Getting a clear view: Lessons from the CLARITY-BPA study

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BPA

Sports & medical equipment

Thermal receipt

Consumer plastics

Canned foods & beverages

Canned foods & beverages
More than 100 human studies suggest associations between BPA and human disease.

- Male infertility
- Obesity
- Hyperactivity
- Female infertility
- Type 2 diabetes
- Heart disease
- Anxiety
- Male infertility
- Obesity
- Hyperactivity
- Serum hormone levels
A 2-minute crash course in chemical safety testing
Prior to the CLARITY study...

*Guideline studies suggested that only high doses of BPA were toxic.*
In contrast, hundreds of academic studies revealed effects of BPA on a wide range of hormone-sensitive outcomes.

Reproduction

Brain & behavior

Metabolic endpoints

Immune system

Mammary gland

Reproduction
Why would guideline and academic studies show vastly different effects of BPA (and other chemicals)?

Why would guideline and academic studies differ in sample sizes?

Why would guideline and academic studies differ in sensitivity?

Why would guideline and academic studies differ in relevance to disease?

Why would guideline and academic studies differ in reliability in study designs?
Regulatory agencies have focused on the guideline studies to conclude that BPA is safe… but the public, and several scientific societies, disagree.
CLARITY-BPA: bringing together a guideline study with academic endpoints

Consortium Linking Academic and Regulatory Insights of Toxicity of BPA
Run a guideline study…
but add ‘academic’ endpoints!
The CLARITY approach:
### Core Study

Broad overview of results from the FDA

Vandenbergh, Hunt & Core, Nat Reviews Endocrinol 2019

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<th>Pituicy</th>
<th>Pancreas</th>
<th>Thyroid/Parathyroid</th>
<th>Adrenal</th>
<th>Kidney</th>
<th>Mammary</th>
<th>Reproductive Tract</th>
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|        | Spleen | Pituicy | Pancreas | Thyroid/Parathyroid | Adrenal | Kidney | Mammary | Reproductive Tract | Testis | Ovary |
|--------|--------|---------|----------|---------------------|---------|--------|---------|---------------------|--------|
| Female |        |         |          |                     |         |        |         |                     |        |
| Male   |        |         |          |                     |         |        |         |                     |        |
Several serious adverse effects of BPA were observed in the FDA-Core study at low doses.

- Increases in the incidence of mammary adenocarcinoma (at 2.5 µg/kg/day in the CONTINUOUS group)
- Increased body weight in adult females (at 250 µg/kg/day in the CONTINUOUS group)
- Inflammation of the dorsal and lateral lobes of the prostate (at 2.5 µg/kg/day in the CONTINUOUS group)
- Kidney nephropathy in females (at 2.5 µg/kg/day in the CONTINUOUS group)
- Increased incidence of the dorsal and lateral lobes of the prostate (at 2.5 µg/kg/day in the STOP group)
Example 1: Low dose BPA exposure increased mammary cancer.

Incidence of mammary adenocarcinoma

- Control: p=0.016
- 2.5BPA: p=0.083
- 25BPA
- 250BPA
- 2500BPA
- 25000BPA
Example 2: Low dose BPA exposure increased prostate inflammation (a cancer risk factor).
There are serious effects of BPA reported in the FDA Core Study. This contrasts with the FDA’s conclusions. Results of the [core study] indicated that BPA produced adverse effects at high doses, but not at the low end of the dose range consistent with its activity as a weak estrogen.
Why does the FDA ignore low dose effects of BPA observed in the FDA-CORE study?
Finding anything in the low dose groups of the guideline study is surprising, based on the prior guideline studies on BPA!!
Many, many effects were observed in academic studies.
Example 1: Low dose BPA exposure induces prostatic adenocarcinoma in the prostatic intraepithelial neoplasia (PIN) and neoplasia (PIN) and "Prins et al., EHP 2018"
Example 2: Seven academic CLARITY publications document effects of BPA on brain and behavior.

- Rebuli et al. Tox Sci 2015
- Johnson et al. Horm Behav 2016
- Arambula et al. Neurotoxicology 2017
- Cheong et al. Epigenetics 2018
- Arambula et al. Neurotoxicology 2018
- Witchey et al. Neurotoxicology 2019
- Witchey et al. Neurotoxicology 2019
- Witchey et al. Neurotoxicology 2019

Brain

Gene expression

Behavior

Expression of hormone receptors

Size of brain regions
CLARITY was an imperfect study

Some academic studies underpowered
Results of positive control do not match prior studies
Reliance on historical controls
Stress of barren

Vandenberg, Hunt & Gore, Nat Reviews Endocrinol 2019
What can we conclude from the CLARITY study?

- Differences in reliability in study
- Differences in relevance to disease
- Differences in sensitivity
- Differences in sample sizes
Conclusions

- CLARITY

- There are serious effects observed in the FDA Core study after exposure to low doses of BPA
- These effects are ignored or dismissed by FDA because they were not observed at high doses, or because they were only observed in one group (stop-dose versus continuous)
- Many effects observed in the academic studies after exposure to low doses of BPA
- Let's learn from CLARITY and develop endpoints that are sensitive and more accurately reflect human diseases

Conclusions - CLARITY: BPA (to date)