Bisphenol A and Human Health: What Does the Science Show?

Julie E. Goodman, Ph.D., DABT
Principal/Gradient
Adjunct Faculty/Harvard School of Public Health

AEI Center for Regulatory Studies
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What is a Health Effect?

- Not merely a biological change
- Must be an adverse outcome
- "Endocrine disruptive" often used when "endocrine active" is more appropriate
  - Change in "normal" hormone system, may or may not be adverse
  - Many natural endocrine disruptors (*e.g.*, soy)
  - Mode of action
  - Not necessarily a health effect

The Low-Dose Hypothesis

- Bisphenol A (BPA) is endocrine-active and causes health effects in animals at high doses (≥ 50 mg/kg-d)
- Low-dose hypothesis: BPA causes adverse effects at low doses that may not be observed at high doses
  - Not been shown in hundreds of studies
  - Do not need more studies
  - Not supported by the weight of evidence

Why the Controversy?

- Misinterpretation (and misrepresentation) of results
- Study-by-study analysis *vs.* endpoint-by-endpoint analysis
- Ignoring results that show no effect (null results)
- Emphasis on studies that don't reflect how humans are exposed
- Mistrust of studies that use Good Laboratory Practices (GLP)

Challenges in Interpreting Individual Studies

- Case study: Kawai *et al.* (2003) dosed pregnant mice, measured testis weight in offspring at 8, 12, and 16 weeks
- Uncertain/variable controls, odd control values lead to observed effects
- Effects at lower dose > higher dose
- Inconsistent patterns over dose and time

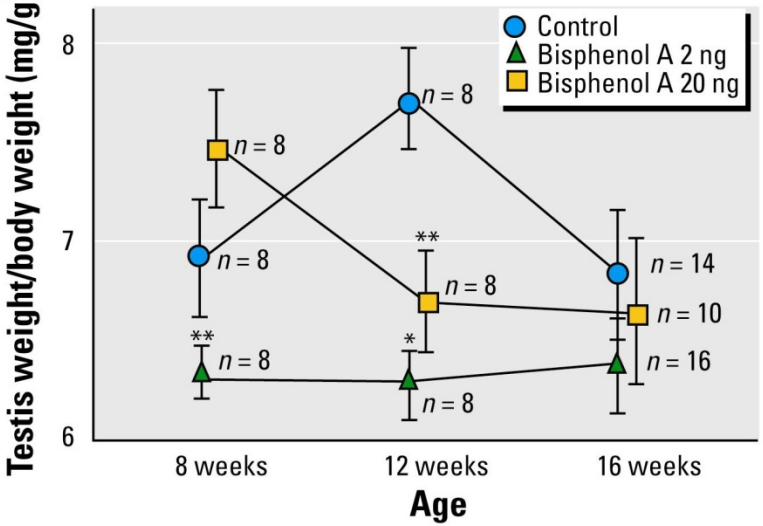


Figure 2. Chronologic change of relative testis weight per body weight (mean ± SE) in control male mice and 2-ng/g bisphenol A and 20-ng/g bisphenol A male mice.

*$p < 0.01$ compared to control. **$p < 0.05$ compared to control.

Issues with Study-by-Study Analysis: Inconsistent Evidence

Study	Prostate Weight	Testis Weight	Sperm Count	Male Fertility
A	↑	–	–	–
B	–	↓	–	–
C	–	–	↓	–
D	↓	–	–	–
E	–	–	–	–
F	–	–	–	–
G	–	–	–	–
H	–	–	–	–
I	–	–	–	–

Issues with Study-by-Study Analysis: Inconsistent Low Dose Effect

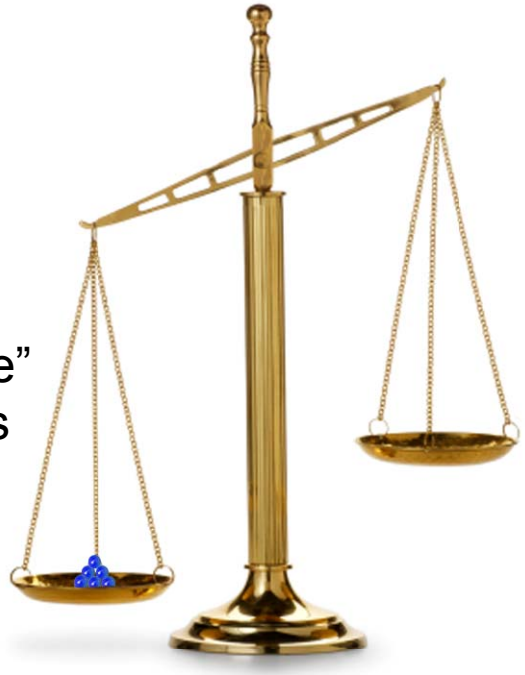
Dose / Study	0	1	10	100	1,000	10,000	100,000
J	–	–	–	–	–	–	–
K	–	–	–	↑	–	–	–
L	–	–	–	–	–	–	–
M	–	–	–	–	–	–	–
N	–	–	–	–	–	–	–
O	–	–	–	–	–	–	–
P	–	↓	–	–	–	–	–
Q	–	–	–	–	–	–	–
R	–	–	–	–	–	–	–

Study-by-Study Analysis: Prostate

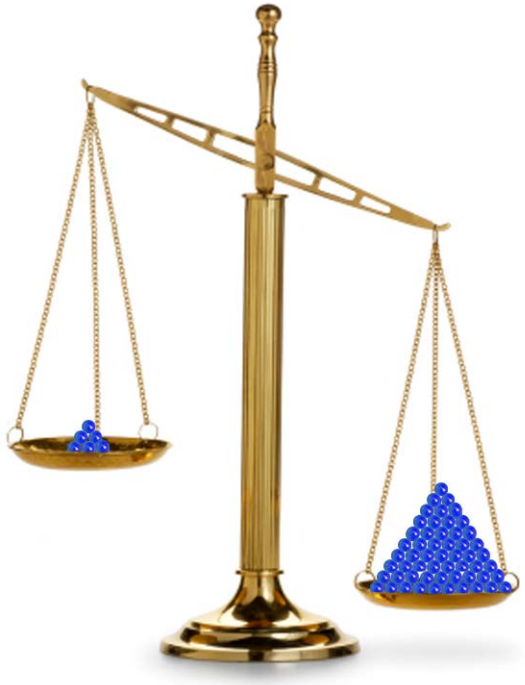
Ref.	Animal	Exposure, vehicle	Time of exposure	Dose (µg/kg-d)	Endpoints
Gupta	Mouse	Oral, oil	GD 14-18	50*	Prostate weight, prostate AR
Ho	Sprague-Dawley rat	Injection s.c.	PND 1-5	10*	Prostate cancer (PIN lesions)
Nagel	CF-1 mouse	Oral, oil	GD 11-17	2*, 20*	Prostate weight
Ramos	Wistar rat	Osmotic pump, DMSO	GD 7-22	25*, 250*	Ventral prostate
Stoker	Wistar rat	s.c. injection, oil	PND 22-32	50,000*	Serum prolactin, lateral prostate weight
Timms	Mouse	Oral, oil	GD 14-18	10*	Fetal development of prostate and urethra

* $p < 0.05$ Richter *et al.,* 2007

Study-by-Study Analysis: Prostate



"positive" studies



Studies showing no effect

Endpoint Analysis: Prostate Weight in Rats and Mice Dosed with Bisphenol A

Exposure	Dose (mg/kg-d) order of magnitude					
	≤10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-1}	1
Oral	00	000	00+0000	00000000+	0+00000	00
		+	00+0	0+00−0	000	0000
			000	0000	0000	000
Non-oral			0	000000	0000	+0
				00	0	+

Goodman *et al.*, 2009

Key:

0 No difference between BPA treated animals and controls (71)

\+ Increase in BPA treated animals (7)

− Decrease in BPA treated animals (1)

The Boston Globe

Is plastic making us fat?

Researchers are exploring whether exposure to common chemicals during early development could set us up for a lifetime battle with the bulge

By Beth Daley, Globe Staff | January 14, 2008

"A study at the University of Missouri-Columbia showed that mice fed bisphenol A during early development– at lower amounts than what would have resulted in the levels found in most people in the CDC study– become markedly more obese as adults than those that weren't fed the chemical. Tufts University scientists observed similar phenomenon in rats."

Bisphenol A and Body Weight

	Exposure	Dose (mg/kg-d) order of magnitude					
		≤10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-1}	1
Oral	Direct to rat or mouse	00	00 0 0	000000 0000−− 00000	0000000 000000−− 00000000	0000000 00+0−−0 00000000	0000 0000−0 000+
Oral	Fetus *via* mother		00 0	00000−++ +00000 000	00000000 0000000 0000	00000 000 −000000	00 00000000 00+000+
Non-Oral	Direct to rat or mouse	00	00 0 0	000000 0000−− 00000	0000000 000000−− 00000000	0000000 00+0−−0 00000000	0000 0000−0 000+
Non-Oral	Fetus *via* mother		00 0	00000−++ +00000 000	00000000 0000000 0000	00000 000 −000000	00 00000000 00+000+

Goodman *et al.*, 2009

0 No difference between BPA treated animals and controls (274)
\+ Increase in BPA treated animals (14)
− Decrease in BPA treated animals (18)

On the Horizon

- New studies showing changes on the genetic or epigenetic level
- Results must be put into context of all other data
- If effects on the molecular cellular level do not result in health effects in animal studies, they are not indicative of health effects in humans

Conclusions

- Many studies report some statistically significant findings
- These findings are not marked or consistently repeatable within or among studies, between rats and mice, or among dose groups and evaluation times
- No common pattern among findings for a hormonal mode of action for adverse effects
- The weight of evidence does not support low-dose adverse health effects from BPA