Toxicology Serves to Protect Human and Environmental Health

Toxicology Must Distinguish Between Agents that Pose a Health Risk and those that do not.

Risk = Hazard (how toxic) x Exposure

BPA and Health: Is Any Exposure Safe?

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Funding and Potential Conflict of Interest

- Funding sources for the work I am going to show you:
- Other major funding sources during that time
  - National Institutes of Health
- Current funding
  - Same as above, but includes a research grant from the American Chemistry Council BPA producers group.

BPA is The Most Highly Reported Endocrine Disruptor

"Bisphenol A and Estrogenicity"

2819 Total Publications
Why the Controversy?

- The U.S. EPA, the U.S. FDA, the European Food Safety Authority, the Japanese and others all conclude BPA is safe at current human exposures.
  - However, a group of scientists claim that although high doses of BPA are safe, effects are expected and have been shown at “low doses.”
- Based on extraordinarily robust data in humans and monkeys, human blood levels of BPA are expected to be below levels causing effects in animals.
  - However, more than 20 poorly controlled studies show much higher levels of BPA in human blood.

We will Answer the Most Critical, Most Frequently Asked Questions

- What is BPA and how does it interact with the body?
- How does BPA get into my body? Where does it come from?
- How much BPA is in the body of adults and children?
- Is there enough BPA in our bodies to cause estrogenic effects?
- What about the fetus, can it have more BPA than adults?
- What are low-dose effects and what are the implications for human health?
How is BPA Absorbed and How Does it Interact with your Body?

How does BPA get into our bodies?

- Ingestion of food, particularly packaged foods
  - >90% of our exposure is via the oral route
  - Multiple studies, adults and children
- Dermal
  - Cash register receipts
  - Ongoing studies suggest absorption is not significant
    (NIEHS Cashier study, report from a public meeting).
- Inhalation
  - Insignificant
How Does it Interact with Mammalian Systems?

<table>
<thead>
<tr>
<th>Compound</th>
<th>Classical</th>
<th>Non-Classical</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β Estradiol (steroid hormone)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>1/10,000</td>
<td>~1</td>
</tr>
<tr>
<td>Genistein (soy isoflavone)</td>
<td>1/250</td>
<td>?</td>
</tr>
</tbody>
</table>

Bisphenol A is Almost Entirely Inactivated before it Reaches our Blood

Outside the Body

Bisphenol A (Active)

Inside the Body

99.7% of an Oral Dose

BPA-Glucuronide

BPA-Sulfate (Inactive)

(1% or less of an Oral Dose)
Citations for Extensive Metabolism of BPA: Rats, Mice, Monkeys, Humans, during Pregnancy, and in the Fetus

Response is Related to Concentrations at the Site of Action (Basic Pharmacology)

What Blood/Tissue Concentrations of UC-BPA Cause Adverse Effects in Test Species?

Similar? Potential for a public health problem.

What are Blood/Tissue Concentrations UC-BPA In Humans at Current Exposure Levels?

Carefully Controlled Clinical Exposure Studies are one Approach to Determining How much BPA is in our Blood

Twenty-Four Hour Human Urine and Serum Profiles of Bisphenol A during High-Dietary Exposure

Clinical Bisphenol A Biomonitoring Study

► Volunteers
- 10 males, 10 female, non-smoking
- 18-54 years old
- No liver or kidney function deficits
- No use of drugs affecting liver or kidney function

► Protocol Highlights
- Volunteers ate 100% of defined meals: breakfast, lunch, dinner
- Urine samples ~ hourly, blood hourly from 7 am to 10 pm and a first morning void @ 24 hours.
- Field blanks: blood, urine, water through blood collection system, and urine collection material, water (all were below detection limit)

► Urine and selected blood samples analyzed for total BPA at the CDC by Dr. Antonia Calafat (LOD 0.1-0.4 ng/ml)

Twenty-four hour human urine and serum profiles of bisphenol a during high-dietary exposure

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Twenty-four hour human urine and serum profiles of bisphenol a during high-dietary exposure

All Samples were Below the Limit of Detection for BPA even at Exposures that Exceeded the 95th Percentile of Human Exposure

- Mean urine concentration nearly three times higher than the in the general population (NHANES)
- The 95th percentile BPA urinary concentration was more than twice the values in the general population
What are human blood concentrations if you use other methods for determining them?

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Human Experimental Data and Models Support Calculations of Serum BPA Concentrations

- **Unconjugated fraction**
  - Völkel et al. (2002): upper bound: 0.1%
  - NIEHS human oral PK study: 0.2%
  - Human PBPK modeling: ~0.1%

- **PBPK**
  - 2 human oral-route PK studies, monkey I.V. and oral PK studies

- **Urine:Blood BPA concentration ratio:**
  - Teeguarden et al. (2011): GM, 42
  - NIEHS human oral-route PK study: GM, 62

- **Ratio of Peak Blood Concentration to Total Exposure:**
  - Teeguarden et al. (2011): 17 nM/μg/kg
  - NIEHS human oral-route PK study: 20 nM/μg/kg

Demographics for Exposure Assessment

19 Countries | 28,765 Individuals

8 Countries | 4,032 Individuals

Total Serum BPA 6 Countries | 418 Individuals

Direct Measures 6 Countries | 120 Individuals

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Convergence of Methods: Mean Serum BPA Concentrations are in the Sub pM range

Exposure = 4x U.S. 95th Percentile

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Fetal Blood Concentration are Lower than Maternal BPA Blood Concentrations

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Are Serum BPA Concentrations Sufficient to Cause Estrogenic/Endocrine Disruptor Effects?


Receptor Occupancy of Less than 0.001 % in Infants and Women of Child Bearing Age

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Intravenous BPA: A Model for Non-Oral Routes of Exposure

Lower Bound BPA Method Limit of Detection

No Observable Changes in Estrogen Regulated Genes in Rat Prostate or Mammary Tissue

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Large, Chronic, Multi-Generation Animal Studies Consistently Show no Adverse Effects of BPA at Exposure Levels 1000’s of Times Higher than Human Exposure

- 2 or 3 generations of exposure, mice and rats (Tyl et al. 2002, 2008)
- Mice, rats, effects on sperm production and prostate (Ashby et al. 1999, 2003)
- Rats, exposed during pregnancy and development (FDA, B. Delclos).

Conclusions

- There is extraordinary convergence between theory, experiment and simulation.
- Environmental, non-occupational exposures most likely lead to extremely low (pM or sub-pM) internal exposures to BPA in the majority of the population.
- “High” blood concentrations reported in studies and in the media are outliers, and are most likely the result of contamination*.
- There is no consistent evidence that BPA at these concentrations is toxic or acts as an endocrine disruptor in animals.

*Researchers at the Food and Drug Administration, the Centers for Disease Control and other academic researchers


I Hear that BPA causes Effects at “Low” Doses.

What are “low” doses? Does the “low” dose data mean I am at risk?

Method

- Systematic review of published “low dose” BPA literature.
  - All BPA toxicology papers self-referring as “low dose” or “environmentally relevant” or “low concentration.”

- Tabulated exposure levels
  - μg/kg/day for in vivo studies
  - nM for in vitro studies
  - No consideration for route or duration of exposure

- Compared to measures of human exposure
  - External: National exposure assessments (NHANES)
  - Internal: Median serum concentrations (analysis above)

Few BPA “Low-Dose” Studies have been Conducted in the Range of Human Exposure
Few BPA “Low-Dose” Studies have been Conducted in the Range of Human Exposure

In Vivo: Independent Tabulation

In Vitro

vom Saal FS, Welshons WV. Environ Res. 2006;100(1):50-76.
Conclusions

- The term “low-dose” is extraordinarily non-specific.
- "Low-dose" does not describe a body of BPA toxicity studies conducted within the range of human exposures.
- Greater care should be taken in inferring human risk from “low dose” studies, or reviews of “low-dose” studies.
- There is an opportunity to utilize the wealth of BPA exposure data to place all toxicity studies in the context of human exposure and to design appropriate toxicity studies.

Final Conclusions

- Broad groups of scientists within regulatory bodies have consistently concluded BPA exposure levels do not pose a risk to human health.
- Human internal exposure is far below levels that consistently show effects in animals and is not expected to be estrogenic.
- The term “low dose” is misleading and applied to BPA has led to tremendous confusion about the risks posed by exposure to BPA.
- Carefully consider your sources of information.