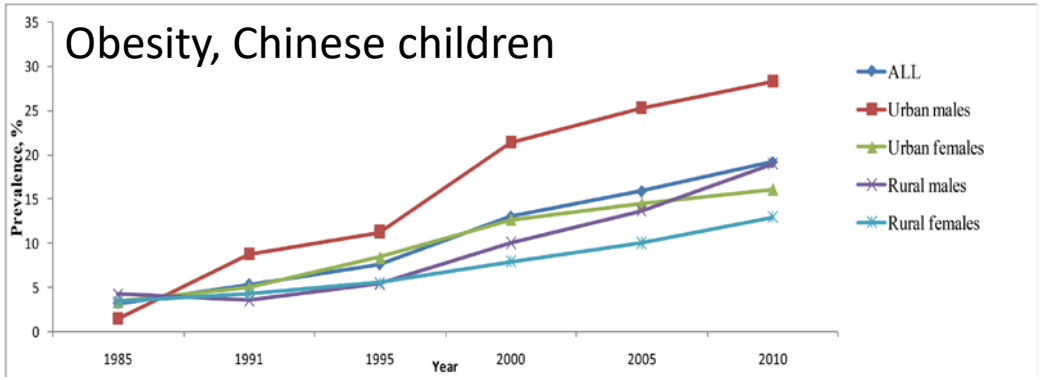
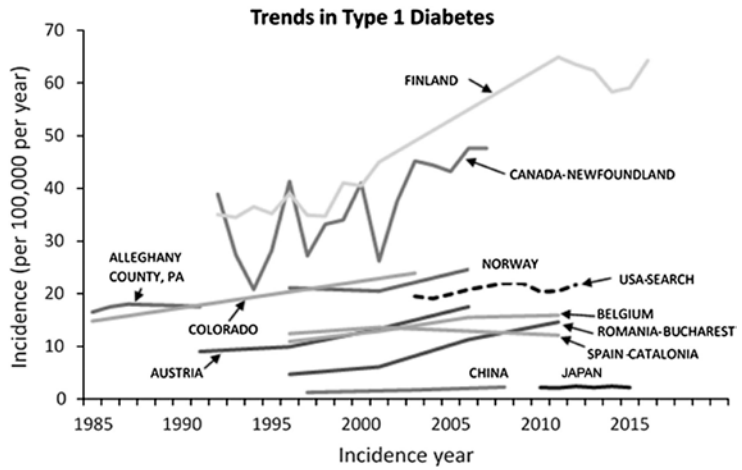
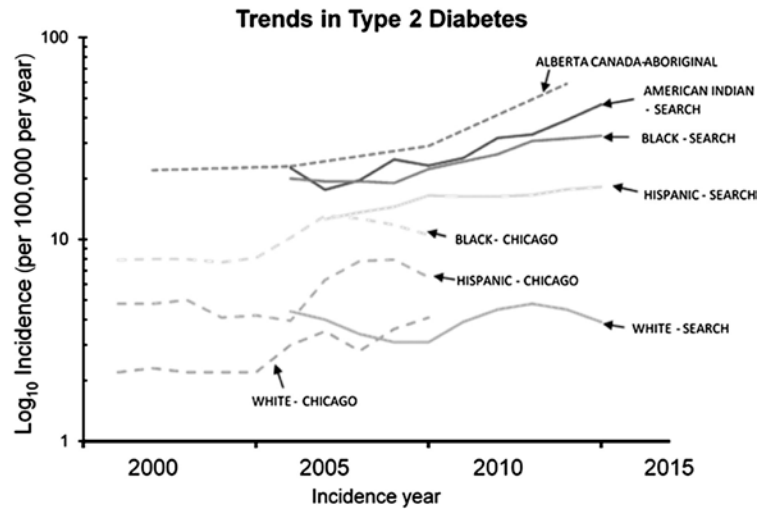




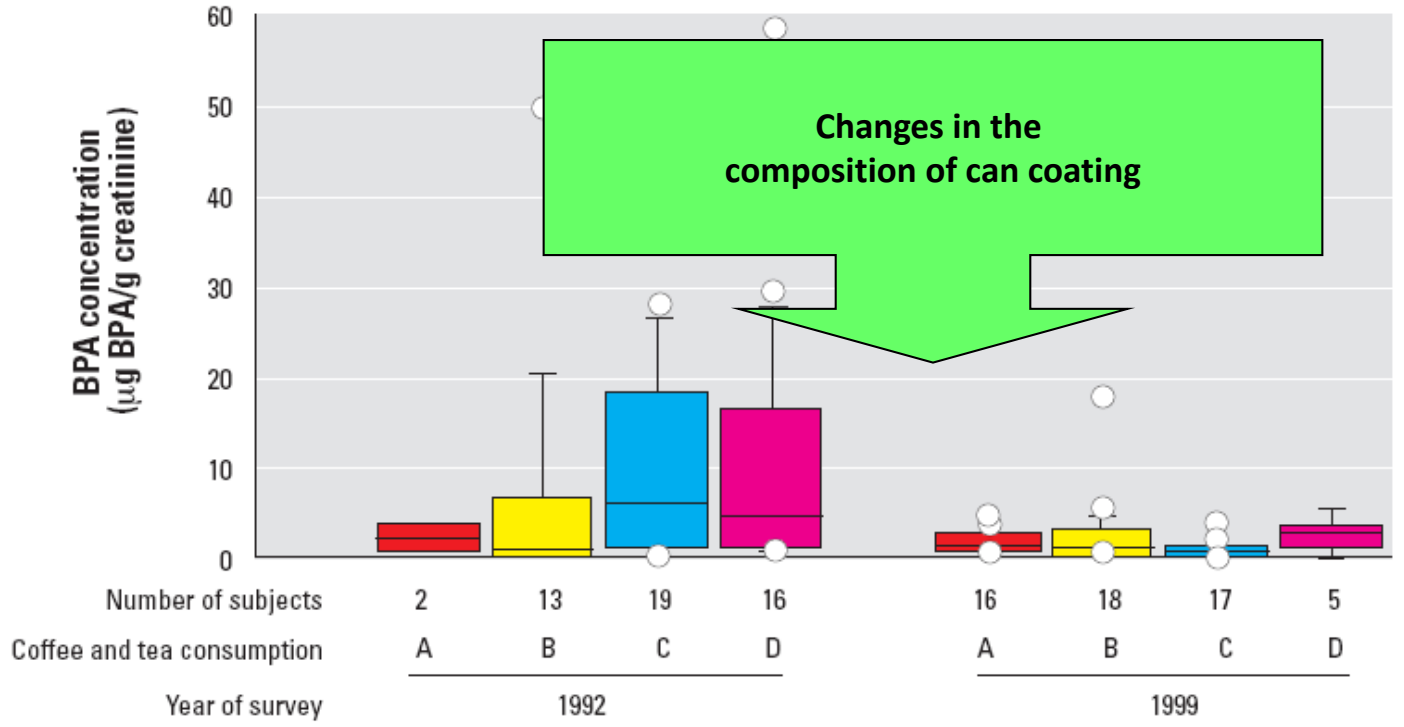


Top: Sun et al., PLoS One (2014);
Middle & bottom: Dabelea, Diabetes Care (2018)

There is a strong case that EDCs affect human health

- Even though exposures are typically low, many dozens of EDCs are associated with adverse health outcomes in human populations
- Increasing numbers of prospective (and occasionally retrospective) cohort studies support a causal relationship between EDC exposures and diseases
- Secular trends indicate that many endocrine-mediated diseases are increasing in prevalence (even though life expectancy has also increased)
- Animal studies have been very helpful in understanding the mechanisms by which EDCs induce adverse health outcomes

Yet, there is hope: relatively small changes can make a difference



Acknowledgements

Mary Catanese
Corinne Hill
Charlotte LaPlante
Durga Kolla
Aastha Pokharel
Mary Morcos
Danny McSweeney
Klara Matouskova

Lauren Hurley
Michelle Levine
Rebecca Goldberg
Brian Martin
Shawn Hallett
Michael Lemieux
Alison Bowler

Archana Gopal
Sarah Sapouckey
D'Andre Quinerly
Deb Pimentel
Anupama Singh
Lauren Masse
Meg Bernier
Alfred Kimani

Support from National Institute of Environmental Health Sciences, National Cancer Institute, Paul G Allen Family Foundation, Cornell Douglas Foundation, Great Neck Breast Cancer Coalition