Bisphenol A:
Mistakes and opportunities

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Environmental Health Sciences
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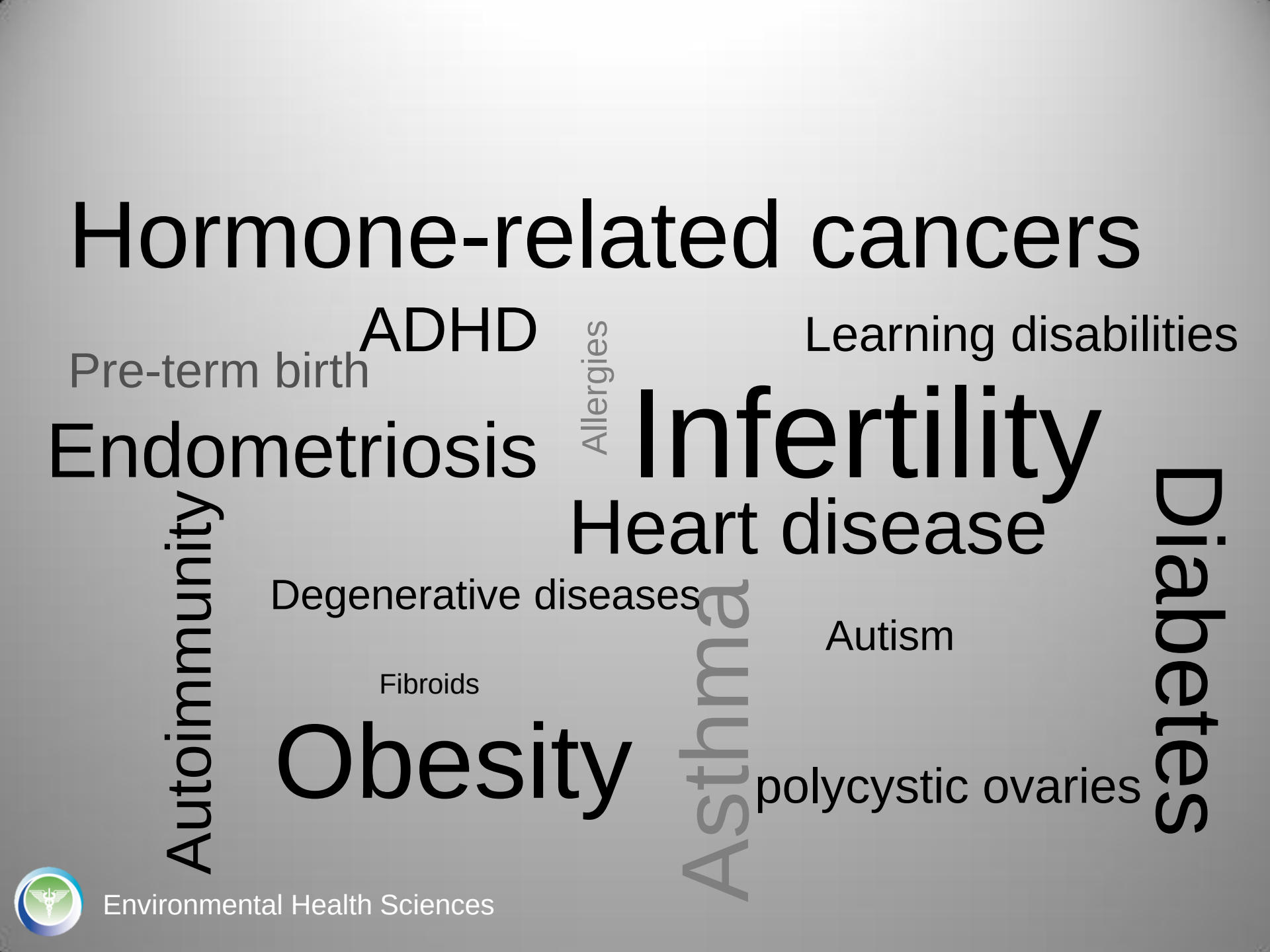
Carnegie Mellon University

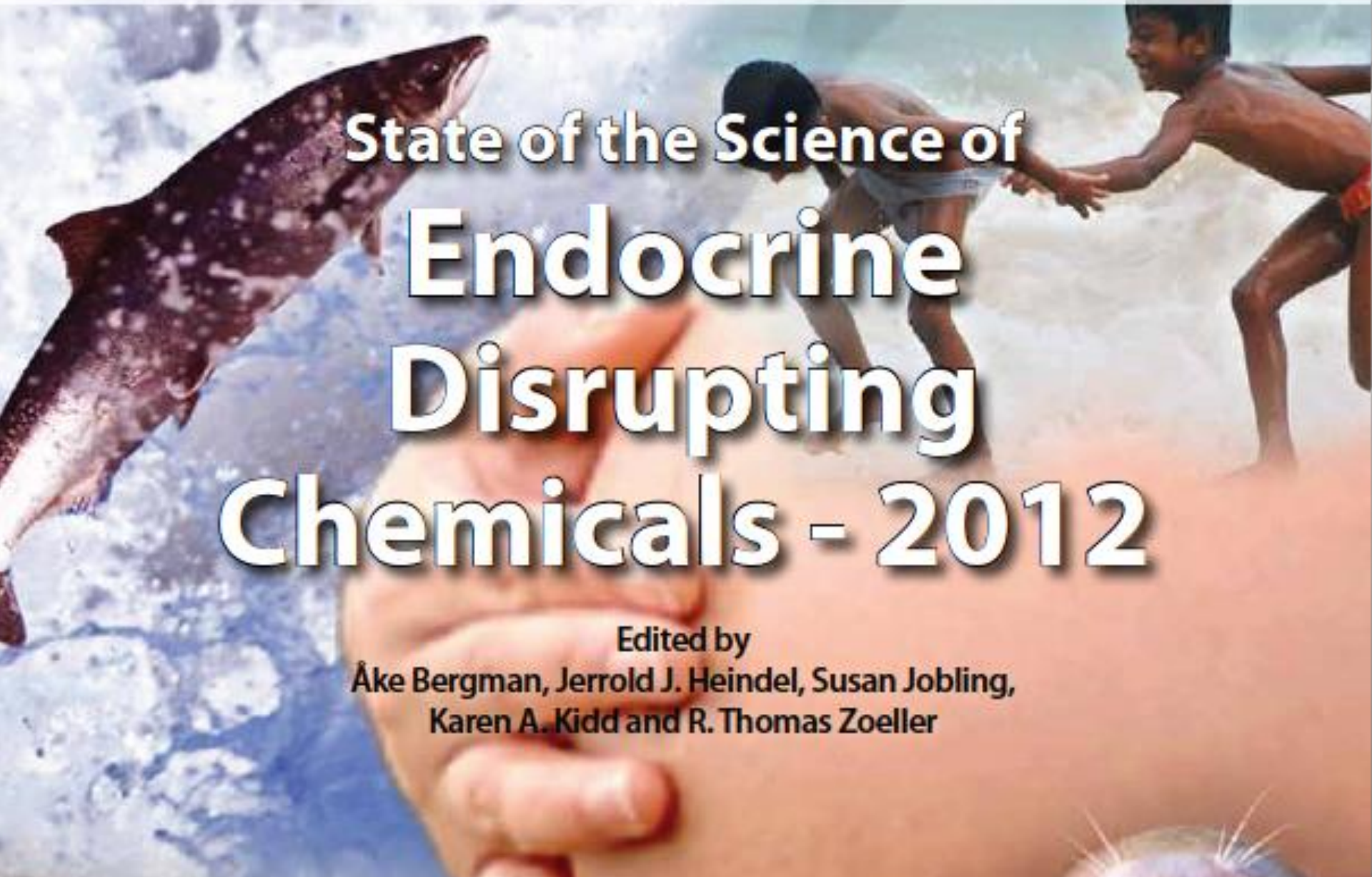
Bisphenol A: Mistakes & opportunities

- Where the FDA went wrong
- Risks of using existing substitutes
- Designing endocrine disruption out of new chemicals


Hormone-related cancers
ADHD
Allergies
Learning disabilities
Pre-term birth
Infertility
Endometriosis
Heart disease
Diabetes
Autoimmunity
Degenerative diseases
Asthma
Autism
Fibroids
Obesity
polycystic ovaries

World Health Organization

UNEP
United Nations Environment Programme



State of the Science of Endocrine Disrupting Chemicals - 2012

Edited by
Åke Bergman, Jerrold J. Heindel, Susan Jobling,
Karen A. Kidd and R. Thomas Zoeller

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.

Basis of this core assumption

Ingested BPA inactivated by liver

Unconjugated vs. conjugated

Any human studies with significant unconjugated BPA can't be trusted

Unconjugated BPA is "an error"

Basis of this core assumption

Many animal studies poorly designed

"Not GLP, inappropriate delivery method, non-standard assays"

Contamination unavoidable

"Low dose results unreliable"

High dose testing reveals low dose impacts

"No need to test directly at low doses"

Why is this wrong?

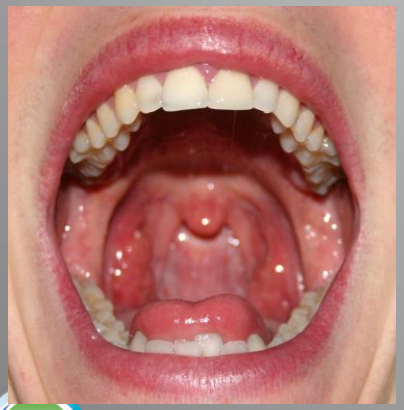
‘Inactive’ BPA can be as powerful as active

In cell membrane receptors

‘Inactive’ BPA can be re-activated

Especially in placenta and fetus

Misleading experiments



Avoided absorption in mouth

Real-world oral exposure can have high ratio of active to inactive, and be relatively high

FDA incompetence demonstrated

Research proves that contamination of human measurements can be avoided

NIH-funded round-robin experiment

FDA withdrew

Major setback for FDA

Circular logic and false assumptions at core of FDA's conclusions

Rejected high human measurements as contaminated because 'impossible'

Ignored all those human data

Concluded levels were too low to cause harm.

Flawed logic on animal data

Single exposure per day does not match what people experience

FDA rejected most realistic delivery method

Best matched by implanted osmotic pumps, but these studies were deemed irrelevant

The fetus doesn't care how BPA gets into Mom's serum

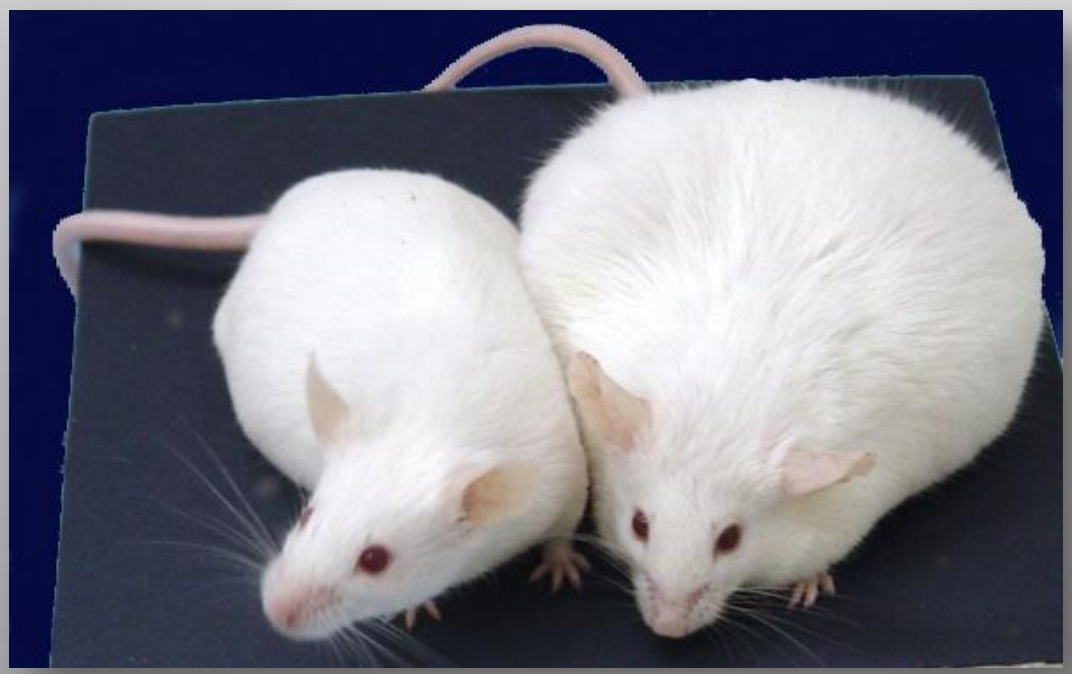
Radically different conclusions.

ADI 20,000x lower.

Fundamental flaw in testing logic

1 part per billion

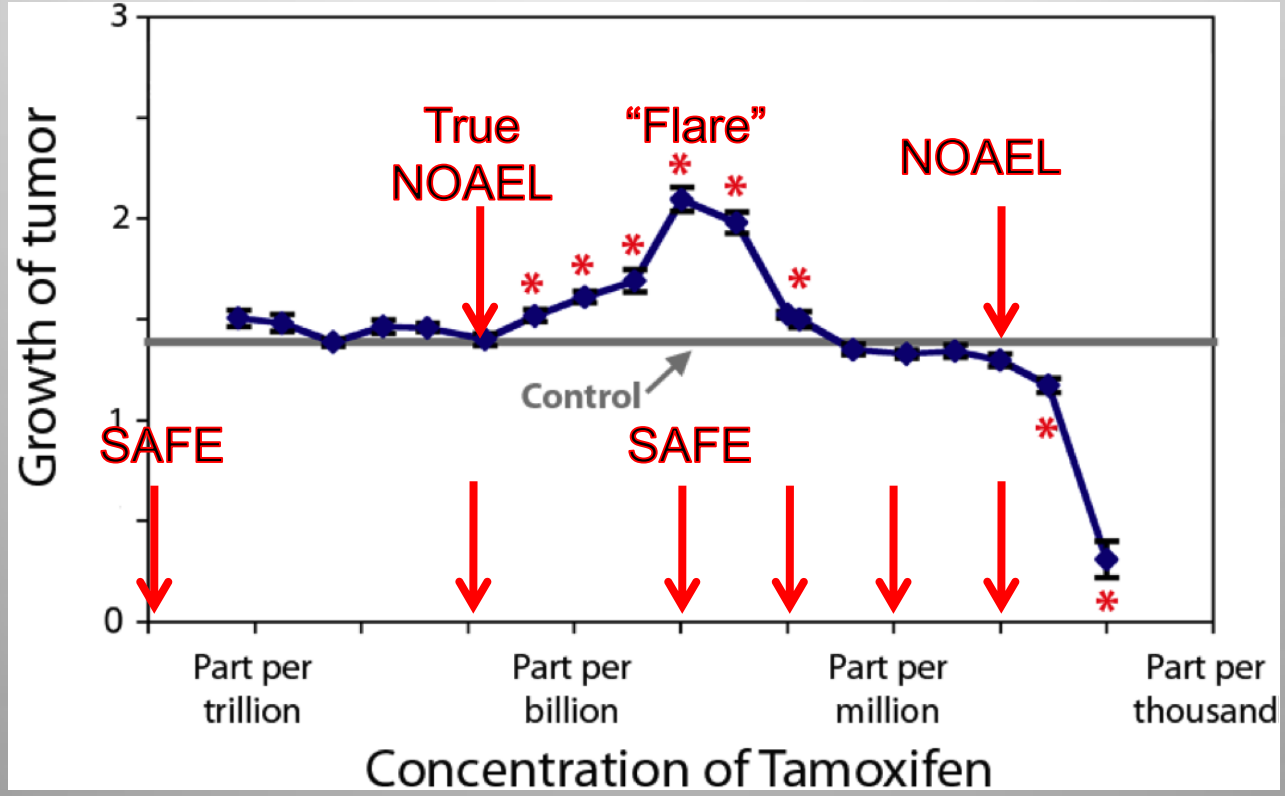
1000 part per billion



Same strain of mice
Same caloric intake
Same activity levels

Newbold *et al*. 2005, 2007

Non-monotonicity of EDCs



Welshons, in Vandenberg et al. 2012

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

We found several hundred examples of non-monotonic responses to EDCs

- DES
- Trenbolone
- R1881
- **BPA**
- DEHP
- Octylphenol
- Nonylphenol
- Phenanthrene
- Naphthalene
- Retene
- Lead
- Cadmium
- Genistein
- Coumesterol
- daidezin
- Resveratrol
- Biochanin A
- Licoflavone C
- Quercetin
- TCDD
- Atrazine
- Endosulfan
- dieldrin
- DDT
- DDE
- hexachlorobenzene
- Prochloraz
- Ketoconazole
- PBDE-49
- PBDE-99

OLD:

Toxic components work by overwhelming the body's defenses by brute force.

NEW:

Some compounds work at profoundly low levels, e.g., by hijacking control of gene expression

Substitution challenge


Ground Turkey
Ground Turkey
Batter Fish Fillet
Mrntd Chick Breast
Ground Turkey
Ground Turkey
1.39 F1
1.39 F1
2.99 F1
6.99 F1
1.39 F1
1.39 F1
1.99 F1


A new way forward: the 4th R
Reduce, reuse, recycle
Redesign

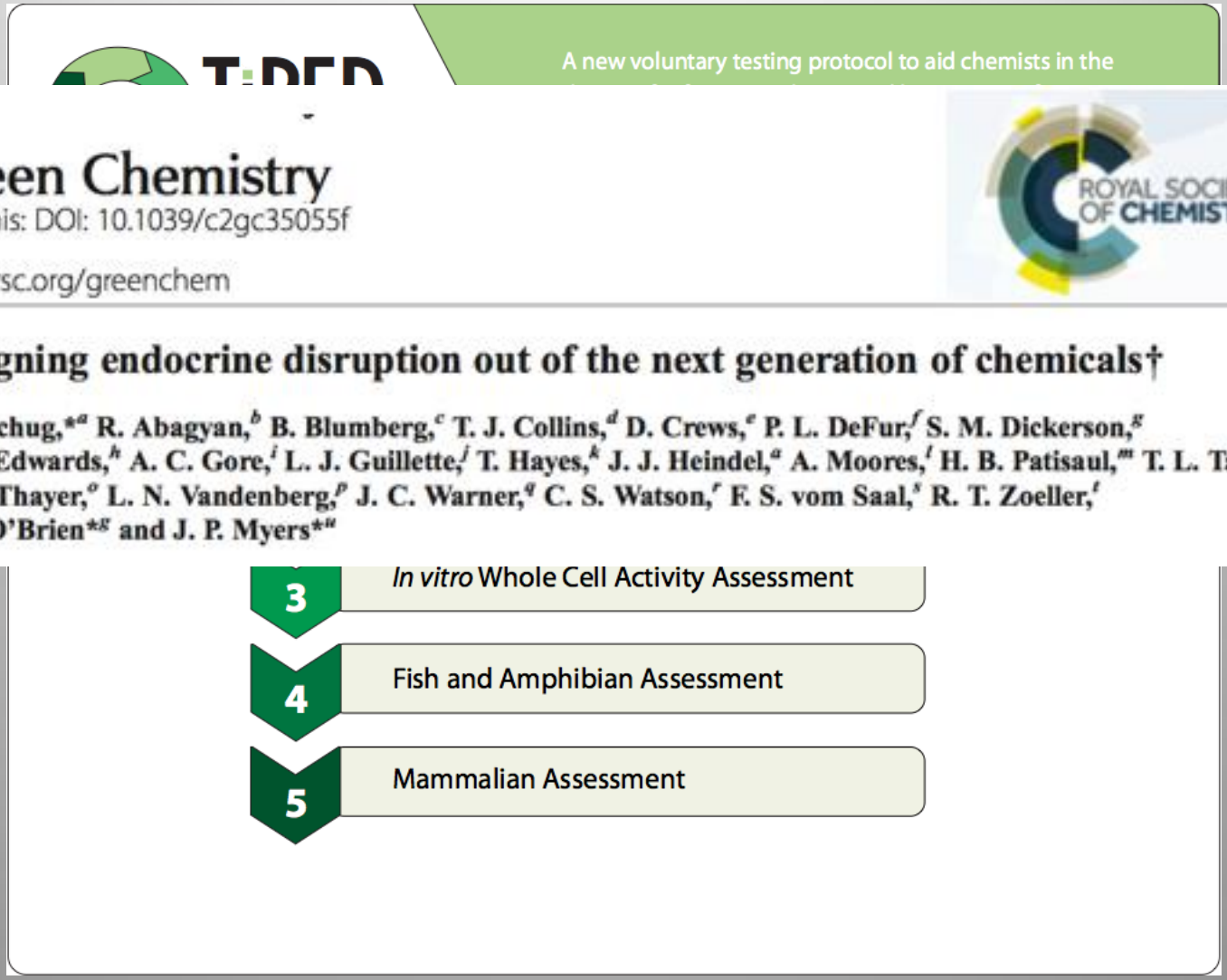

Terry
John

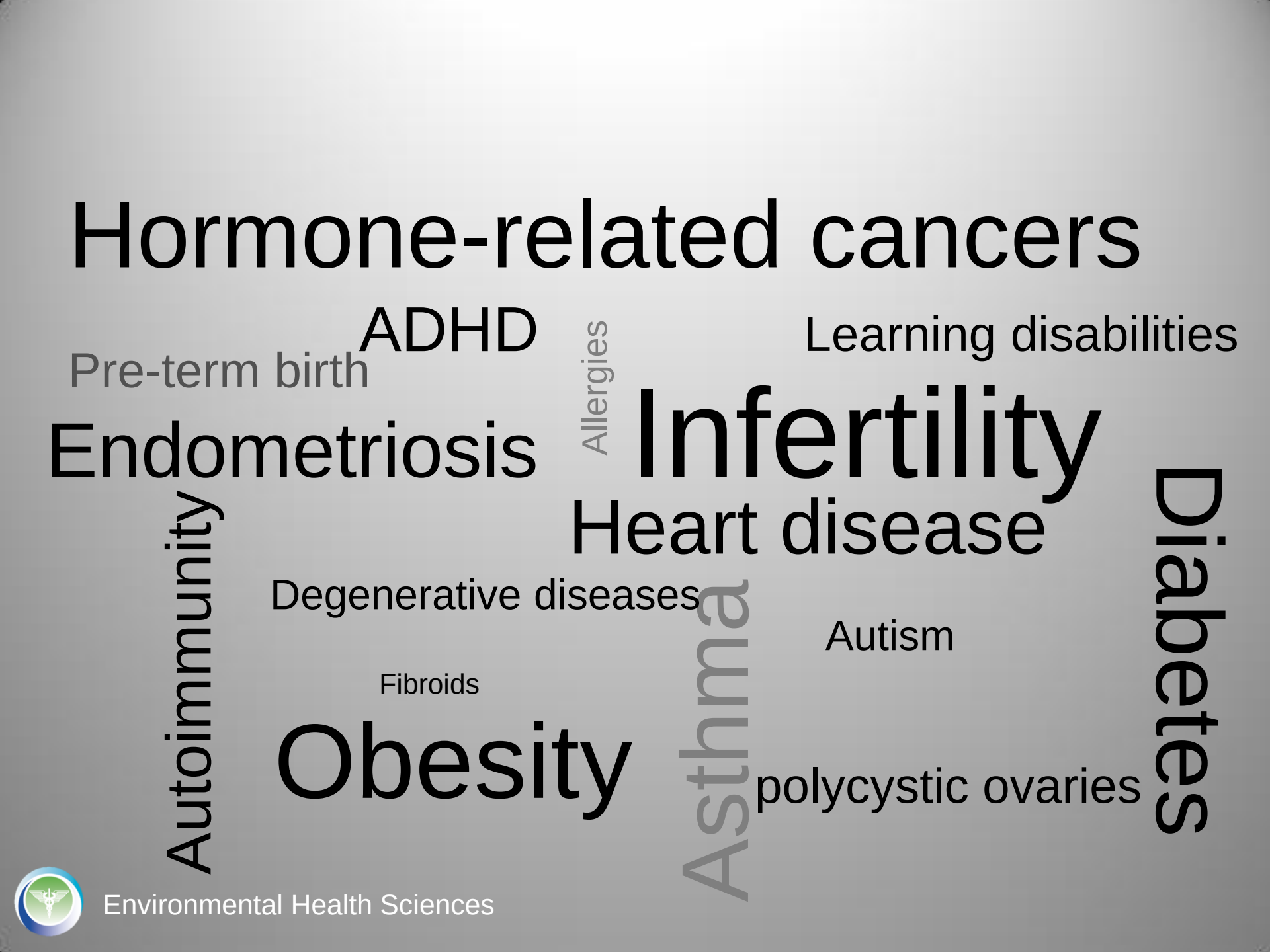
Designing against EDC hazard

Tiered Endocrine Disruptor Protocol

- Voluntary… based on current science
- Not about current replacements
- Economically efficient
- Driven by endocrinological principles
- Designed to evolve with the science

Redesign


A new voluntary testing protocol to aid chemists in the
Green Chemistry
Cite this: DOI: 10.1039/c2gc35055f
www.rsc.org/greenchem
ROYAL SOCIETY OF CHEMISTRY
Designing endocrine disruption out of the next generation of chemicals†
T. T. Schug,*[a] R. Abagyan,[b] B. Blumberg,[c] T. J. Collins,[d] D. Crews,[e] P. L. DeFur,[f] S. M. Dickerson,[g] T. M. Edwards,[h] A. C. Gore,[i] L. J. Guillette,[j] T. Hayes,[k] J. J. Heindel,[a] A. Moores,[l] H. B. Patisaul,[m] T. L. Tal,[n] K. A. Thayer,[o] L. N. Vandenberg,[p] J. C. Warner,[q] C. S. Watson,[r] F. S. vom Saal,[s] R. T. Zoeller,[t] K. P. O'Brien*[g] and J. P. Myers*[u]
3
In vitro Whole Cell Activity Assessment
4
Fish and Amphibian Assessment
5
Mammalian Assessment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