When the dose *doesn't* make the poison: low dose effects & endocrine disrupting chemicals

Laura N. Vandenberg, PhD

Tufts University

A three-year effort, analyzing over 800 studies from a wide range of fields

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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

Increasingly, EDCs at current levels are found to be associated with adverse health outcomes

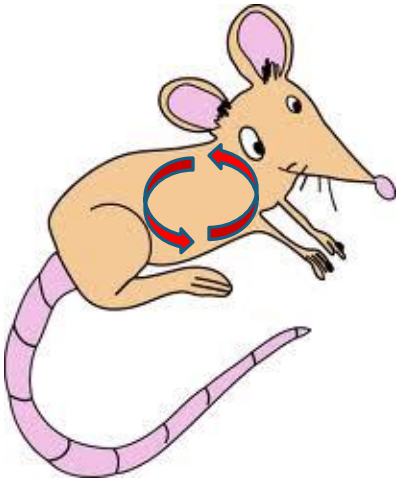
Chemical	Human Diseases
Phthalates	neurobehavior, adult fertility, metabolic syndrome, anogenital distance
Dioxin	metabolic syndrome, male infertility, age of pubertal onset (males)
BPA	metabolic syndrome, infertility, neurodevelopment
DDT	body weight, cancer, neurodevelopment, oxidative stress
Atrazine	size at birth, pre-term birth, abdominal defects, cancer, sperm quality
PBDEs	thyroid hormone levels, neurodevelopment, autism

These studies suggested that we should re-visit "The Low Dose Hypothesis"

In 2001, it was proposed that:

* 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

What are low doses?



Max Tolerated Intake

Reference Dose

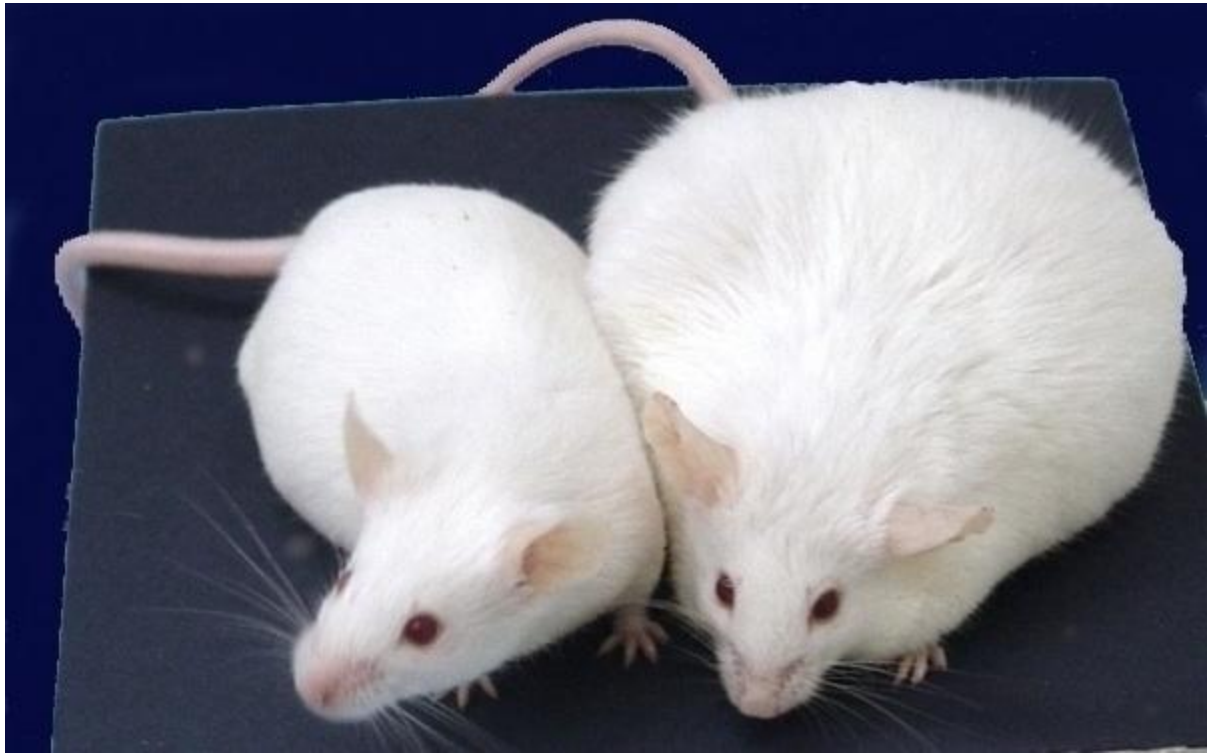
LOAEL

NOAEL

Low Dose Effects

* Defined simply as any effect occurring in the low dose range. Makes no assumptions about what happens at higher doses. Therefore, it is different from non-monotonicity.
* We examined 5 examples in detail
* We also examined more than 20 other examples
* Low dose effects were observed for a variety of endpoints including brain development, sexually dimorphic behaviors, prostate weight, spermatogenesis, hormone levels, bone health, and metabolic endpoints, among others.

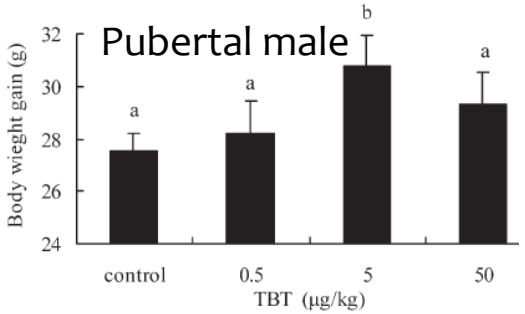
An example: DES and Obesity



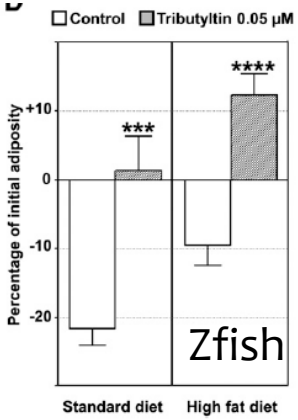
Newbold et al. 2009

- 1000 ppb exposures cause weight loss (not shown here)
- 1 ppb exposures cause extreme obesity

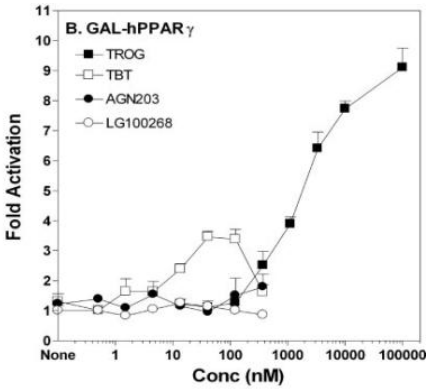
An example: TBT and obesity

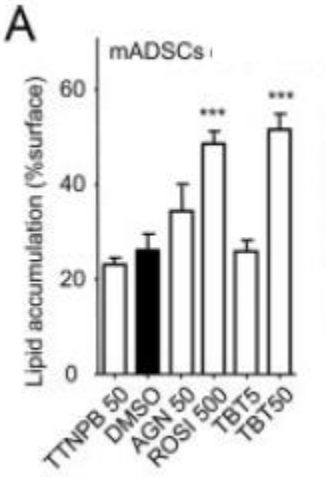


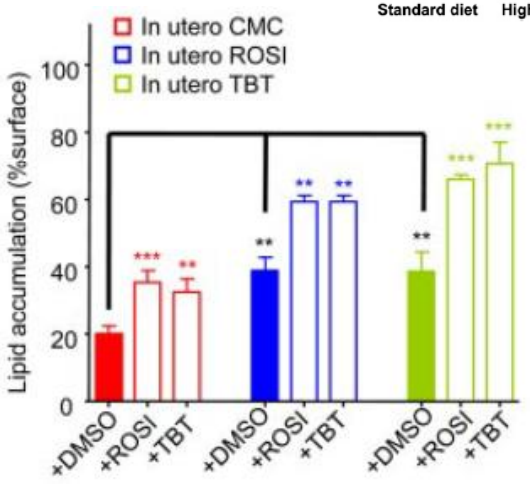
Zuo et al. 2009



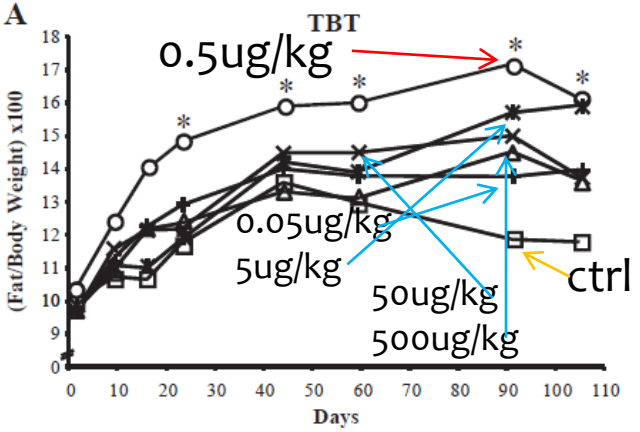
Tingaud et al. 2011



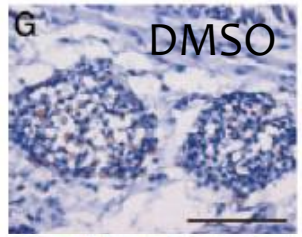


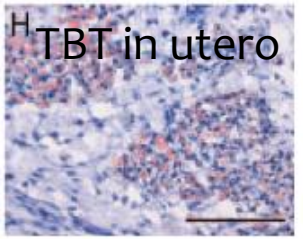


Kirchner et al. 2010



Penza et al. 2011

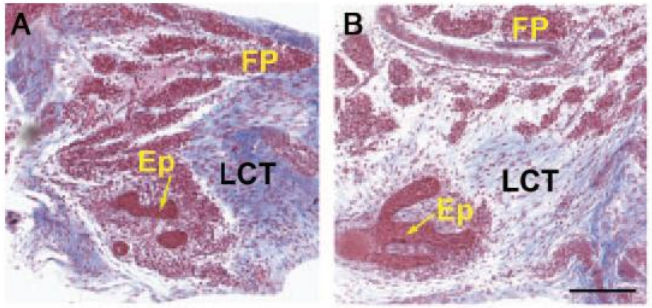


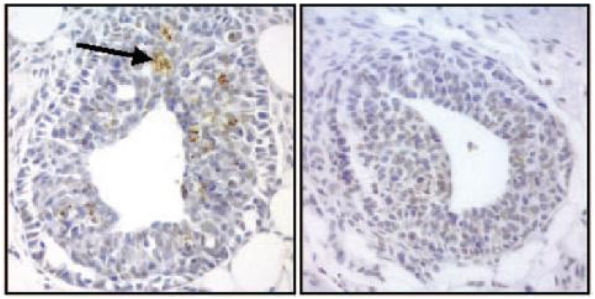


Grun et al. 2006

BPA and the mammary gland: changes in gland morphology

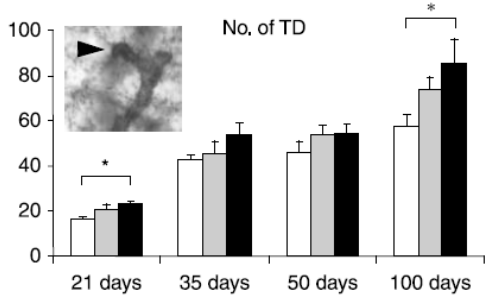
Vandenberg et al. 2007

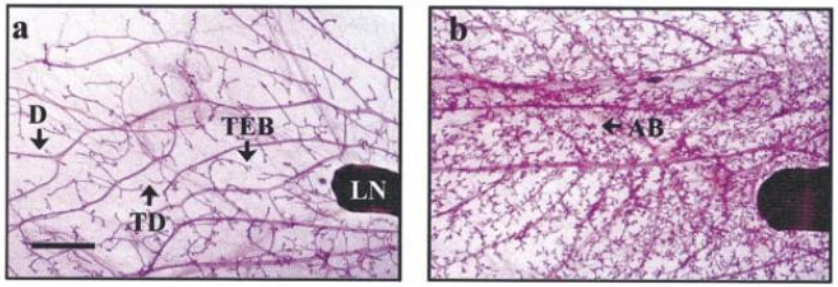




Munoz-de-Toro et al. 2005

Moral et al. 2008

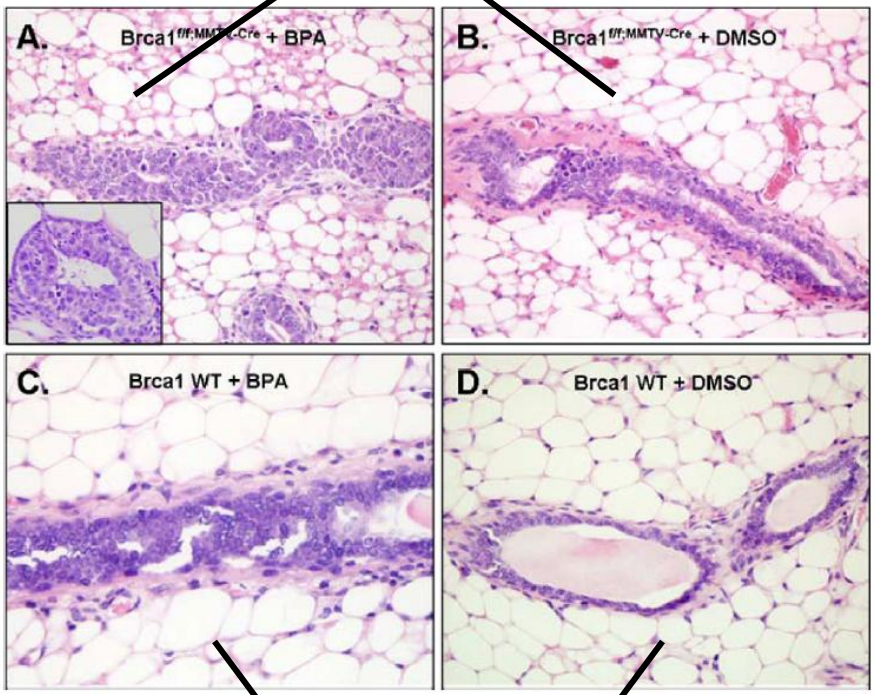




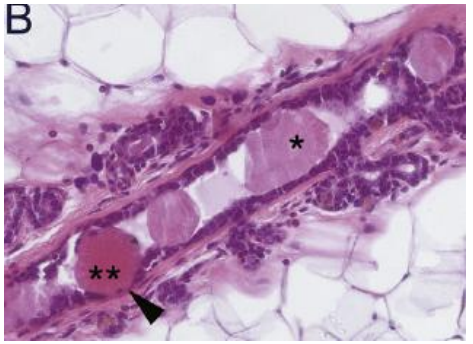
Markey et al. 2001

BPA induces precancerous and cancerous lesions in the mammary gland

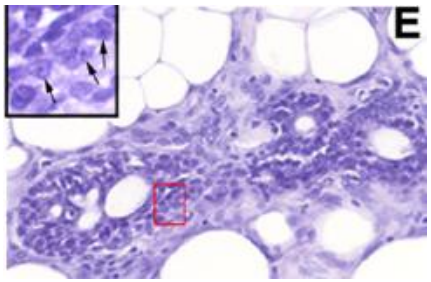
BRCA mutant = prone to mammary cancer



Jones et al. 2010



Vandenberg et al. 2008

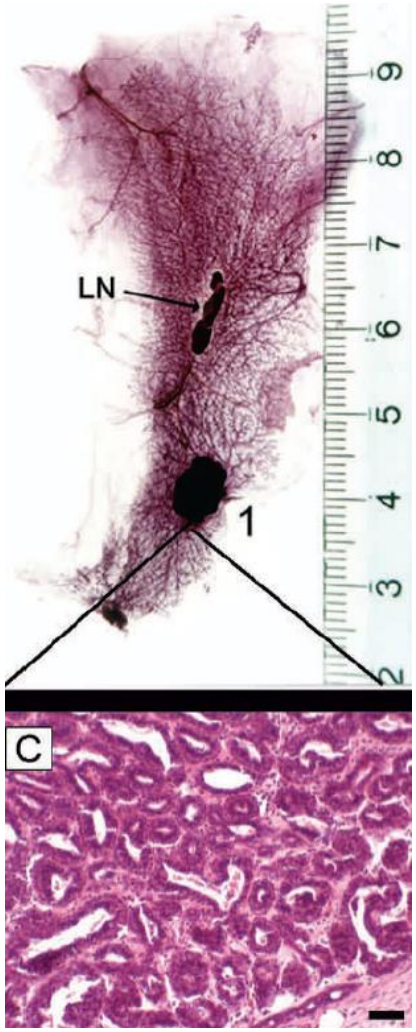


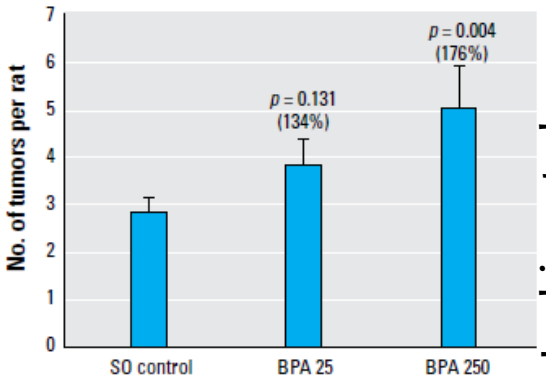
Murray et al. 2007

Wildtype (not genetically cancer prone)

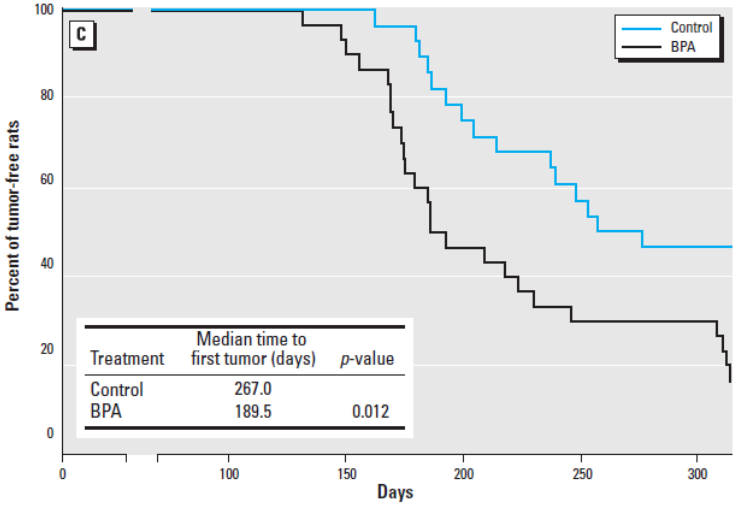
BPA alters the mammary gland's response to chemical carcinogens

Durando et al. 2007



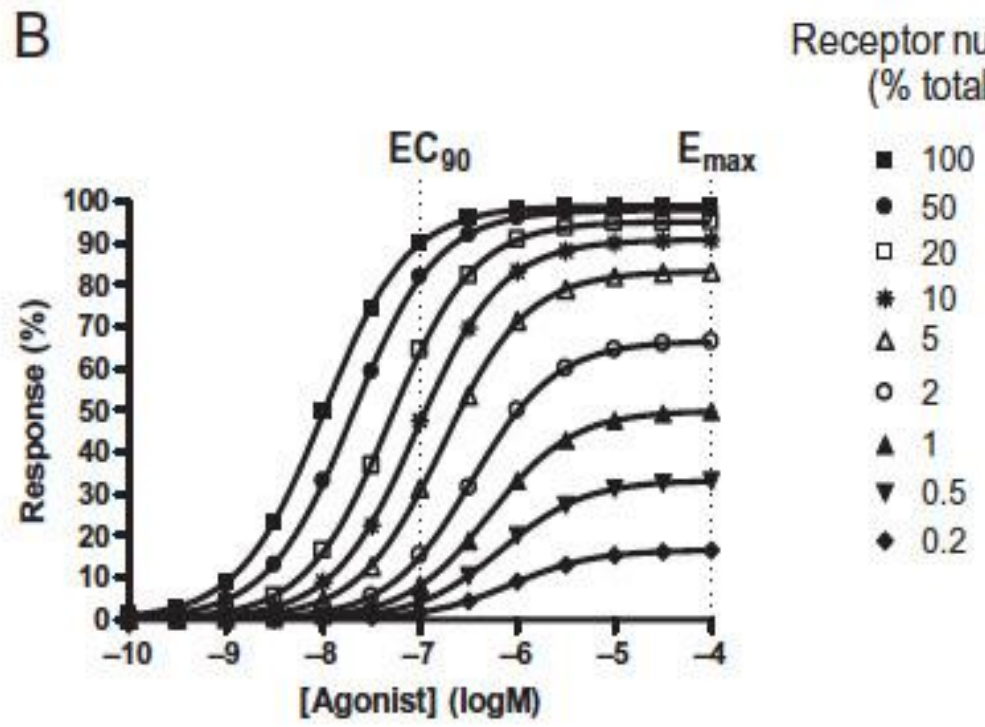


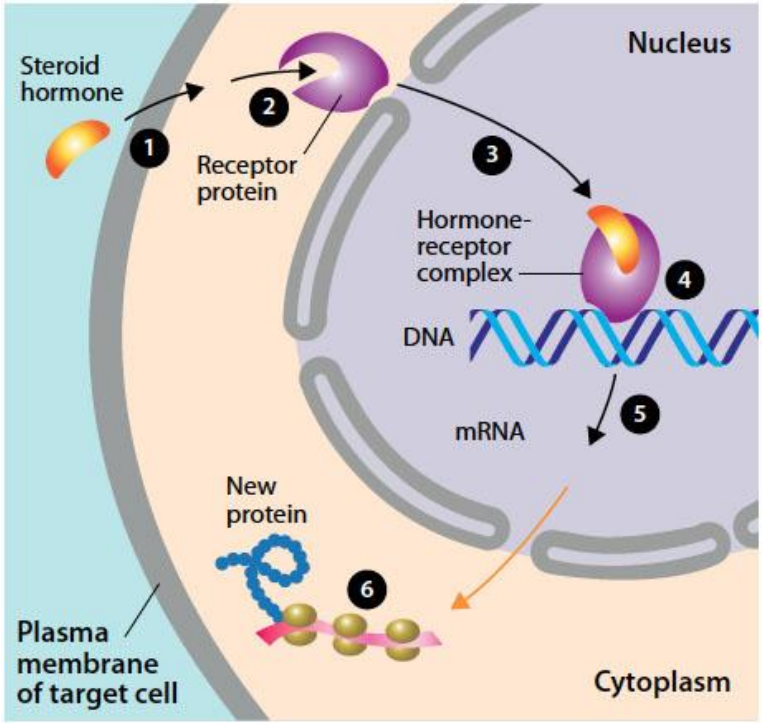
Jenkins et al. 2009



Betancourt et al. 2010

How do low dose effects occur?

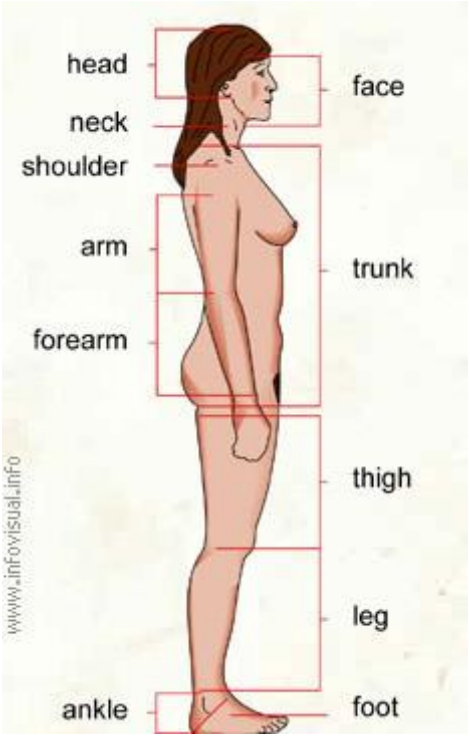




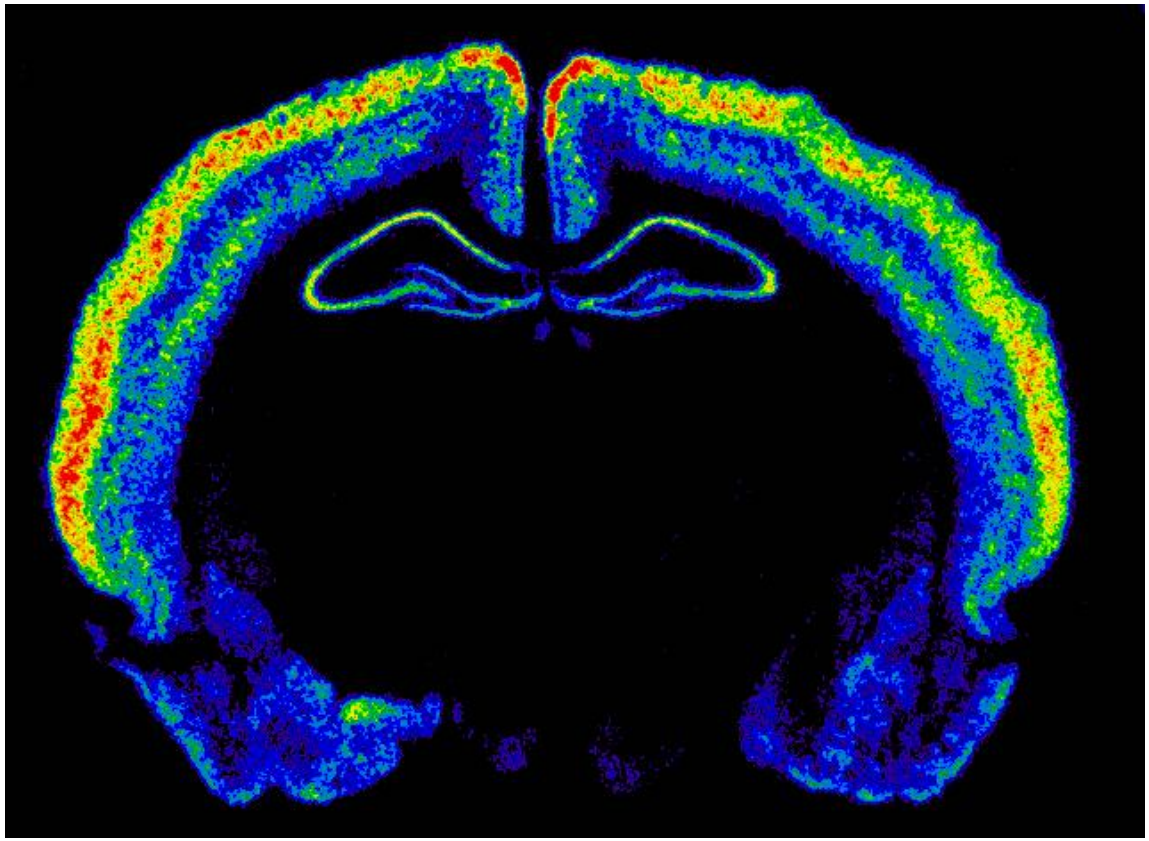
The timing of exposure matters – and even low doses affect developing individuals

"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.

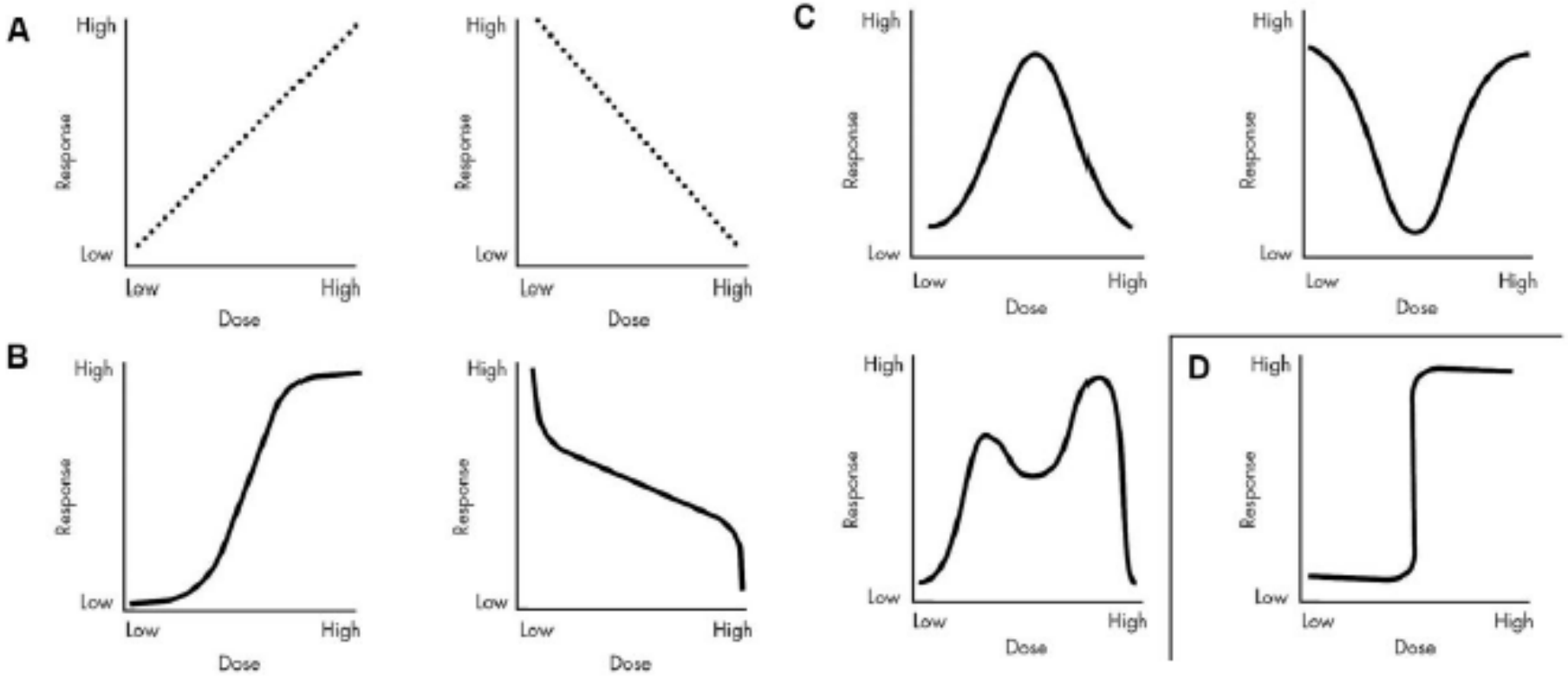
Changes that happen during development are far less reversible [than those occurring in an adult]; you can't go back and rewire the brain".
-Theo Colborn, zoologist, writer



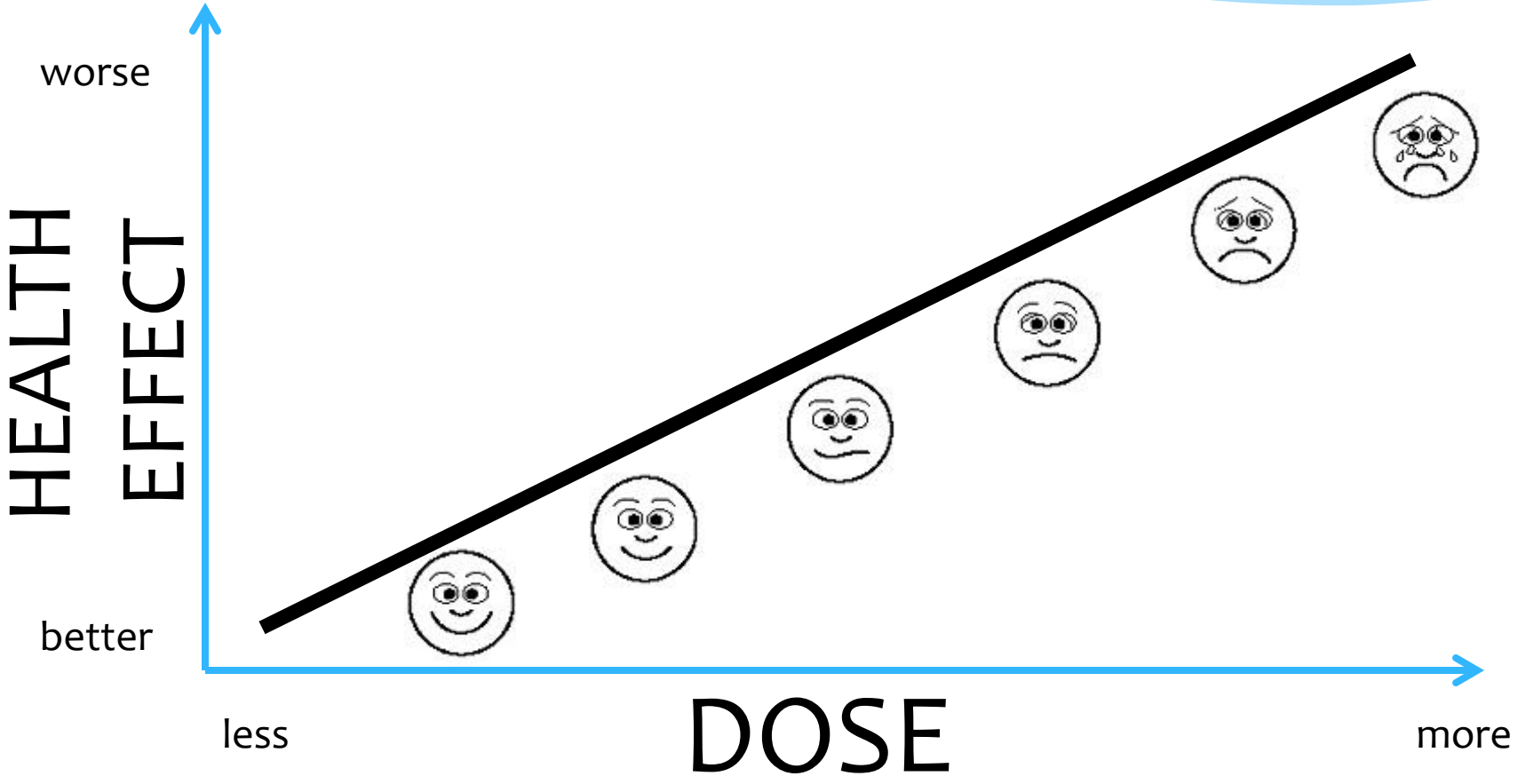
Can these effects be considered adaptive?



Distinguishing non-monotonicity from low dose effects

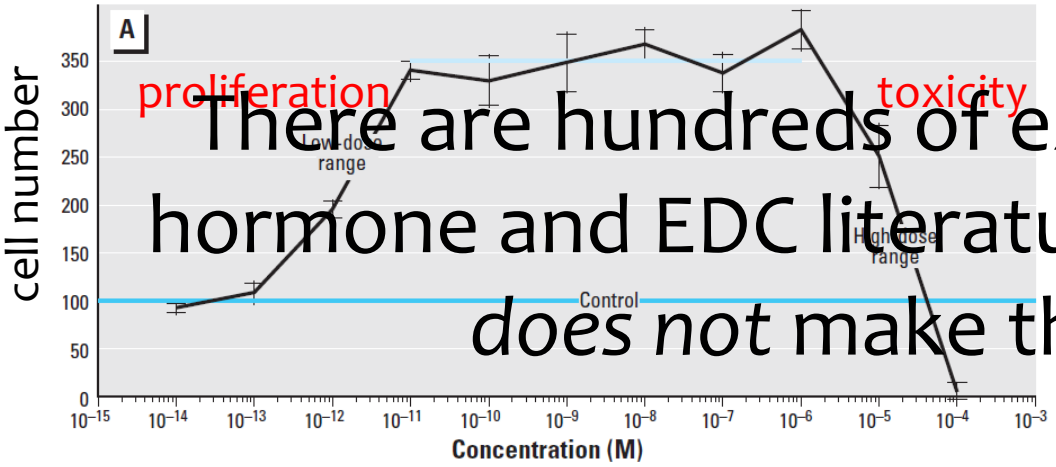


Toxicology predicts that “the dose makes the poison”

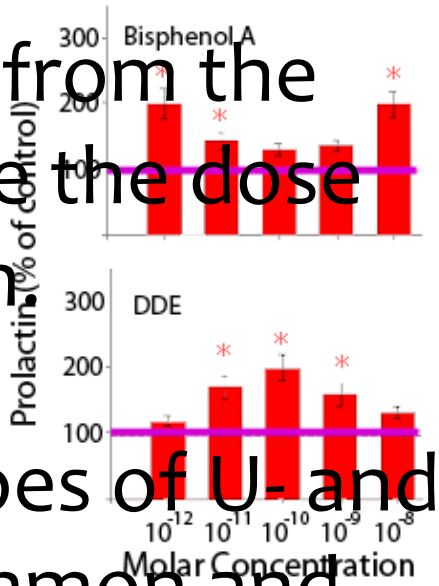


What happens when the dose doesn't make the poison?

There are hundreds of examples from the hormone and EDC literature where the dose *does not* make the poison.

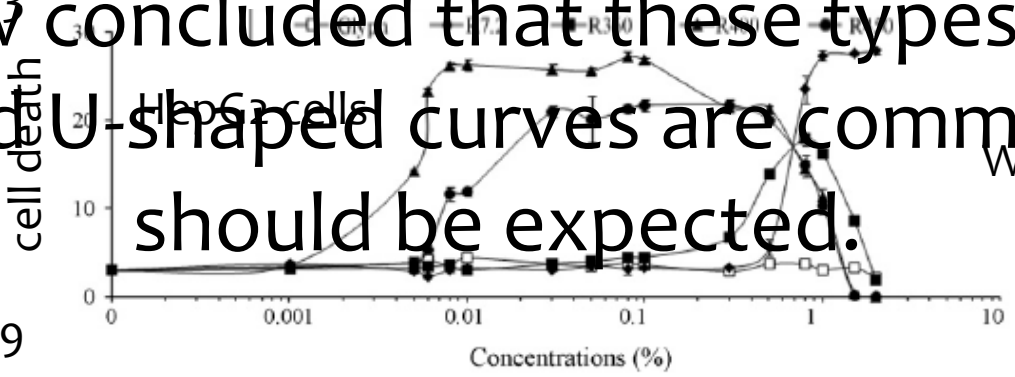


Welshons et al. 2003



Wozniak et al. 2005

Our review concluded that these types of U- and inverted U-shaped curves are common and should be expected.

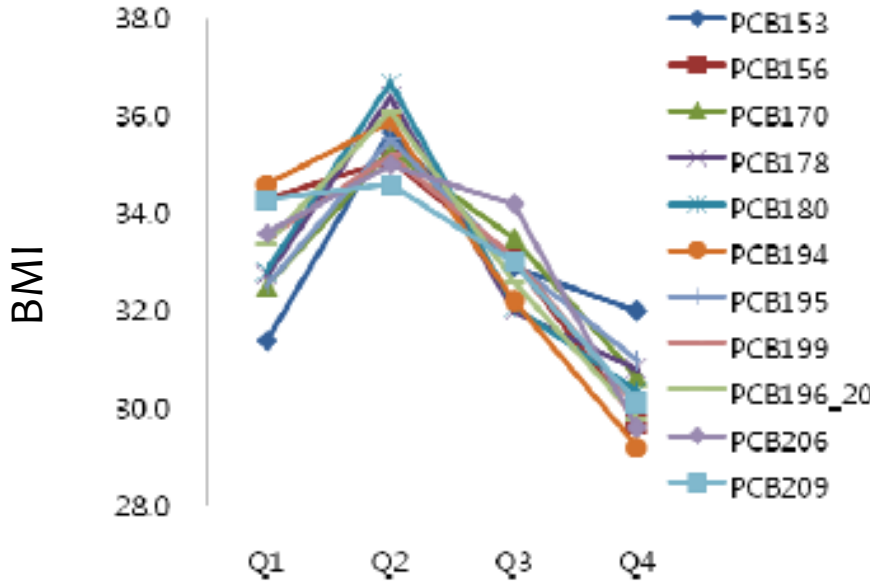


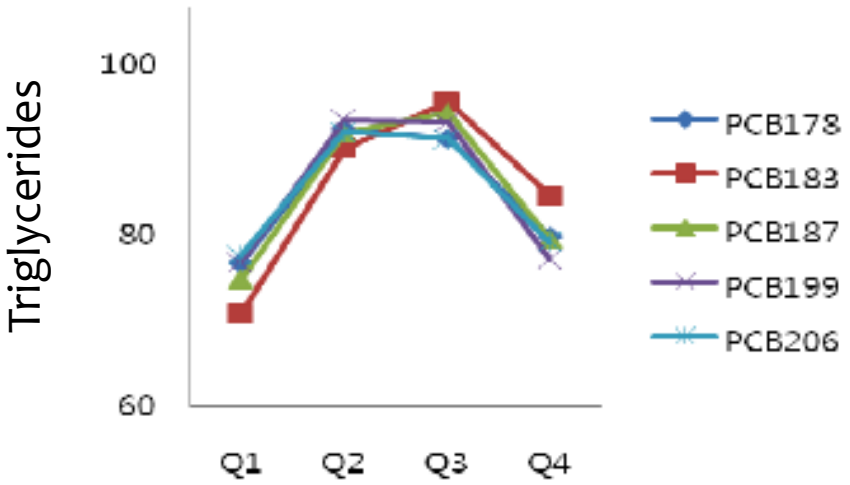
Gasnier et al. 2009

There are well-established mechanisms for non-monotonicity in endocrinology

* Cytotoxicity
* Cell- and tissue-specific receptors, cofactors, etc.
* Receptor selectivity
* Receptor down-regulation
* Competition with endogenous hormones

Human populations: when the dose doesn't make the poison

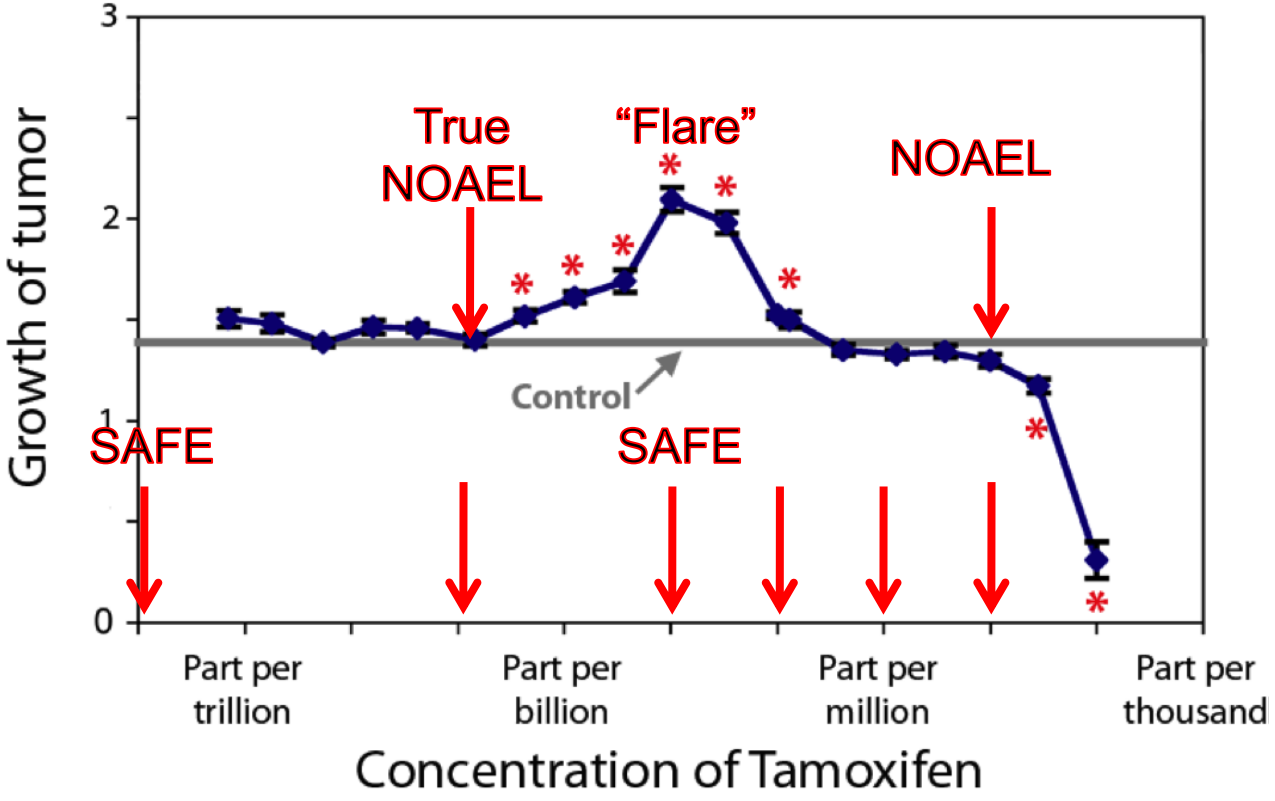




Lee et al. 2011

Does this mean that high doses are safer??

A practical example, with implications for risk assessment: tamoxifen flare



Theoretically, the number and types of non-monotonic responses are infinite…

"The question is no longer whether nonmonotonic dose responses are 'real' and occur frequently enough to be a concern; clearly these are common phenomena with well-understood mechanisms. Instead the question is which dose-response shapes should be expected for specific environmental chemicals and under what specific circumstances."

-Linda Birnbaum, Director, NIEHS (NIH)

Summary

* In 2002, the NTP found there was sufficient evidence for low dose effects for 4 chemicals.
* Our recent analysis suggests this isn't a chemical-specific phenomenon. We identified 28 chemicals with low dose effects on a variety of endpoints.
* Many EDCs have not been tested at low doses.
* EDCs, like hormones, do not obey "the dose makes the poison."
* Low dose effects and non-monotonic dose responses are expected because EDCs follow the same "rules" as hormones.

Acknowledgements

* Theo Colborn, Tyrone Hayes, Jerry Heindel, David Jacobs, Duk-Hee Lee, Pete Myers, Toshi Shioda, Ana Soto, Fred vom Saal, Wade Welshons, Tom Zoeller
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