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Are Endocrine Disruptors Special?

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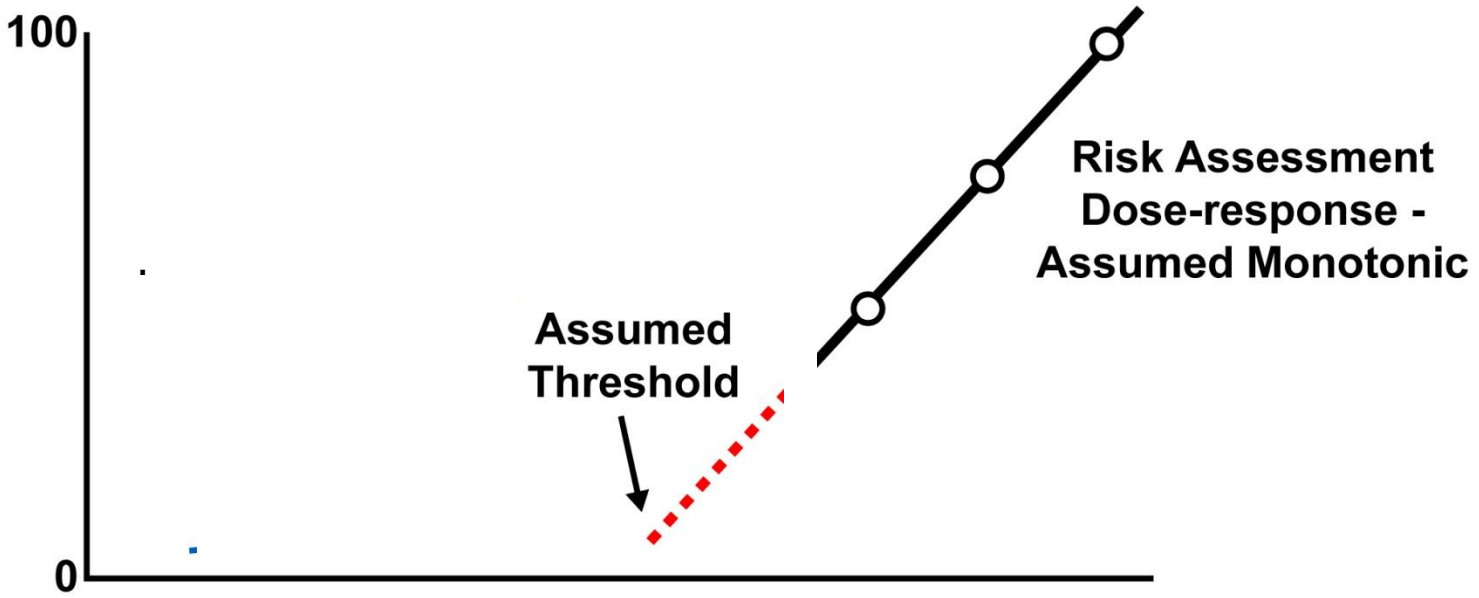
National Institutes of Health

Current Paradigm: All chemicals Treated the Same

Test at high doses and extrapolate effects to low doses…

High doses predict low dose effects.

Assume Threshold



Question: Are Endocrine Disrupting Chemicals Different and therefore should be assessed using different criteria?

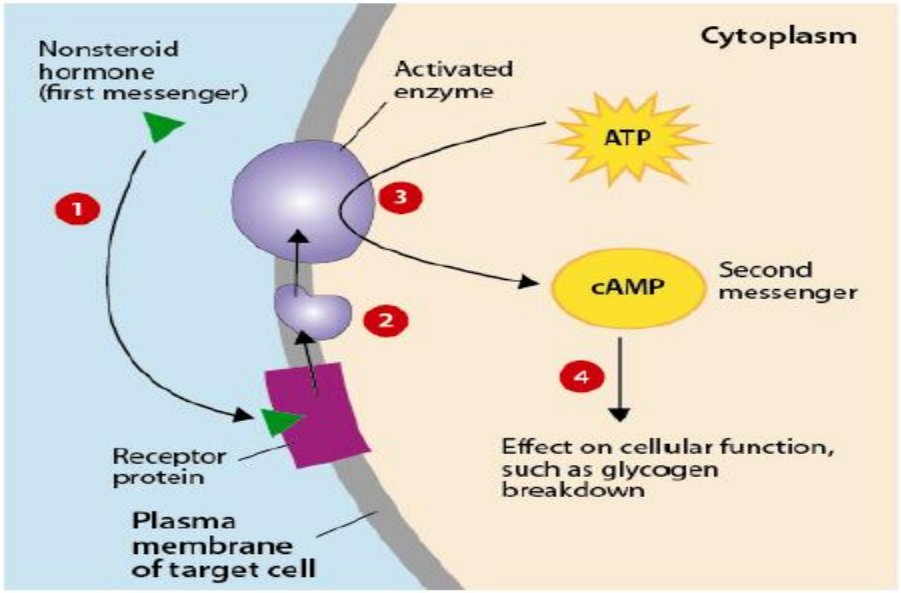
Premise

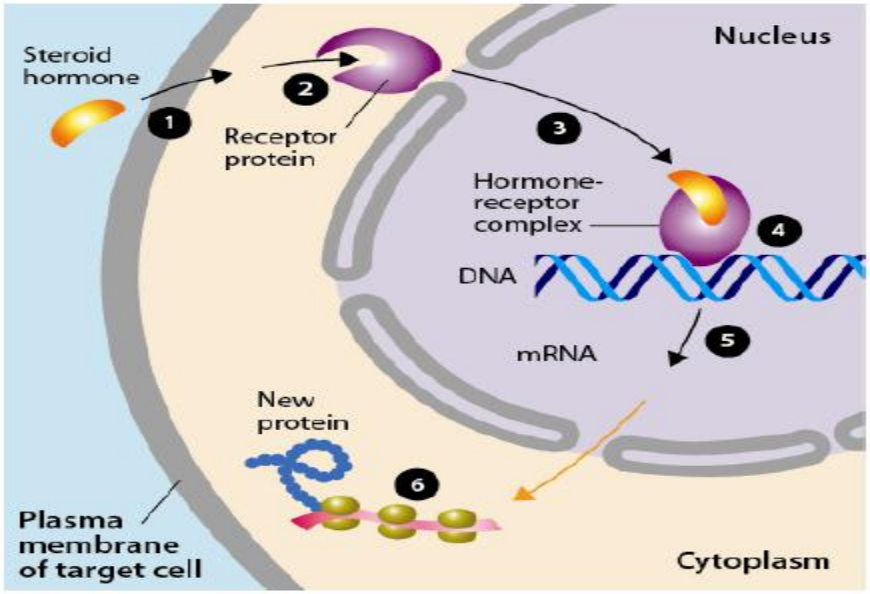
There are principles by which the endocrine system functions: Principles of Endocrinology.

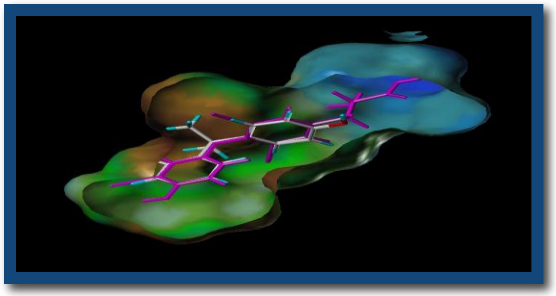
EDCs specifically disrupt the action of the endocrine system.

Therefore they are subject to the principles of endocrinology.

First Principle: Hormones Act via Receptors





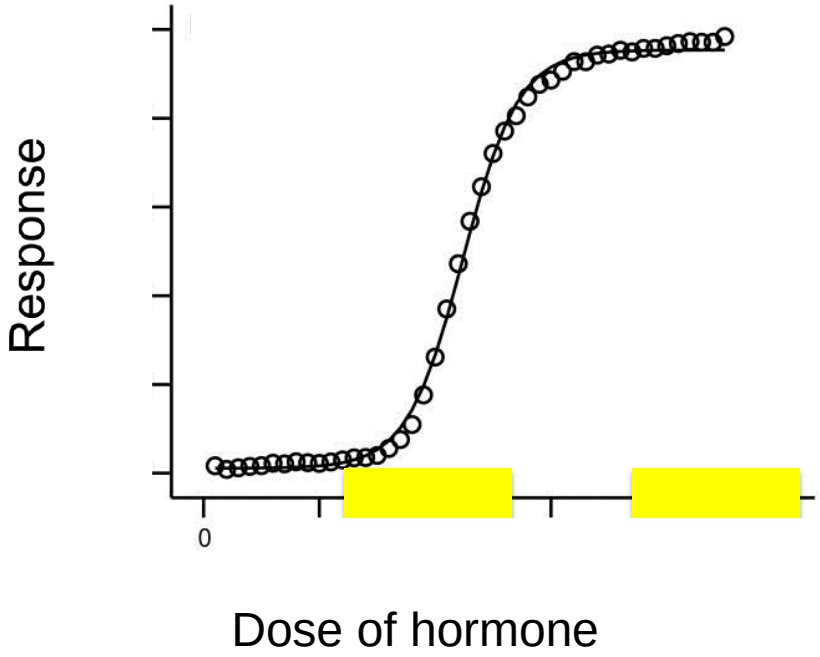


EDCs produce adverse effects either by interfering with native hormone action, or by recruiting hormone receptors to act in abnormal ways.

- Direct
- Indirect

Heindel et al. 2012

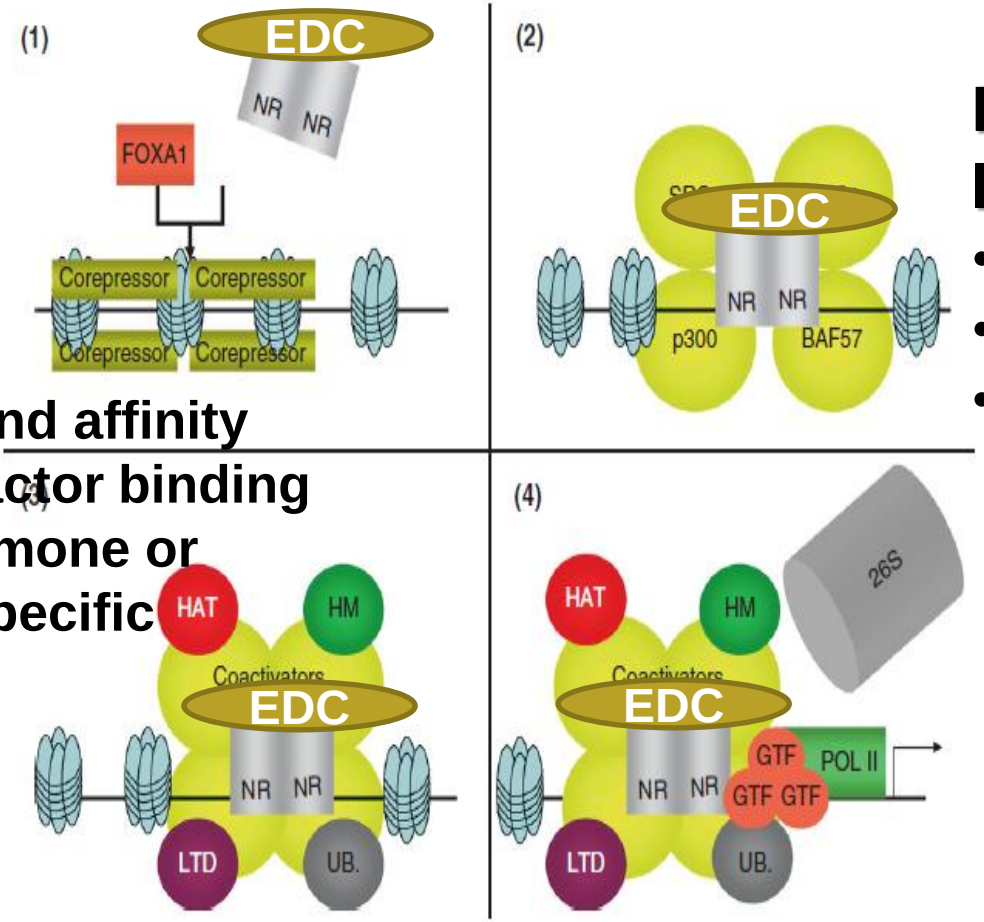
Consequences of Receptor-Mediated Signaling



- Hormones act at low levels
- Largest effect at lower doses
- Saturation of receptors and thus effect at high doses
- Desensitization and down-regulation of receptors at high hormone levels
- EDCs that act via receptors are subject to same consequences.

Tissue Response is not Just Due to Receptor Affinity

Receptor binding = Affinity



Type and affinity of cofactor binding is hormone or EDC specific

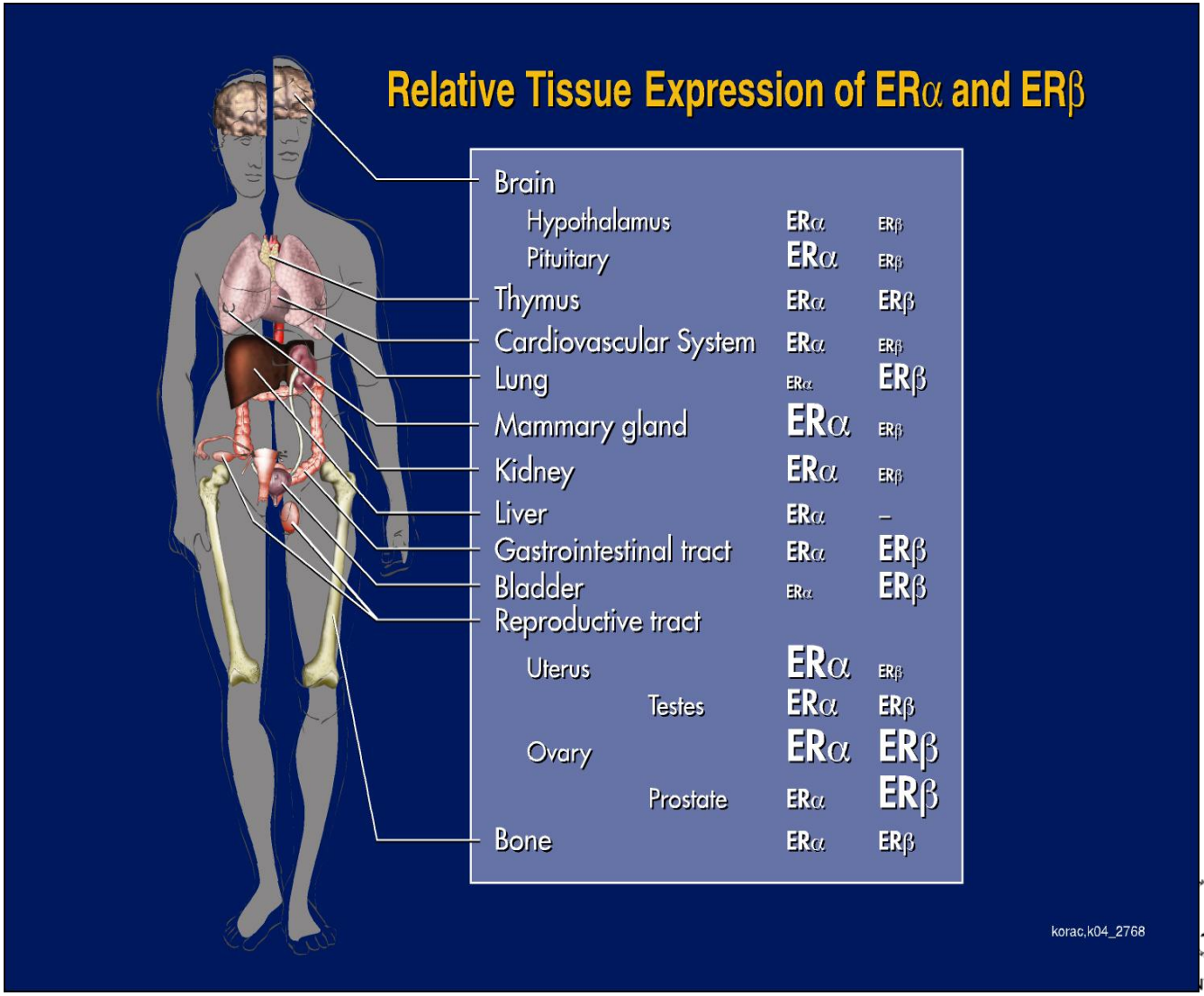
Response (Potency) Is context dependent

- **Receptor affinity**
- **Number of receptors**
- **Cofactors (tissue specific)**

Note: EDC response may not be same as hormone

Stanisic et al Prog Brain Res 2010

Receptors are Tissue Specific Providing Tissue Specificity



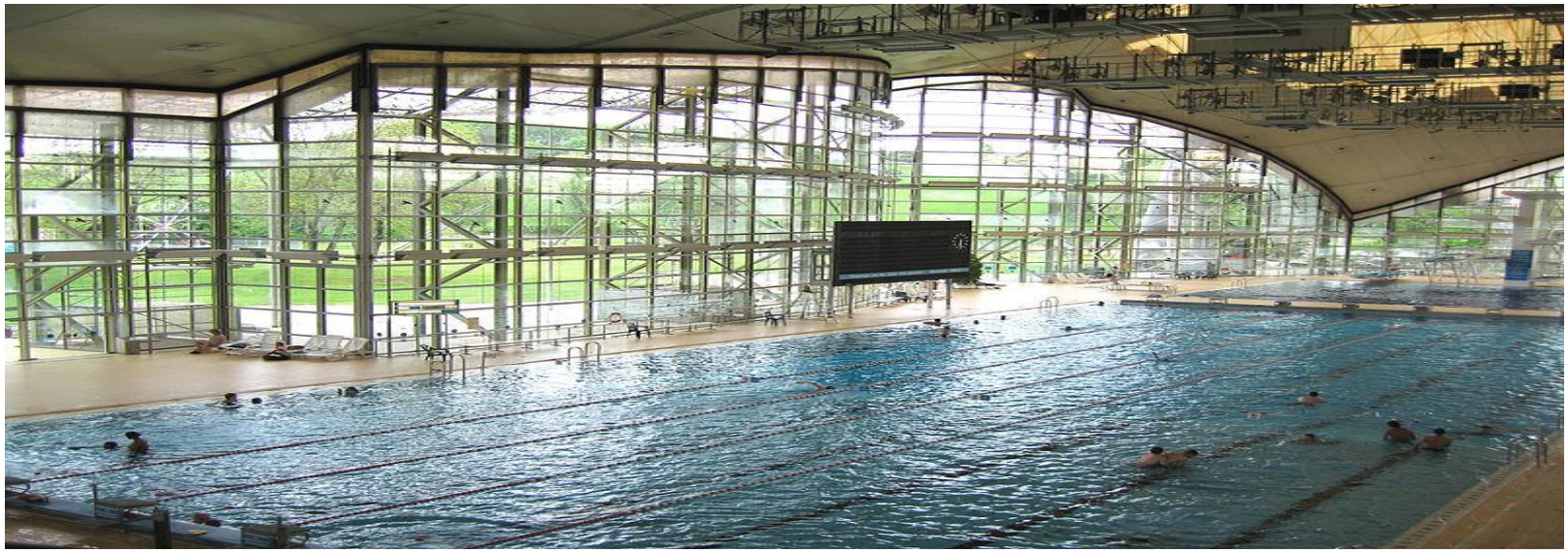
Hormones act at Very Low Doses: PPT

Adult blood levels of free testosterone: 3.0-205 ppt

Adult blood levels of free estradiol: 9 ppt

Adult blood levels of thyroid hormone: 30ppt

Adult blood levels of growth hormone: 2-6 ppt



One part per trillion (ppt) is equivalent to about 1/20 of a drop of water in olympic swimming pool.

Endocrine Disrupting Chemicals with Documented Low Dose Effects in Animal Studies (below noel, human exposures)

Insecticides/Fungicide

- Chlordane
- Chlorothalonil
- Chlorpyrifos
- DDT
- Heptachlor
- Hexachlorobenzene
- Maneb
- Parathion
- Methoxychlor
- Tributylin oxide
- Vinclozolin

Industrial/General

- Arachlor 1221
- Bisphenol A/Genistein/DES
- Dioxin
- 4-methybenzlidine
- Methyparaben
- Nonphenol
- Octylphenol
- Phthalates
- Sodium Fluoride
- PBDEs/ PCBs
- Perchlorate

Vandenberg et al Endo Reviews 2012

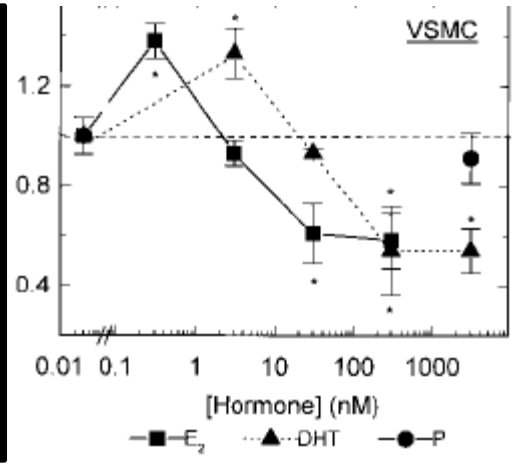
Examples of "Low Dose Effects" in Humans

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

Vandenberg et al, 2012

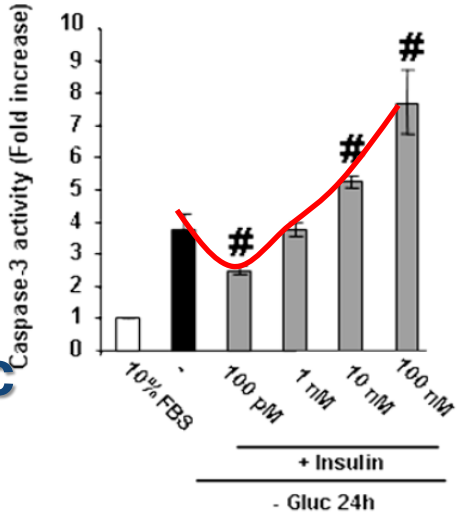
Third Principle:
Hormones Produce non-monotonic Dose Responses

Cell proliferation

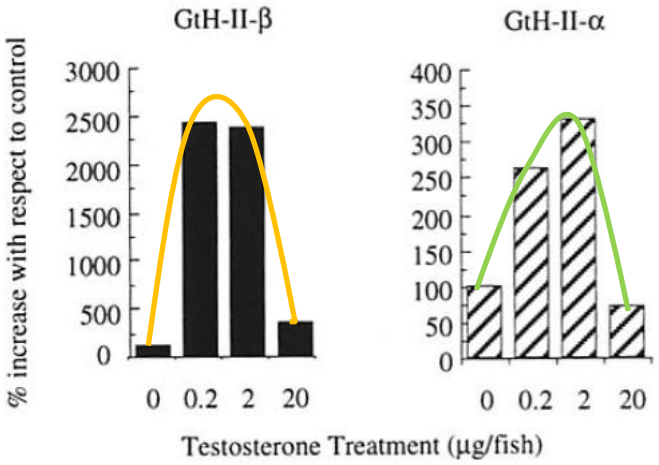


Somjen et al. 2008

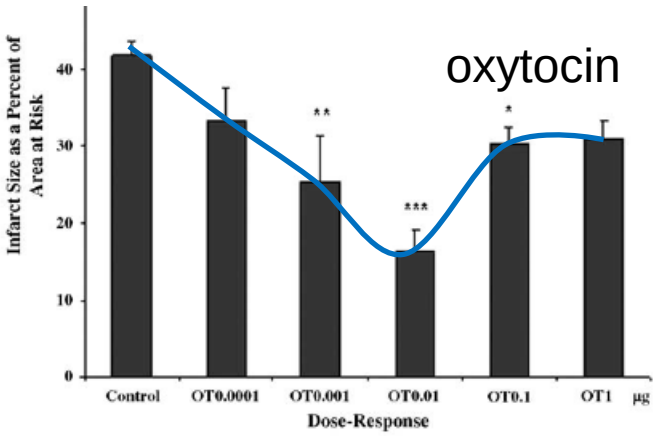
Implication: EDCs will produce non-monotonic dose responses



Guillen et al. 2008



Huggard et al.



Houshmand et al. 2009

Examples of Chemicals that Produce Non-monotonic Dose Responses In Vivo

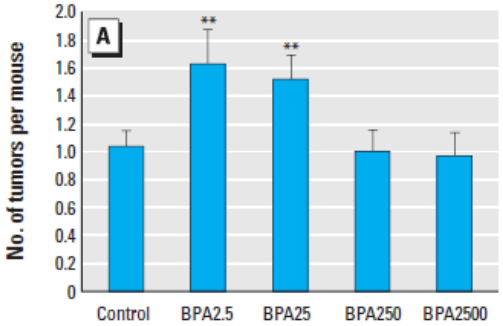
- DES
- Ethinyl estradiol
- Tamoxifen
- Fluoxetine
- Fadrozole
- BPA
- DEHP
- Nonylphenol
- Octylphenol
- Semicarbazide
- Triclocarban
- PCB mixture
- B-naphthoflavone
- Dioxin
- Cadmium
- Selenium
- Genistein
- Resveratrol
- Phlorizin
- Atrazine
- Pendimethalin
- Simazine
- Permethrin
- Heptachlor
- DDT
- Methoxychlor
- Chlorpyrifos
- Carbendazim
- Chlorothalonil
- Vinclozolin

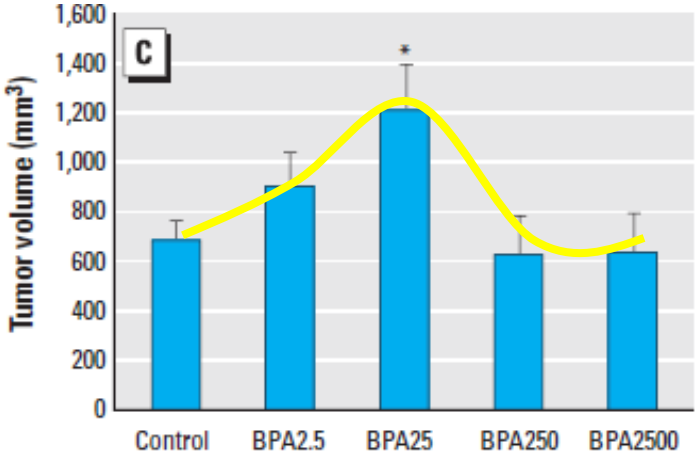
Vandenberg et al
Endo Reviews 20

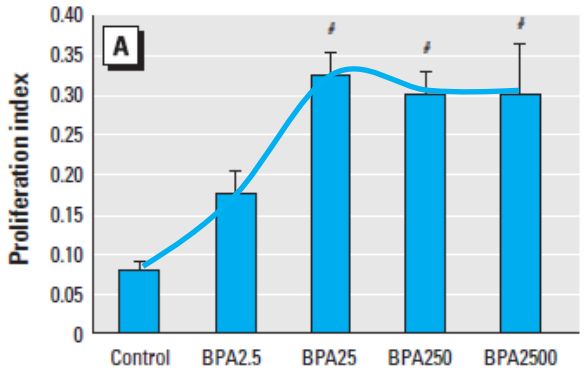
Why do Hormones and EDCs Produce Non-monotonic Dose Responses?

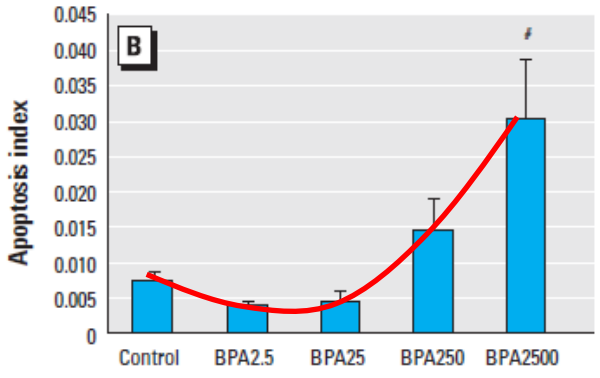
- Receptor feedback: Receptor desensitization and down-regulation & (known for >40 yrs)
- Intersection of multiple linear pathways along a dose response curve
- Non specific cytotoxicity at high doses
- ???

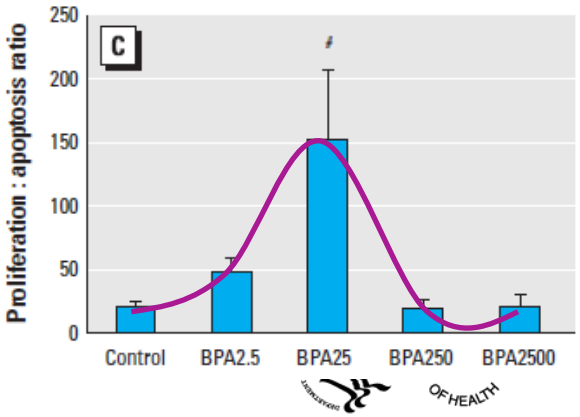
Non-Monotonic Dose Response Due to Overlapping Pathways











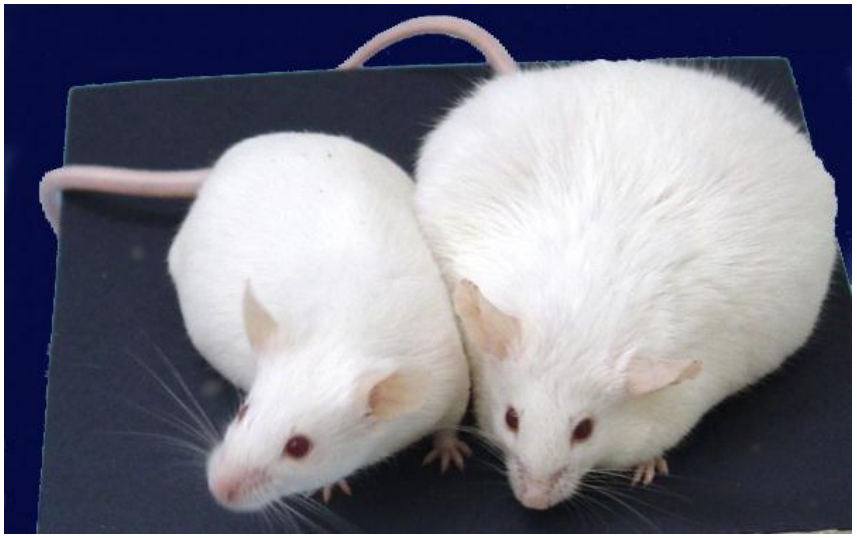
Jenkins et al. 2011 [Ref 293]

Fourth Principle: Hormonal Action is Life-Stage Specific

Development is the most sensitive time for EDC effects:

- **Lower doses**
- **Latent and persistent effects**
- **Increased disease risk later in life**

Developmental effects are different from adult effects.



1. Low Doses Matter
2. Effects at high dose does not predict effects at low dose
3. Early life exposures produce adverse effects in adulthood

Newbold, NIEHS

Disease Risk Increased by Developmental Exposures to EDCS (Human)

Reproductive/Endocrine

- Breast/prostate cancer (BPA)
- Endometriosis (Dioxin, PCBs)
- Infertility (Phthalates, Estrogens, Pesticides)
- Diabetes/metabolic syndrome (BPA)
- Early Puberty (Estrogens, BPA)
- Obesity (BPA, Tributyl Tin, Organochlorine Pesticides)

- **Immune/Autoimmune**
  - **Susceptibility to infections** (Dioxin, Perfluorinated compounds)

- **Pulmonocardiovascular**
  - Asthma (Air Pollution)
  - Heart disease/ hypertension (BPA)
  - Stroke (PCBs)

- **Brain/Nervous System**
  - Alzheimer's disease (Lead)
  - Parkinson's disease (Pesticides)
  - ADHD/learning disabilities (PCBs, Lead, Ethanol, Organochlorine Pesticides)

Conclusions

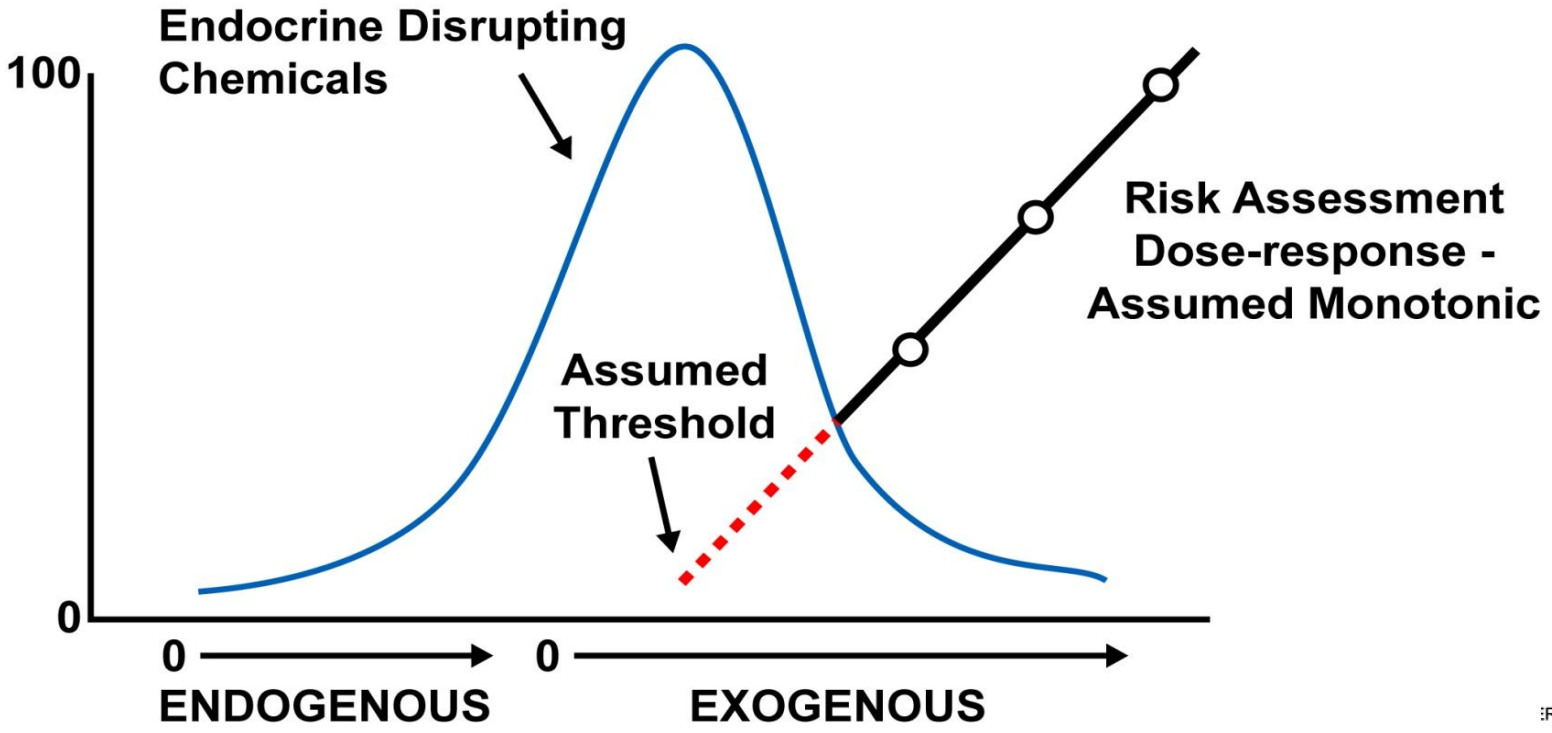
Not all chemicals can be treated the same with regard to toxicity testing and risk assessment.

Chemicals with endocrine activity act via principles of endocrinology and thus:

- **May act at low doses**
- **Should be expected to have non-monotonic dose responses**
- **Will have tissue specific and time specific effects**
- **Will show different effects and dose responses during development relative to adults**
- **Will likely not have a threshold**

Implications for Human Health

Chemicals with endocrine activity may be either missed completely or have a "safe level" that is not protective of human health.



SAVE THE DATE!

An International Workshop
***September* 11-13**, 2012
Berlin, Germany

Low Dose Effects and Non-monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice

Scientific Sessions:

- How hormones and endocrine disruptors act
- Low dose effects for endocrine active chemicals
- Non-monotonic dose responses for endocrine active chemicals
- Impact on risk assessment
- Updates from EFSA, PEW Trust, ANSES, European Commission, NIEHS Endocrine Society
- Breakout group: Strength of low dose data and data needs
- Breakout group: Impact on risk assessment
- Defining a path forward

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anses French agency for food, environmental and occupational health & safety
Umwelt Bundes Amt Für Mensch und Umwelt
DTU Food National Food Institute
DTU
Danish Ministry of the Environment Environmental Protection Agency
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Website: http://tools.niehs.nih.gov/conference/dert_endocrine_2012/

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