

Public Comments on the FDA Draft Assessment of Bisphenol A

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Precautionary Legislation

BPA-Free Kids Act of 2008

April 29th, 2008: Senators Dianne Feinstein (D-Calif.)
and Charles Schumer (D-N.Y.)

Prohibit the use of bisphenol A in children's products.
Require the CDC to study the health effects of bisphenol A
exposure in all age groups and in pregnant women.

Ban Poisonous Additives Act

June 10th, 2008: Representative Edward Markey (D-Mass.)

Prohibit the use of bisphenol A in food containers.

***“We cannot let the health of our children hang in
the balance while we wait for more studies...”***

- Senator Dianne Feinstein

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Reliance on animal tests delays regulation

Cigarette smoke:

Landmark epidemiological studies by the American Cancer Society in the 1950's linked smoking to cancer.

For decades, the tobacco industry cited tests showing that animals forced to inhale smoke did not develop cancer.



Other examples include **asbestos**, **arsenic** and **benzene**.

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Bisphenol A: More of the same

FDA continues to rely on animal studies proposing a tiered testing strategy

Tier 1, in rodents, evaluate:

- internal dose with respect to multiple routes of administration in adult, pregnant and neonatal animals;
- developmental onset of adult UDP-GT activity;
- neural and behavioral developmental endpoints.

Tier 2, in non-human primates, evaluate:

- internal dose with respect to multiple routes of administration in adult, pregnant and neonatal animals;
- developmental onset of adult UDP-GT activity;
- equilibrium ratios of unconjugated BPA to BPAG;
- continuous exposure through gestation (in utero exposure);
- oral exposure to neonatal animals from non-maternal transfer;
- neural and behavioral developmental endpoints.

The proposed studies would consume thousands of animals' lives but could only delay regulation that is needed now.

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Proposed rodent studies unlikely to reproduce low-dose effects

Rochelle W. Tyl, et al. Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD-1 (Swiss) Mice. *Toxicol Sci.* 2008.104(2): 362–384.

- Conducted in response to 2003 EU risk assessment with oversight by the EU Bisphenol A Steering Group.
- EU: *“the gold-standard, definitive study of the reproductive toxicity of BPA”*.
- Dietary BPA was evaluated in a two-generation study at 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg BPA/kg/day.
- Concurrent positive control using 17 β -estradiol confirmed the sensitivity of CD-1 mice to an endogenous estrogen.
- *“At lower doses [0.003 – 5 mg BPA/kg/day], there were no treatment-related effects and no evidence of non-monotonic dose response curves for any parameter.*

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Results in rodents are not predictive of results in humans and other primates

Völkel, W et al. Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. *Chem. Res. Toxicol.* 2002. 15: 1281-1287.

“The obtained data indicate major species differences in the disposition of bisphenol A. Enterohepatic circulation of bisphenol A glucuronide in rats results in a slow rate of excretion, whereas bisphenol A is rapidly conjugated and excreted by humans due to the absence of enterohepatic circulation. The efficient glucuronidation of bisphenol A and the rapid excretion of the formed glucuronide result in a low body burden of the estrogenic bisphenol A in humans following oral absorption of low doses.”

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Results in rodents are not predictive of results in humans and other primates

European Food Safety Authority (EFSA). Scientific Opinion of the Panel on Food additives, Flavourings, Processing aids and Materials in Contact with Food on a request from the Commission on the toxicokinetics of Bisphenol A. *The EFSA Journal*. 2008. 759: 1-10.

Oral clearance of BPA analogs lorazepam, paracetamol and lamotrigine increases during pregnancy.

- Indicates that glucuronidation activity is induced.
- Results in decreased plasma concentrations of BPA analogs.
- Glucuronidation activity induced during pregnancy likely to result in decreased fetal exposure to free BPA in humans.

In rodents, glucuronidation activity is similar in non-pregnant and pregnant animals.

- Availability of unconjugated BPA expected to be higher compared with that in humans.

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Low-dose effects unlikely to be detectable in non-human primates

Humans and other primates are far less sensitive to BPA than are rodents.

Neural and behavioral developmental effects of BPA are observed only at low doses in rodents.

Therefore, it is extremely unlikely that these effects will be detectable in non-human primate studies, given the insensitivity of the model, and the large sample sizes required to detect low-frequency events.

Such effects must be observed in large-scale epidemiological studies.

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Summary and Recommendations

There is already an extensive body of literature on the toxicity of bisphenol A in animals.

The proposed rodent studies are unlikely to reproduce effects observed at low-doses, as evidenced by recently published studies.

Since humans and other primates are far less sensitive to BPA than are rodents, it is extremely unlikely that neural and behavioral developmental effects observed only at low doses in rodents will be detectable in non-human primates.

The proposed animal tests are unnecessary and are unlikely to provide more useful information. Instead the time has come for concerns over BPA's development effects to be addressed by precautionary regulation.

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