Low-dose effects, non-monotonic dose responses and endocrine disrupting chemicals

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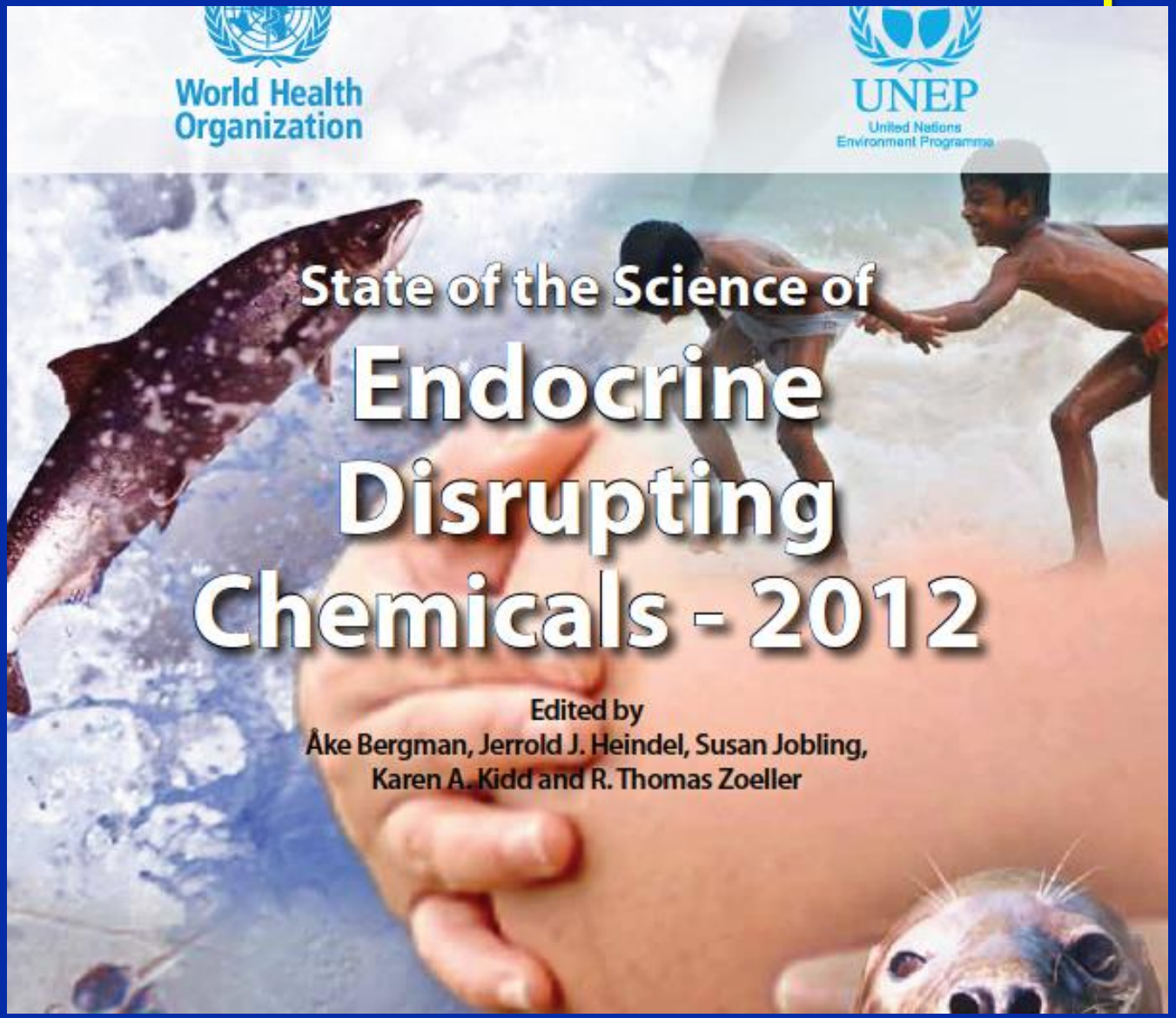
19 Feb 2013: WHO – UNEP report



Report from the CRO Forum

Chaired by Swiss Re CRO
David Cole, Zurich

"The highest risk for the insurance industry emerges from the probable link between low-level EDC exposure and bodily injury."

"We recommend to minimise the use and release of EDC and we encourage the removal of EDC/micropollutants from waste water and drinking water taking into account individual circumstances."

Today's epidemics

Hormone-related cancers

Endometriosis, autoimmunity

Learning disabilities, ADHD

Fibroids and polycystic ovaries

Degenerative diseases

Pre-term birth

Obesity and diabetes

Heart disease

Asthma

Infertility

Autism

What is endocrine disruption?

An EDC is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.

Endocrine Society Position Statement 2012

2013 WHO-UNEP report

Many endocrine related disorders are on the rise, far too rapidly to be a change in gene frequency.

~800 chemicals in common use are known to disrupt endocrine function.

Human and wildlife exposure is ubiquitous.

Numerous laboratory, wildlife and epidemiological studies are consistent with endocrine disruption impacts on human health.

Disease risk due to EDCs may be significantly underestimated.

Significant opportunities for disease prevention by reducing exposures may be within reach.

Scientific revolution: 8 key discoveries

-EDCs interfere with hormone action, including through epigenetic alteration of gene expression

-These effects can be caused at extremely low concentrations

-Low dose exposures in the womb can set in motion processes that play out over a lifetime

-Exposures are ubiquitous, and in mixtures they can interact in unexpected ways

Scientific revolution: (cont'd)

-Epigenetic change can be inherited, when the change is in the germ line.

-The tools we have used to tell us what is safe and what is not have failed us. Neotoxic.

-EDCs are now linked to a wide array of human diseases and disabilities

-Chemistry can use design signals from this new science to guide innovative development of new materials that are inherently safer.

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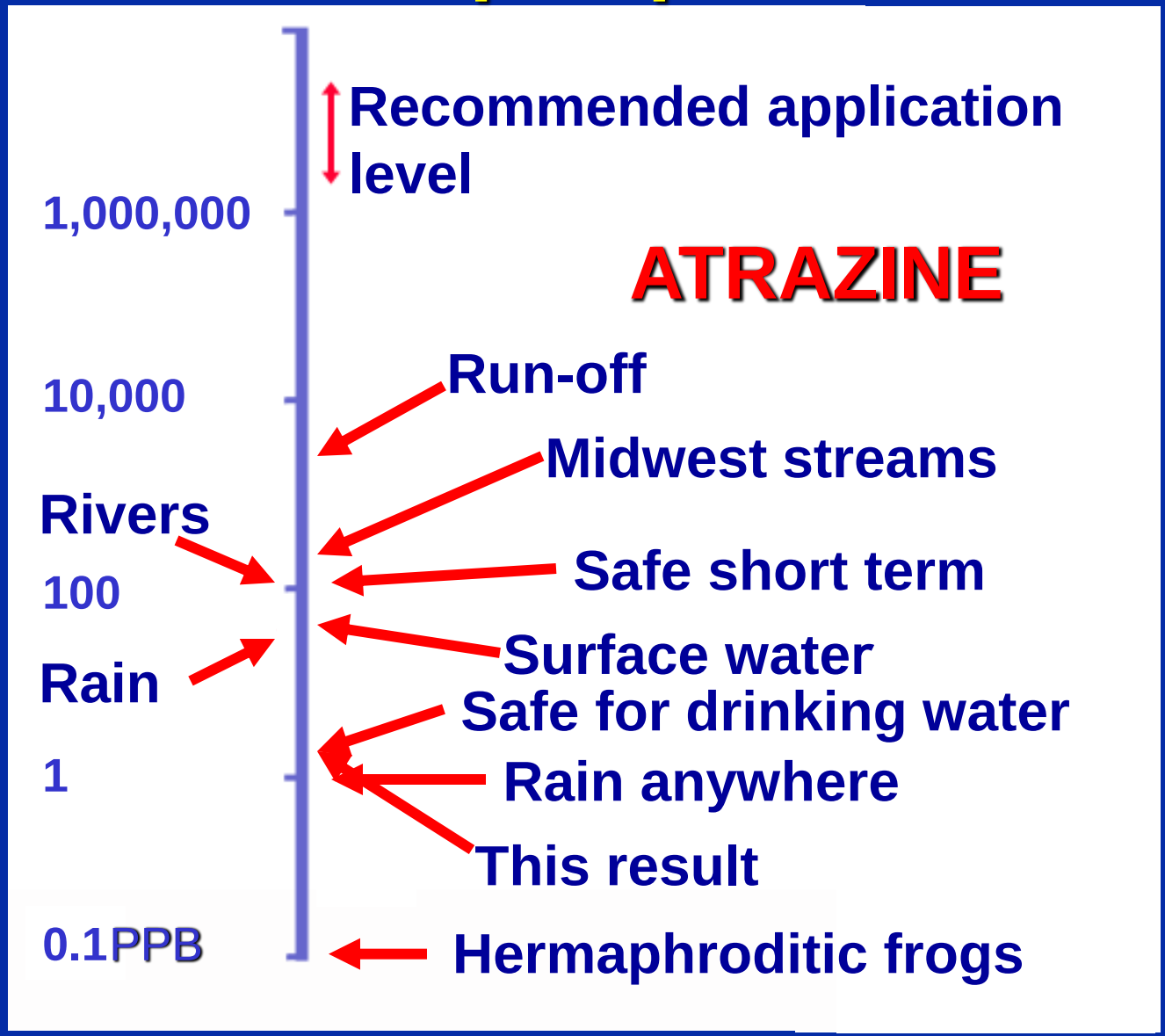
Low doses of atrazine

2.5 ppb Atrazine from hatching through metamorphosis

Hayes *et al*. 2010

Atrazine levels in perspective



Hayes *et al*. 2002

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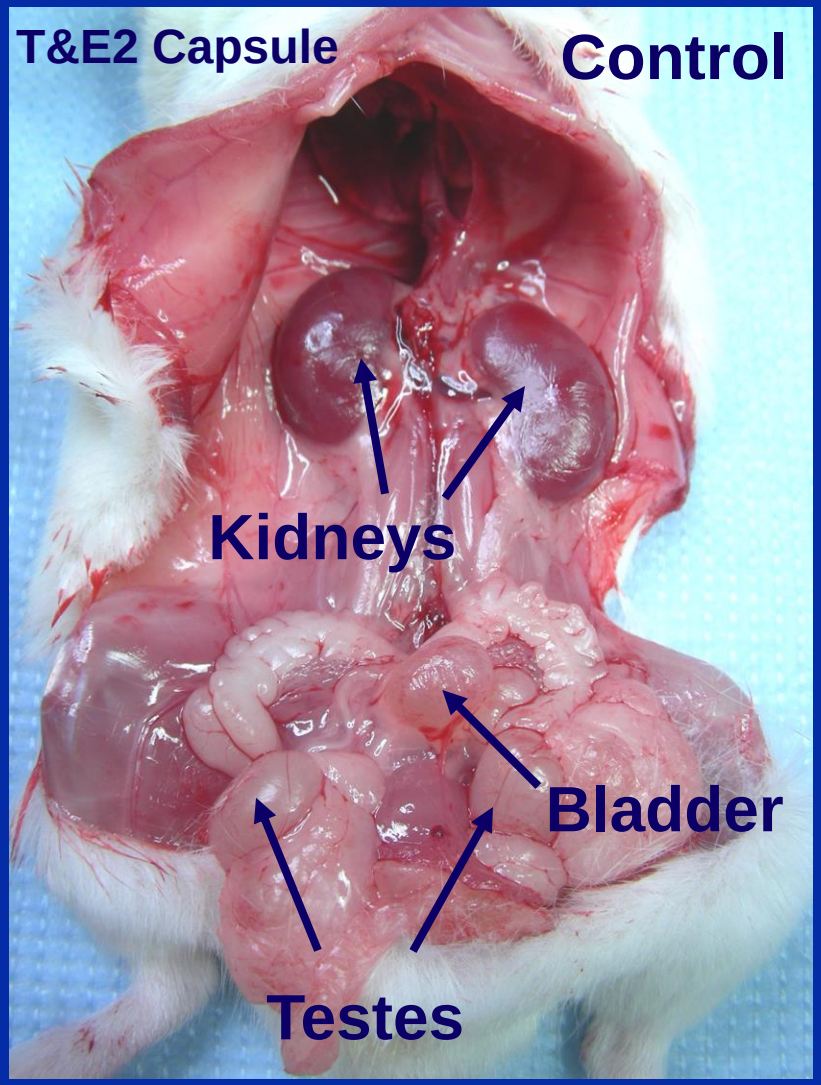
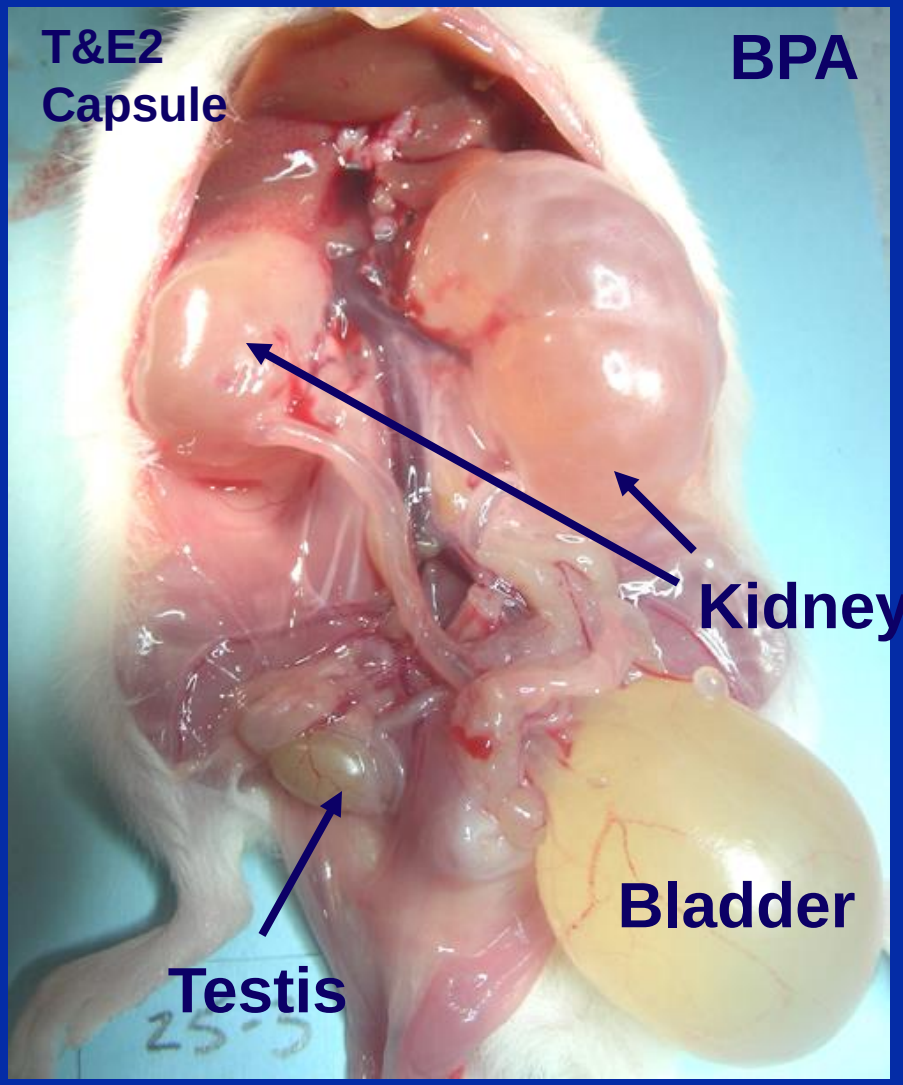
Fetal origins of adult disease





Bell Jones *et al*. 2007

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False assumptions:

Standardized assays relevant to today's epidemics

Gavage relevant to human oral exposure

High dose testing can predict low dose results

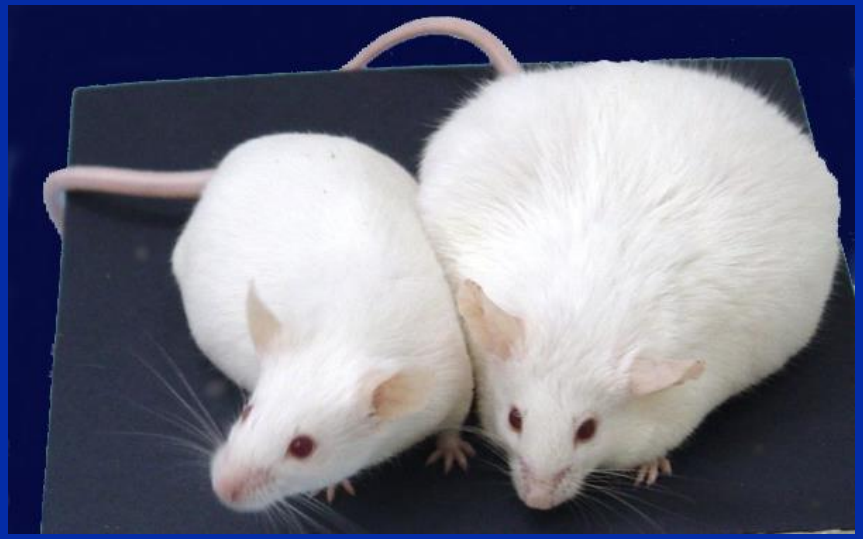
Reliance on out-dated tools

Agency risk assessments use old tests that don't incorporate modern molecular biology

decades out of date

Gavage inappropriate

Non-monotonicity



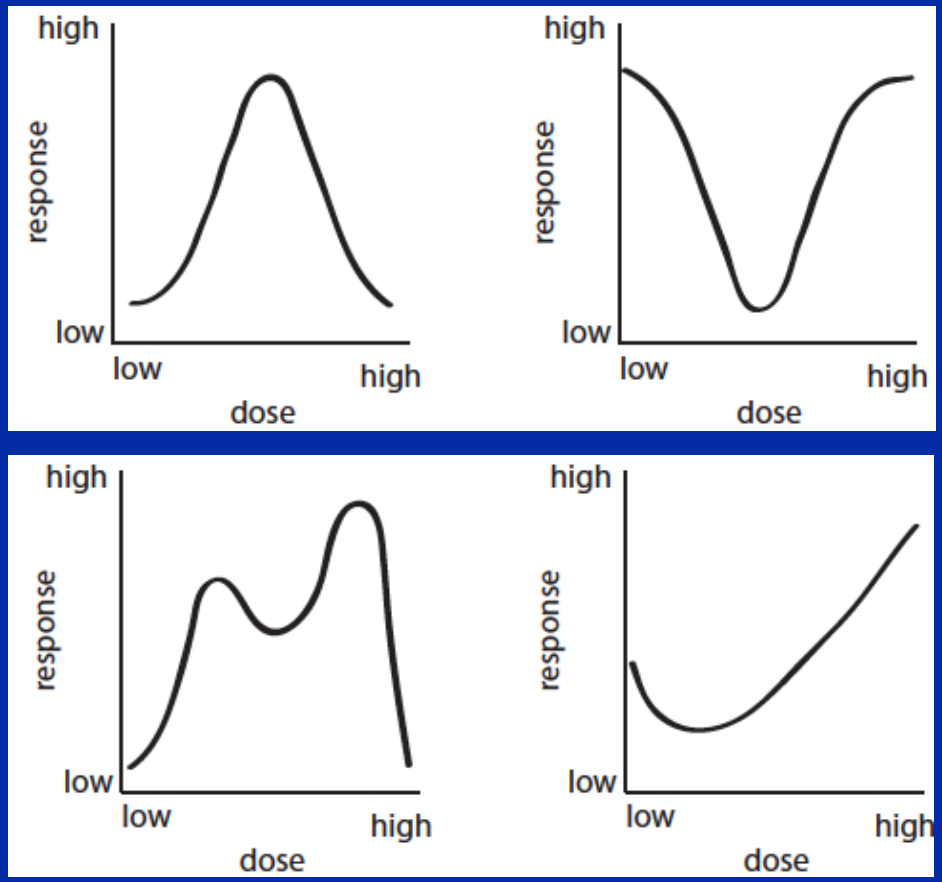
Newbold *et al*. 2005, 2007

1 part per billion DES

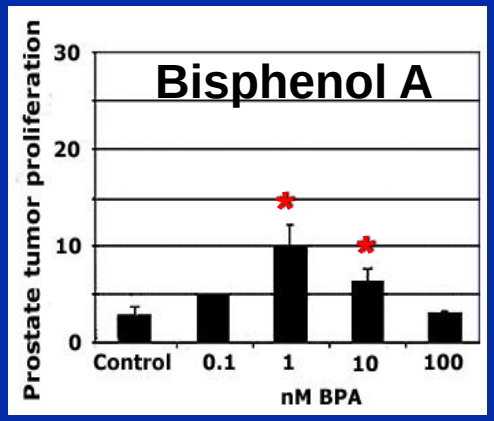
1000 ppb causes weight loss

Same strain of mice
Same caloric intake
Same activity levels

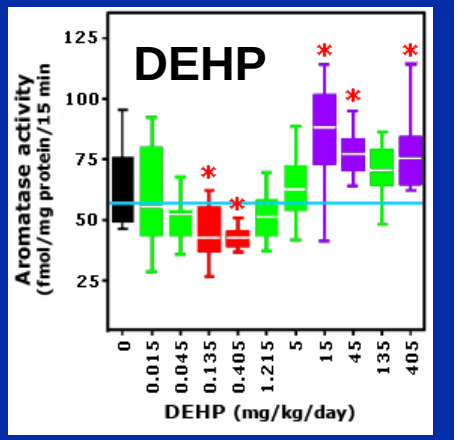
Non-monotonicity: Change in sign of the slope of the curve



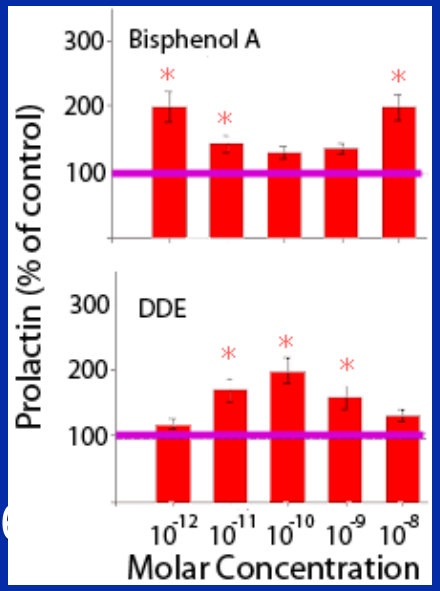
Non-monotonicity



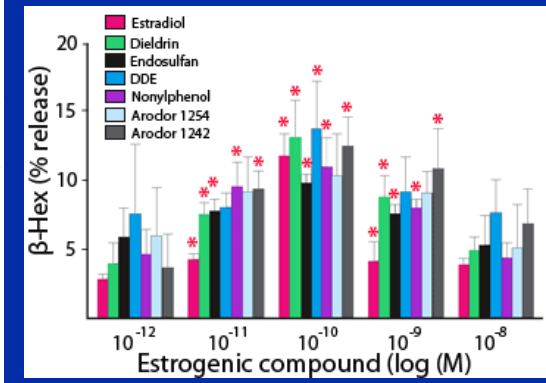
Wetherill *et al*. 2002



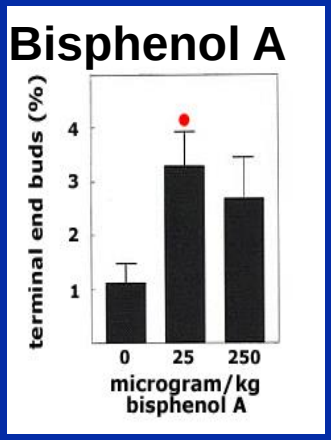
Andrade *et al*. 200

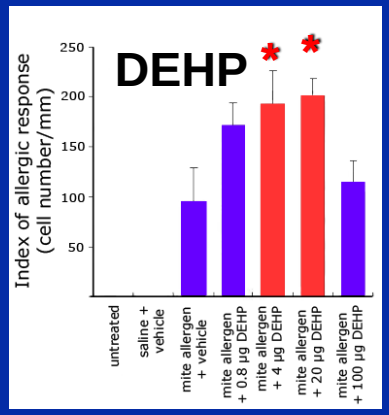


Wozniak *et al*. 2005

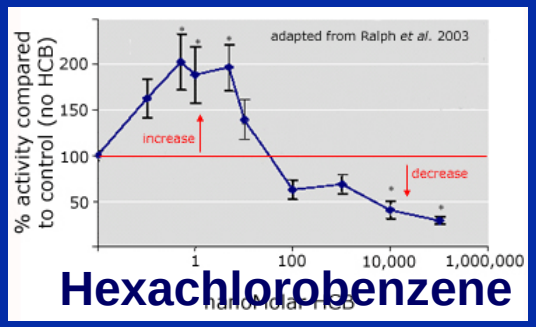


Narita *et al*. 2007





Markey *et al*. 2001 Takano *et al*. 2007



Ralph *et al*. 2003

Endocrine Reviews

Endocrine Reviews. First published ahead of print March 14, 2012
doi:10.1210/er.2011-1050

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

"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.”

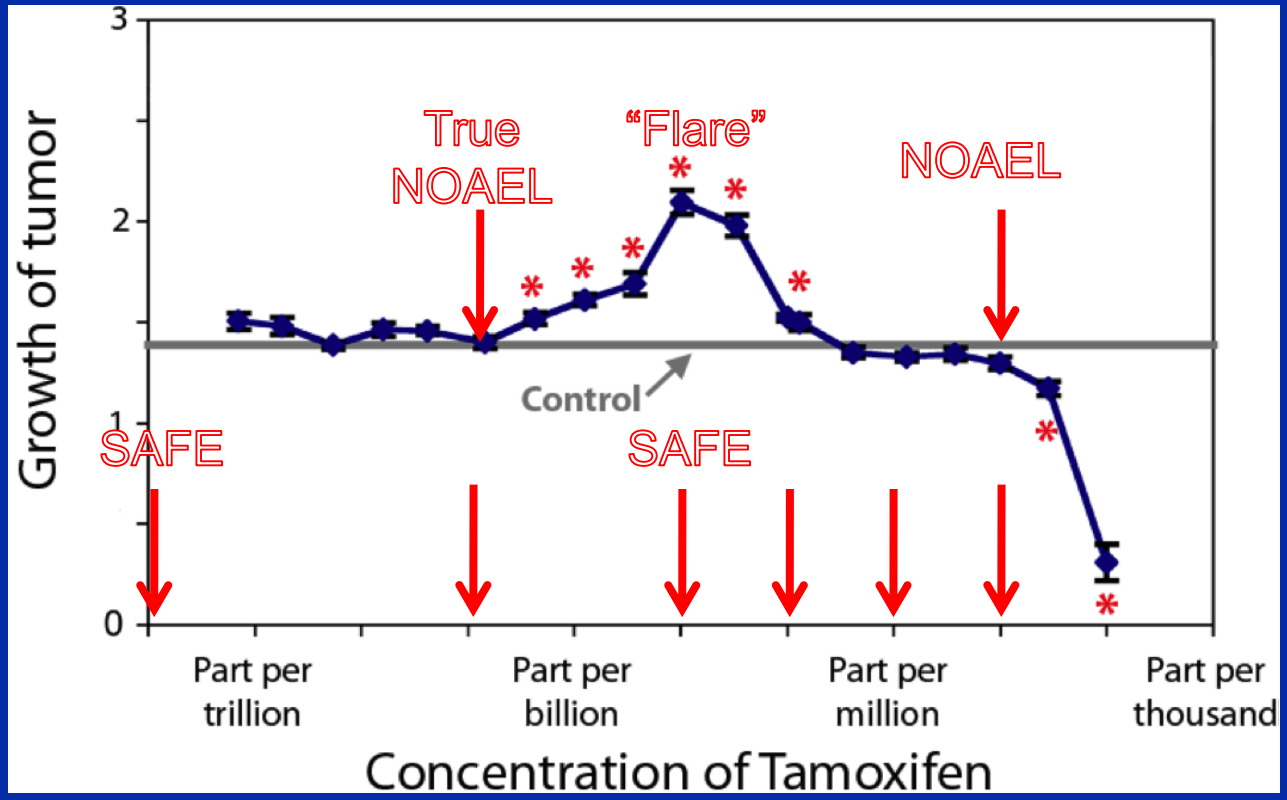
Linda Birnbaum, Director, NIEHS

Many chemicals show NMDRCs

	In vivo	Human Epi	Total
Natural hormones	>>22	10	32
Pharma hormones	>>6		6
Plastics	11	1	12
Surfactants/detergents	4		4
Anti-microbials	1		1
Aromatic hydrocarbons	2		2
Heavy metals	7		7
Phytochemicals	4		4
POPs (dioxins/PCBs)	3	17	20
Mixtures of POPs		4	4
Pesticides	16	7	23
Flame retardants		4	4
UV filters	1		1

Does dose make the poison?

Applying traditional safety factors to Tamoxifen's high dose NOAEL



Wade Welshons, in Vandenberg *et al*. 2012

Next challenge

- Many scientific questions still need to be answered.
- But we know enough now to start incorporating this scientific revolution into a new generation of precautionary health standards
- And to give better design signals to chemistry: ‘green chemistry’