

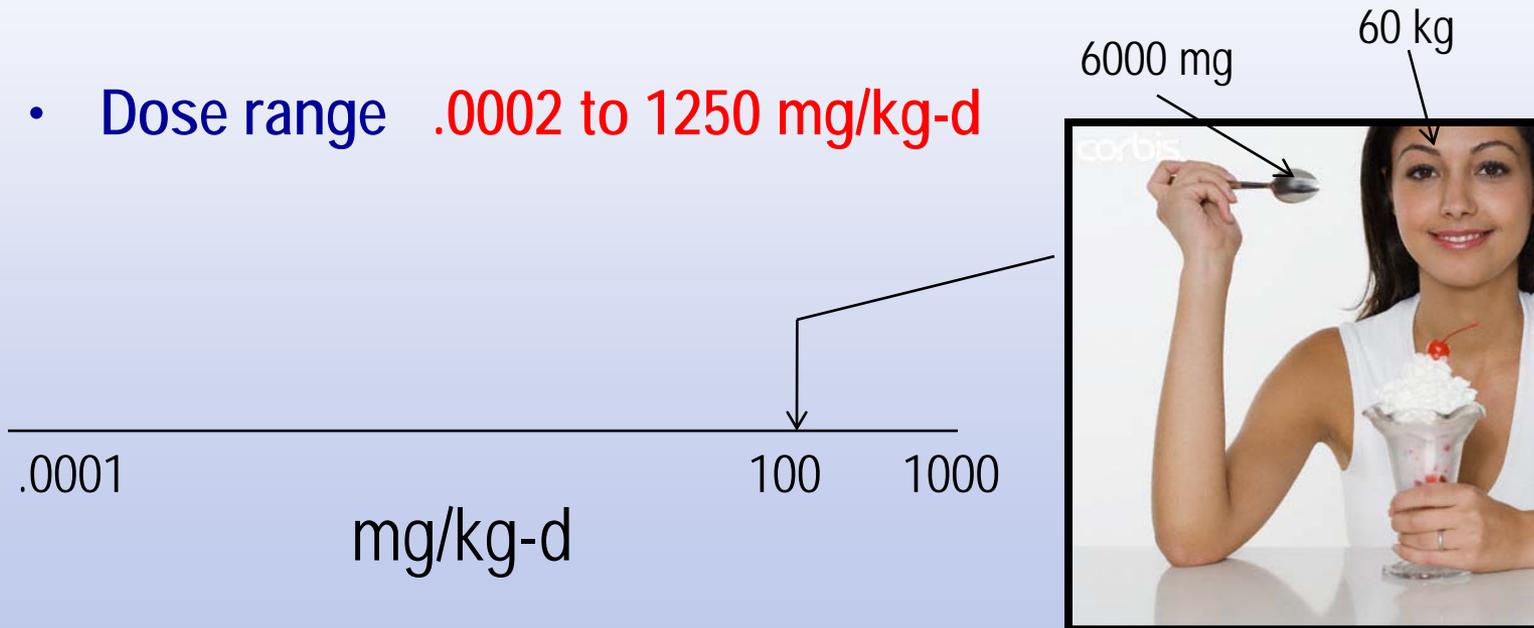
Bisphenol A: Laboratory Animal and Human Data on Developmental Toxicity

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Studies reviewed

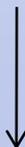
- Studies in humans $n=2$
- Studies in laboratory rodents $n=63$
 - Routine toxicology guideline studies $n=6$
 - Investigator initiated studies $n=57$
- Dose range $.0002$ to 1250 mg/kg-d



Developmental Studies in Humans

Study/Design	Population/Exposure Measure	Results
<i>Padmanabhan et al., 2008</i> Cross-sectional	Pregnant women in Michigan n=40 Plasma BPA	No association with birth weight or gestational age
<i>Wolff et al., 2008</i> Prospective	Pregnant women in New York City n=404 Urinary BPA	No association with birth weight, birth length, head circumference, or gestational age

Rodent studies



Endpoints: pregnancy outcome

Pregnancy outcome 8 studies

0.0002-1250 mg/kg-d

- Offspring viability at doses > 100 mg/kg-d
 - Fetal loss
 - Decreased litter size
 - Decreased live pups/litter
- Fetal/neonatal weight



Endpoints: gene expression in the embryo and fetus

12 studies; 11 with *in vivo* dosing; 5 oral

0.2-400 mg/kg-d

- Gene activation patterns in placenta, fetal ovaries and fetal testes
- Expression of retinoic acid receptor and aryl hydrocarbon receptor, homeobox genes
- Gene methylation and chromosome integrity
- Epigenetic effects



Endpoints: Postnatal Growth

9 studies

4-1250 mg/kg-d • weight decrease relative to control;

— 5 higher dose studies;

• 4 with fetal or neonatal weights;

0.0024-3 mg/kg-d • weight increase relative to control;

— 4 lower dose studies;

• 3 with postweaning weights;



Endpoints: Postnatal Immune Function

4 studies

0.003-3 mg/kg-d

- **BPA increased**
 - inflammation
 - cytokine production
 - cell proliferation
 - antibody production
- **BPA decreased CD4+CD25+ “suppressor” T lymphocytes**



Endpoints: Sex-differentiated Brain and Behavior

21 studies

0.01-0.1 mg/kg-d

- **Brain**

- Size of brain regions

- Number and types of neurons in brain regions

- **Behavior**

- Mating behavior, maternal behavior

- Social interaction

- Affective behavior, exploratory behavior

- Spatial learning and memory



Summary of Endpoints

- **Studies in humans**
 - Birthweight, gestation length, birth length, head circumference
- **Studies in rodents**
 - Gene expression in embryo/fetus
 - Pregnancy outcome -Offspring viability
 - Postnatal outcome
 - Growth -Greater weight
-Lower weight
 - Immune function -Immune hypersensitivity
 - Sex-differentiated brain and behavior
 - Changes in sex-differentiated morphology and chemistry of the brain
 - Altered sexual behavior
 - Altered maternal behavior
 - Loss of sex-differentiated affective and exploratory behavior



Nonhuman Primate Studies

- **Previous BPA work**
 - PK studies in rats and nonhuman primates
 - Developmental behavior studies in rats
- **New BPA monkey study**
 - 10 µg/kg-d delivered from a subcutaneous implant to the pregnant dam
 - Equivalent to 5 mg/kg-d oral in rats
 - Videotapes of mother and infant 1-3 months old
 - BPA effect on clinging, social exploration, “looking outward” at $p < 0.0037$

