

Bisphenol A: No Reproductive or Developmental Effects at Low Doses

By Julie E. Goodman, Ph.D., DABT, Carrie J. Yu, M.S., and Lorenz Rhomberg, Ph.D.

Summary

Bisphenol A (BPA) is used predominantly in the production of polycarbonate plastic – which is used in water bottles, baby bottles, and food containers – and epoxy resins – which line food and beverage cans. People are generally exposed to minute levels of BPA, mostly from the ingestion of food or beverages that have been in contact with these materials. These exposures are well below the intake levels set by government bodies that are considered to be without harm.

Studies have shown that BPA has weak estrogen-like activity, and that it may cause effects at high doses in animals. Although BPA exhibits generally low toxicity, considerable controversy still surrounds the so-called “low-dose hypothesis” that very low doses of BPA may act as a synthetic estrogen and cause adverse reproductive and developmental toxicity.

To address the “low-dose” controversy, the Harvard Center for Risk Analysis convened a panel of scientific experts to critically review the relevant low-dose BPA studies of reproductive and developmental effects. In 2004, the Harvard Panel “found no consistent affirmative evidence of low-dose BPA effects for any endpoint.” In 2006, Gradient organized and participated in an expert scientific panel that conducted an updated weight-of-evidence evaluation, looking at articles published since the Harvard review and using the same methodology as the Harvard Panel.

This year, Gradient conducted another expert scientific panel review, again using the same methodology as the Harvard Panel, and including literature published through July 2008. The effort was funded by the Polycarbonate/BPA Global Group and the panel’s report has been published in the peer-reviewed journal, *Critical Reviews in Toxicology* (Goodman et al., 2008). As summarized below, the findings of all three reviews were consistent with one another and with reviews conducted by government bodies worldwide. As concluded overall, “The weight of evidence does not support the hypothesis that low oral doses of BPA adversely affect human reproductive and developmental health.”

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The Low-Dose Controversy

The concern for low-dose effects was sparked by a 1997 study conducted in the laboratory of Frederick vom Saal. In this study, pregnant mice were given oral doses of BPA at 0.002 or 0.020 mg/kg-d throughout their pregnancies. When male offspring were six months old, they were reported to have increased prostate weights compared with unexposed mice. These results, however, have not been replicated or repeated consistently in similar experiments. Since then, many studies have been conducted that examine low-dose reproductive and developmental effects of BPA.

The Harvard Center for Risk Analysis convened the Harvard Panel to critically review relevant studies regarding low-dose (≤ 5 mg/kg-d) reproductive and developmental effects of BPA. This panel concluded that the low-dose BPA effects were questionable, citing inconsistent responses across rodent species, a lack of adverse effects in two large multi-generational reproductive and developmental studies, and issues related to extrapolation from studies with non-oral routes of administration. Based on the weight of evidence, the Harvard Panel overall “found no consistent affirmative evidence of low-dose BPA effects for any endpoint” (Gray et al., 2004).

In 2006 and 2008, we participated in expert scientific panels that reviewed studies published through July 2008 that had not previously been reviewed by the Harvard Panel, following the same methodology that the Harvard Panel used. Both of our reviews are published in the peer-reviewed journal, *Critical Reviews in Toxicology*, and our findings were consistent with the earlier Harvard study (Goodman et al., 2006; 2008).

Weight-of-Evidence Methods

For our current review, we organized and participated in an expert scientific panel that conducted an updated weight-of-evidence evaluation of reproductive and developmental effects of low doses of BPA. The panel included Gradient scientists Drs. Lorenz Rhomberg and Julie Goodman along with three prominent independent scientists: Professor Raphael J. Witorsch of the Virginia Commonwealth

University School of Medicine, Professor I. Glenn Sipes of the University of Arizona, and Dr. Ernest E. McConnell, formerly of the National Toxicology Program. Drs. Rhomberg, Sipes, and McConnell provided continuity, having also served on the review panel convened by Harvard.

Literature searches were performed to identify relevant studies. Studies were considered to be relevant if they were peer-reviewed, examined reproductive and developmental effects in mammals using whole animals, used doses of ≤ 5 mg/kg-d, were published through July 2008, and were not included in the Harvard Panel review or in our previous review. The Harvard panel review and the Goodman et al. (2006; 2008) reviews examine all published animal studies through July 2008 – regardless of funding source or study design – that examine reproductive or developmental toxicity of BPA at low doses. Thirty-seven BPA studies were identified and critically reviewed, including an important multi-generation study in mice by Tyl and coworkers, and a notable rat study by Howdeshell and coworkers conducted in US Environmental Protection Agency laboratories. Specific endpoints of interest for our review included body and reproductive organ weights, structural changes in organs pertinent to reproduction or development, fetal and newborn characteristics, pubertal characteristics, birth defects, and reproductive function. Many other papers that provided related information from human and animal studies were also reviewed, but we did not comprehensively consider biochemical effects, such as changes in endocrine activity or gene expression, because these findings by themselves are not adverse reproductive or developmental effects.

As in the previous reviews, studies with oral dosing were given more weight than studies with non-oral dosing, although all studies with low doses were considered. The main reason is that the predominant route of human exposure is oral, and orally-administered BPA is subject to extensive ($\geq 99\%$) detoxification by conversion to a non-estrogenic metabolite upon first pass through the intestinal wall and liver. Other routes of exposure, such as injection or implantation, allow BPA to avoid this first-pass effect, making non-oral studies of limited relevance to the assessment

of low-dose human risks.

Our review used a weight-of-evidence approach, which included an examination of the statistical significance of responses, the adequacy of study design and statistical analyses, the presence of dose-related responses, and evidence of modes of chemical action that could result in low-dose reproductive and developmental toxicity. For each endpoint examined, there was an emphasis on the assessment of the consistency of effects within and across studies.

Findings from Animal Studies

Our full report provides a detailed study-by-study review and an overall weight-of-evidence evaluation. Here we summarize our overall findings and compare our conclusions with those of the Harvard Panel and our previous review. A tabular summary of findings from all animal studies reviewed by each panel (total of 110 studies), with results organized by endpoint and dose, is presented in Tables 1 (oral exposure) and 2 (non-oral exposure).

In rat and mouse studies, we found no consistent effects on any of the reproductive or developmental endpoints investigated. Notably, we found no consistent effects on mouse epididymis or prostate weight, the endpoints that initiated the low-dose controversy.

As can be seen in the tables, there are no consistent effects for endpoints with data from multiple studies. For endpoints for which effects have been reported, some effects are consistent with estrogen-like activity but others are not, or are seen in some settings but not others, or with marginal magnitude at a single low dose but no apparent effect at higher doses. Some effects are opposite to what one would expect from an estrogen-like compound. Overall, there is no consistent and repeatable pattern of effects that would be expected if BPA were acting as an estrogen at low doses.

Findings from Human Studies

Recently, the United States Centers for Disease Control and Prevention released data on spot urinary BPA levels in 2,517 participants of the

National Health and Nutrition and Examination Survey. In the form of metabolites, BPA was detected in the urine of nearly 93% of the participants aged six years and older at levels that correspond to mean intakes ranging from 0.07 $\mu\text{g}/\text{kg-d}$ in young children to 0.04 $\mu\text{g}/\text{kg-d}$ in older adults. Levels ranged from non-detectable to a 95th percentile estimate of 0.35 $\mu\text{g}/\text{kg-d}$ in 12- to 19-year-olds. Because urinary BPA represents recent exposure for such a readily and quickly cleared compound, the modest variation seen in the population of spot urine samples indicates that most people have very small exposures on most days.

In a recent review of human biomonitoring studies, urine levels of BPA were found to be consistently low across studies, with substantial agreement among studies conducted in Asia, Europe, and the United States. Estimates of typical total daily BPA intake were consistently found to be a fraction of 0.1 μg per kg of body weight. These values are well below the intake levels set by government bodies that are considered to be without harm during a lifetime and even well below the doses examined in almost all “low-dose” animal studies. Moreover, BPA is entirely excreted by humans in urine, avoiding enterohepatic circulation that occurs extensively in rodents, and resulting in lower human bioavailability of BPA for a given oral intake. In addition, BPA is efficiently converted to a non-estrogenic metabolite after oral exposure, resulting in little or no systemic exposure to BPA itself.

Only a few studies have examined human health outcomes and BPA exposure. Most early studies were conducted with a small number of subjects and used an analytical method that has been reported to be unsuitable for measurement of BPA levels in biological samples. Studies reporting statistically significant effects have major methodological shortcomings and it is not evident whether the findings are biologically meaningful. More recently, several studies with reliable analytical methods found no association between BPA exposure and birth outcomes (e.g., birth weight and length), puberty development in 9-year-old girls, or endometriosis in adult women. No credible human findings of reproductive toxicity at any BPA exposure level have been reported.

Table 1. Outcome by Dose for Rat and Mouse Studies – Oral Administration

Endpoint	Dose (mg/kg-d) Order of Magnitude					
	≤ 10 ⁻⁵	10 ⁻⁴	10 ⁻³	10 ⁻²	10 ⁻¹	1 ⁺
Body weight (absolute weight or weight gain)	00	0000 00	0000000000-++ 0000+00--000		000000000000 00+0--0000	000000 0000- 0000000000
		0	00000000		00000000- 0000000	00+00+0 0+00
MALE ORGAN WEIGHTS						
Cowper's gland			0	0	0	
Epididymis	00	000 -	0000000- 0-0 00	000000000+ 0-00000 00	0000000- 0000 000	00 000 00
Glans penis			0	0	0	
Levator ani and bulbocavernosus muscles			0	0	0	
Preputial gland			00+ 0	000 0	00 0	0
Prostate and ventral prostate	00	000 +	000000+ 00+0 000	00000000+ 0+00-0 0000	000000+ 000 0000	00 0000 000
Seminal vesicles	00	000 0	0000000- 0-0-- 00	0000000000 0000- 00	0000000 00000 000	0 0000 00
Testes	0000	000 -	000000000+ 00-0000- 000	0000000-000+ -00-000 000	00000000 0+0000 000000	000 00000-- 00
FEMALE ORGAN WEIGHTS						
Cervix			0	000	00	
Ovaries		0	000 00 0	00000 000 0	0000 00+ 00	0 0 00
Uterus		0	000 0000 0	00000 0000+ 0	0000 000++ 00-	000 000 000
Vagina			0	000	00	
MALE ORGAN MORPHOLOGY/ CYTOLOGY		--	0 0000000000-00	-0000+ 000000000 000	00+00	0 00++0- 0000
FEMALE ORGAN MORPHOLOGY/ CYTOLOGY			00 000	0-00 0000000	0-0-0++ 0-000000000	000 00 000000000
SPERM CHARACTERISTICS		0000000 --0-0-		000000-000- 00000-+ 00--0-0-000- 0000	00000-000-0000 00000- 00+00+000	000- 0000 00
PERINATAL						
Anogenital distance – females		0	00	000+ 0	000 0	0 0
Anogenital distance – males		0	00 000	0 000+ 0	000 000 0	00 0 0
				00	00000	00

Table 1 (continued). Outcome by Dose for Rat and Mouse Studies – Oral Administration

Endpoint	Dose (mg/kg-d) Order of Magnitude					
	≤ 10 ⁻⁵	10 ⁻⁴	10 ⁻³	10 ⁻²	10 ⁻¹	1†
PUBERTY						
Age at first estrus			- 0	00	00 -	0
Age at vaginal opening		0	0000 0 0	00000 0 0	0000 0 0+0	000
Age at preputial separation	00	000	000 0	00000 0	0000 +0	0
Age at testis descent		0	0 0 0	0 0 0	0 0 +0	0
OTHER REPRO ENDPOINTS						
Estrous cycle (dams/offspring)		00	00 00 0	00 00 0	00 00 -00	00 0 0-0
Female fertility (based on % of pregnant females)	00	0	00 00 0	0000 000 000	000 00 00	0 0 0
Gestation period			0	0	0	0
Litter size		-	00 00	00 00	0 00000	0000 0000
Number of uterine implantations			000 0	000 0	00 0	
Percent fetal/neonatal mortality			0	0	0	
Pup survival		0	00- 0 0	00 00 0	00 0 0	0 0
Sex ratio		0	000 0 0	000 0000 00	00 0 0000	0 00 000
Mean number of zygotes				00	0	
Number of live births			0	00	0	0
Number of stillbirths			0	0	0	0
Percent of animals with resorptions			0+ 0	++ 0	++ 0	0
Percent post-implantation loss			0	+	+	
Oocytes in unfertilized females				00	0	
Male fertility (based on % of pregnant females)			0 0	- 0	- 0	0

Each dose of each study is represented by a “0” if endpoints measured in treated animals were not significantly different from controls, with a “-” if endpoints were significantly lower than controls, and with a “+” if endpoints were significantly higher than controls. Purple symbols indicate studies reviewed by Gray et al. (2004), black symbols indicate studies reviewed by Goodman et al. (2006), and dark blue symbols indicate studies reviewed by Goodman et al. (2008). †Results reported up to 5 mg/kg-d.

Table 2. Outcome by Dose for Rat and Mouse Studies – Non-oral Administration

Endpoint	Dose (mg/kg-d) Order of Magnitude					
	≤ 10 ⁻⁵	10 ⁻⁴	10 ⁻³	10 ⁻²	10 ⁻¹	1 ⁺
Body weight (absolute weight or weight gain)	0	-0 0	00 00	00	00	-0- 00000000000 0-000000
MALE ORGAN WEIGHTS						
Epididymis			0	0000000 00	00000 0	0000 000
Glans penis			0	00	0	
Preputial gland				000	000	0
Prostate and ventral prostate			0	000000 00	0000 0	+0 +
Seminal vesicles			0	00000000 0	0000000 0	000000 0
Testes			0	000000000 000	00000000 0	000000 000
FEMALE ORGAN WEIGHTS						
Ovaries	0	0		000 0	+00 0	00+00 0
Uterus	0 00	0 00 00	0	0 000 00	0+0 000 00	000 0000000 00
Vagina	00	-0				
MALE ORGAN MORPHOLOGY/ CYTOLOGY						
		0	0 00	+0--0 00000000	+----00 0000000	00-0 000000
FEMALE ORGAN MORPHOLOGY/ CYTOLOGY						
	0 +++0000- 00000	0	0 0+0	++++000 0000	0++-+0000 000+++00	00000 000+
SPERM CHARACTERISTICS						
			00	+0-000000000- 000 0	+00- +00000---- 0000	++00-0-0-0-0- -00 0

Table 2 (continued). Outcome by Dose for Rat and Mouse Studies – Non-oral Administration

Endpoint	Dose (mg/kg-d) Order of Magnitude					
	≤ 10 ⁻⁵	10 ⁻⁴	10 ⁻³	10 ⁻²	10 ⁻¹	1 [†]
PERINATAL						
Anogenital distance – females			0	0	0	
			0	00	0	
			0	0000	-0	-0
Anogenital distance – males			0	0	0	
			0	00	0	
			0	000	0-	00
PUBERTY						
Age at mammary gland maturation	+					
Age at vaginal opening	0	00	0	-+	0	00-
			0	0-0	00	00
Age at preputial separation			0	00	0	
				0	0	0
OTHER REPRO ENDPOINTS						
Age at first estrus			0	-		
Estrous cycle (offspring)	+	+	+	+0	+0	0
Female fertility (based on % of pregnant females)			0	000	00	
				0		
Gestation period			0	000	000	00
			0	00	0	
Number of implantations				0	0	00
Number of offspring (live)			0	000	00	0
			00	00	00	0
Number of offspring (total)	0	00	0	00000	0000	000
				00000	00	000
Sex ratio	0	0	0	00000	00000	000
			00	00000	0000	0000
Percent of females giving birth				000	00	000
Percent of time in diestrus					+	
Percent of uterine implantations			0	0	0	0
Percent post-implantation loss			0	0	0	0
Pup survival		-		0	00	0
			0	00	0	00

Each dose of each study is represented by a “0” if endpoints measured in treated animals were not significantly different from controls, with a “-” if endpoints were significantly lower than controls, and with a “+” if endpoints were significantly higher than controls. Purple symbols indicate studies reviewed by Gray et al. (2004), black symbols indicate studies reviewed by Goodman et al. (2006), and dark blue symbols indicate studies reviewed by Goodman et al. (2008). †Results reported up to 5 mg/kg-d.

Finally, circulating endogenous hormone levels are much higher in humans than in rodents during pregnancy. Thus, if an animal and a human received the same dose of BPA, the BPA concentration would pale in comparison to endogenous estrogens in humans but not in animals. This would likely result in a lesser effect (if any) in humans. Given the limited and inconsistent results from human and animal studies and the low exposure levels in humans, it is unlikely that exposure to BPA causes adverse effects on human health.

Comparison with Other Recent Reviews

A number of reviews of the safety and potential health effects of BPA have been conducted recently by various governmental and non-governmental organizations. These include:

- The European Union, in a comprehensive 2008 update to its 2003 risk assessment, stated, “Given the very large margins of safety [for worst-case consumer exposure], there are no concerns for repeated dose toxicity and reproductive toxicity... There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.” The update also reaffirmed the overall no observable adverse effect level (NOAEL) of 50 mg/kg-day (EU, 2003; 2008).
- In a comprehensive assessment of BPA focused on food-contact applications, the European Food Safety Authority established a Tolerable Daily Intake (TDI) of 0.05 mg/kg-day and further concluded that human exposures to BPA are well below the TDI. The conclusions and TDI reported in November 2006 were confirmed in a July 2008 update that focused specifically on infants and children (EFSA, 2006; 2008).
- In November 2007, the Center for the Evaluation of Risks to Human Reproduction (CERHR) released an expert panel report on the reproductive and developmental toxicity of BPA. For potential low-dose effects of BPA, the panel had ‘minimal concern’ for effects on the prostate gland and an earlier age for puberty in females, and ‘some concern’ for neural and behavioral effects. There were no concerns expressed at the highest two levels of the qualitative five-level scale (CERHR, 2007).
- Based on the CERHR expert panel report and new information, the National Toxicology Program (NTP) prepared its report on BPA. Similar to the CERHR panel, NTP expressed ‘minimal concern’ for effects on the mammary gland and an earlier age for puberty in females, ‘some concern’ for effects on the brain, behavior, and the prostate gland, and no concerns at the highest two concern levels. Additional research was recommended to understand whether the concerns identified, which were based on limited and inconclusive evidence, were of any relevance to human health (NTP, 2008).
- In mid-2008, the US Food and Drug Administration released a draft safety assessment on BPA in food-contact applications. Overall, “FDA concludes that an adequate margin of safety exists for BPA at current levels of exposure from food contact uses, for infants and adults.” The lowest margins of safety supporting this conclusion are approximately 2,000 and 27,000 for infants and adults, which indicates that exposure to BPA is well below a level that could cause harm. The draft assessment will be peer-reviewed before finalization, which is expected in late 2008 (US FDA, 2008).
- In early 2008, Health Canada released a draft screening risk assessment of BPA. Overall, it stated “In general, most Canadians are exposed to very low levels of bisphenol A and it does not pose a significant health risk.” The lowest margins of safety supporting this conclusion are approximately 1,200 for infants and 2,200 for adults, indicating that human exposure to BPA, including infants and children, is below levels that may pose a risk. The assessment is expected to be finalized in October 2008 (Health Canada, 2008).

- A review of the health effects of BPA, published by NSF International in early 2008, established a NOAEL of 5 mg/kg-day. From the NOAEL, a Reference Dose of 0.016 mg/kg-day was established (Willhite et al., 2008).
- A group of scientists funded by the National Institute of Environmental Health Sciences, the National Institute of Dental and Craniofacial Research, and Commonwealth, convened at Chapel Hill, NC in November 2006. The panel stated, “We consider it likely, but requiring further confirmation, that adult exposure to BPA affects the brain, the female reproductive system [i.e., mammary gland], and the immune system, and that developmental effects occur in the female reproductive system.” The panel also stated, “There is extensive evidence that BPA impacts the reproductive system in male rats and mice, although there appear to be species and strain differences in the sensitivity of specific outcomes to BPA,” and “There is a significant amount of evidence that adult exposure to BPA has adverse consequences for testicular function in male rats and mice” (vom Saal, 2007).
- Several older reviews were conducted by government bodies, including the European Union Scientific Committee on Food (SCF, 2002); the European Union Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2002); the Japanese National Institute of Advanced Industrial Science and Technology (AIST, 2005); and NTP (NTP, 2001). Thus far, none have concluded that adverse effects reported to occur below the traditionally defined NOAEL of 5 mg/kg-d are sufficiently plausible to support government action.

In short, the weight-of-evidence conclusions of our review regarding low-dose reproductive and developmental toxicity of BPA, which confirm and reinforce the conclusions in our earlier reviews, are notably at odds with the conclusions of the Chapel Hill panel. In contrast, our conclusions are substantially in accord with the findings of all the other agencies, which stressed that the clear and

reproducible estrogen-like effects of BPA appear to be confined to quite high doses, with no effects evident at 5 mg/kg-d or possibly higher. All cited the lack of effects in several large multi-generation studies, in which animals were exposed during all life stages, as particularly telling. All have noted the lack of consistency and reproducibility of reported effects on reproductive function or on the structure of reproductive tract organs at lower doses, and, in view of their weighing of the evidence, none has given credence to the hypothesis that doses well below the 5 mg/kg-d range should be regarded as able to disrupt reproductive function or pose a risk to reproductive health in humans.

Conclusions

Overall, our conclusions on specific reproductive and developmental endpoints, and on the weight of evidence for low-dose effects in rodents in general, are consistent with our two previous reviews and those of many other scientists and agencies. Although some statistically significant findings in rodents exist at BPA doses \leq 5 mg/kg-d, they are generally countered by more numerous studies showing no effect for the same or similar reproductive and developmental endpoints. No effect is marked or consistent across studies, doses, or time points. We found little scientific support for the assertion that very low oral doses of BPA are capable of disrupting the development or functioning of the reproductive system in people in the general population.

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