Bisphenol A: Mistakes and opportunities

John Peterson Myers, Ph.D.
Environmental Health Sciences
and
Carnegie Mellon University
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Where the FDA went wrong

Risks of using existing substitutes

Designing endocrine disruption out of new chemicals
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.
FDA’s core assumption: exposures too low to affect health. BPA is safe.
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

Non-monotonicity of EDCs

Welshons, in Vandenberg et al. 2012
"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
Substitutions problematic

Not a new problem: e.g., PCBs => PBDEs => Firemaster 500 & Tetrabromobisphenol A

Chemicals available today at best were tested using same flawed criteria that permitted the bad stuff to get into the market

BPA vs. BPS
A new way forward: the 4th R
Reduce, reuse, recycle
Redesign
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

In vitro Whole Cell Activity Assessment

Fish and Amphibian Assessment

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