Low doses have large effects: the case of Bisphenol A

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Development is an open system

- drugs & alcohol
- food
- vitamins
The Fragile Fetus
Prostate growth
Serum hormone levels
Responsiveness to T
Steroid metabolism
steroid receptor levels
aggression

Stress responses
Serum hormone levels
Aggression
Ano-genital distance
Timing of puberty
Length of estrus cycles

uterus
Hormones also influence human fetal development

For instance, prenatal estrogen exposure, higher in twin births, is associated with breast cancer
Bisphenol-A (BPA) acts as an estrogen mimic.
Why low doses?

MTI (1000mg/kg)

“safe” dose = 50 ug/kg

LOAEL (50 mg/kg)

Safety factors for genetic differences, extrapolations from adults to children & animal to human
Humans are exposed to BPA in the ppb range.

Vandenberg et al, 2010
BPA is regulated by EPA

http://www.epa.gov/ncea/iris/subst/0356.htm

- Reference (“safe”) dose: 50 micrograms/kilogram body weight/day

**DOSES USED IN OUR STUDIES**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>25µg/kg/day</th>
<th>2.5µg/kg/day</th>
<th>0.25µg/kg/day</th>
<th>0.025µg/kg/day</th>
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<tbody>
<tr>
<td>25 ppb</td>
<td>25 ppb</td>
<td>2.5 ppb</td>
<td>0.25 ppb</td>
<td>0.025 ppb</td>
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<tr>
<td>1/2</td>
<td>1/20</td>
<td>1/200</td>
<td>1/2000</td>
<td></td>
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</tbody>
</table>

OF THE EPA SAFE REFERENCE DOSE
preg day 8- birth

brain, behavior, body weight & metabolism, female reproductive tract & fertility, mammary gland development & cancer
Prenatal BPA exposure alters brain development

Rubin et al, 2006
Perinatal BPA exposure alters sex-specific behaviors

Other behaviors are also affected by low doses of BPA, including aggression, maternal behavior, anxiety & cognitive learning

Rubin et al, 2006
Hyperactive & obsessive behaviors

Vandenberg et al. unpublished
Low dose BPA alters development of the mammary gland during the period of exposure…

Embryonic Day 18

Control  BPA

Vandenberg et al. 2007
...And low dose BPA alters development of the mammary gland long after exposures have ended.

Markey et al. 2001, 2003
Munoz-de-Toro et al. 2005
Low doses of BPA induce precancerous lesions

Vandenberg et al., 2008
Even the male mammary gland is affected by low doses of BPA

Vandenberg et al., in preparation
Low doses of BPA induce obesity & metabolic syndrome

5A: Female Insulin Tolerance Test, 0.75U Insulin / kg BW

Rubin et al., in preparation
Low doses of BPA affect the size and morphology of the brown fat pad

Rubin et al., in preparation
BPA is regulated by EPA
http://www.epa.gov/ncea/iris/subst/0356.htm

- Reference dose: 50 micrograms/kilogram body weight/day

We have not yet found a “safe” dose of BPA for the brain, behavior or mammary gland

25μg/kg/day  2.5μg/kg/day  0.25μg/kg/day  0.025μg/kg/day
25 ppb  2.5 ppb  0.25 ppb  0.025 ppb
1/2  1/20  1/200  1/2000

OF THE EPA SAFE REFERENCE DOSE
BPA has diverse effects at low doses

- Brain, behavior, mammary gland
- Female reproductive tract, reproductive aging, fertility, timing of puberty
- Body weight regulation, metabolism, adiposity
- Male reproductive tract, fertility
- Immune & cardiovascular systems
- Cancers (blood, mammary, prostate)

Low doses of BPA adversely affect development & therefore are worth our attention