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Bisphenol A:
Hazard and health risk assessment of a food contact material

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Uses of Bisphenol A

- Component in polycarbonates and in epoxy phenolic resins
- Both materials used in food contact

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Issues in the request for reassessment of Bisphenol A

- Some studies applying low doses of bisphenol A (from ng to µg/kg bw/day) given during gestation report a number of effects in offspring
- All available GLP- and guideline studies using low doses of Bisphenol A are unable to confirm low-dose effects

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Previous evaluations of Bisphenol A

- Scientific Committee on Food, 2002
  - NOAEL of 5 mg/kg b.w./day from 3-generation reproductive toxicity study in rats
  - TDI of 10 µg/kg b.w./day using safety factor of 500

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Previous evaluations of Bisphenol A

- European Union Risk Assessment Report, 2002

Table 4.32 Conclusions for reproductive effects and liver toxicity, for combined exposure scenarios

Exposure		Effect (systemic)					
		Reproductive effects NOAEL 50 mg/kg/day				Liver LOAEL 120 mg/kg/day	
Source	Value (mg/kg/day)	Effects on fertility		Effects on development			
		MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
Regional	$9 \cdot 10^{-3}$	5,500	ii	5,500	i	$1 \cdot 10^{4}$	ii
Local	0.069	725	ii	725	i	1,700	ii

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Exposure assessment for Bisphenol A from food

- Based on bisphenol A migration, content in food and food consumption patterns
  - up to 13 µg/kg b.w./day (6 month infant) fed with PC-bottle and commercial foods
- Based on biomonitoring of bisphenol A glucuronide excretion
  - 0.17 µg/kg b.w./day for adult

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Mouse, 2-generation reproductive toxicity study, Tyl et al., 2007

ABSTRACT

A 2-generation study (OECD Test Guideline 416), incorporating estrogen sensitive endpoints, was conducted to evaluate the potential reproductive/developmental effects of BPA in mice. The following groups (28 parental mice/sex/group) were: 6 BPA groups with doses from ~0.003 to 600 mg/kg/day (mkd; 0.018-3500 ppm); 17-β-estradiol (E2) positive control (0.08 mkd; 0.5 ppm); 2 negative control groups; 1 unbred F1 male/litter/group exposed concurrently with the F1 parental males. The F0 generation

of delayed development. At **300 ppm BPA (~55 mkd)**; the only treatment-related effect was an increased incidence of centrilobular hepatocyte hypertrophy in adults (both sexes). The NOEL was **30 ppm BPA (~5.5 mkd)** for systemic toxicity and **300 ppm BPA** for developmental toxicity. There were no reproductive effects at any BPA dose.

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Other toxicity studies

- Studies reporting low-dose effects
  - Often low numbers of animals per group
  - Often only one dose used or effect only at one dose
  - Adversity of effects reported?
  - Consistency and reproducibility

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Summary of low dose effects

- Goodman et al., Crit. Rev. Toxicol., 36(7), 2006

findings are consistent with the Harvard study: some statistically significant findings in rats and mice exist but they are generally countered by more numerous studies showing no effect for similar endpoints. No effect is marked or consistent across species, doses, and time points. Some mouse studies report morphological changes in testes and sperm and some non-oral mouse studies report morphological changes in female reproductive organs. Owing to lack of first-pass metabolism, results from non-oral studies are of limited relevance to oral human exposure. Human biomonitoring indicates exposures lower than the "low" doses in the reviewed animal studies. Reports of human health impact are very limited and inconsistent. Taken together, 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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New TDI for Bisphenol A

Using safety factor of 100

- Large number of GLP- and guideline studies without low dose effects
- Differences in toxicokinetics between humans and rodents with very low blood concentrations of free Bisphenol A in humans
- Mice are very sensitive to estrogens due to physiology of gestation

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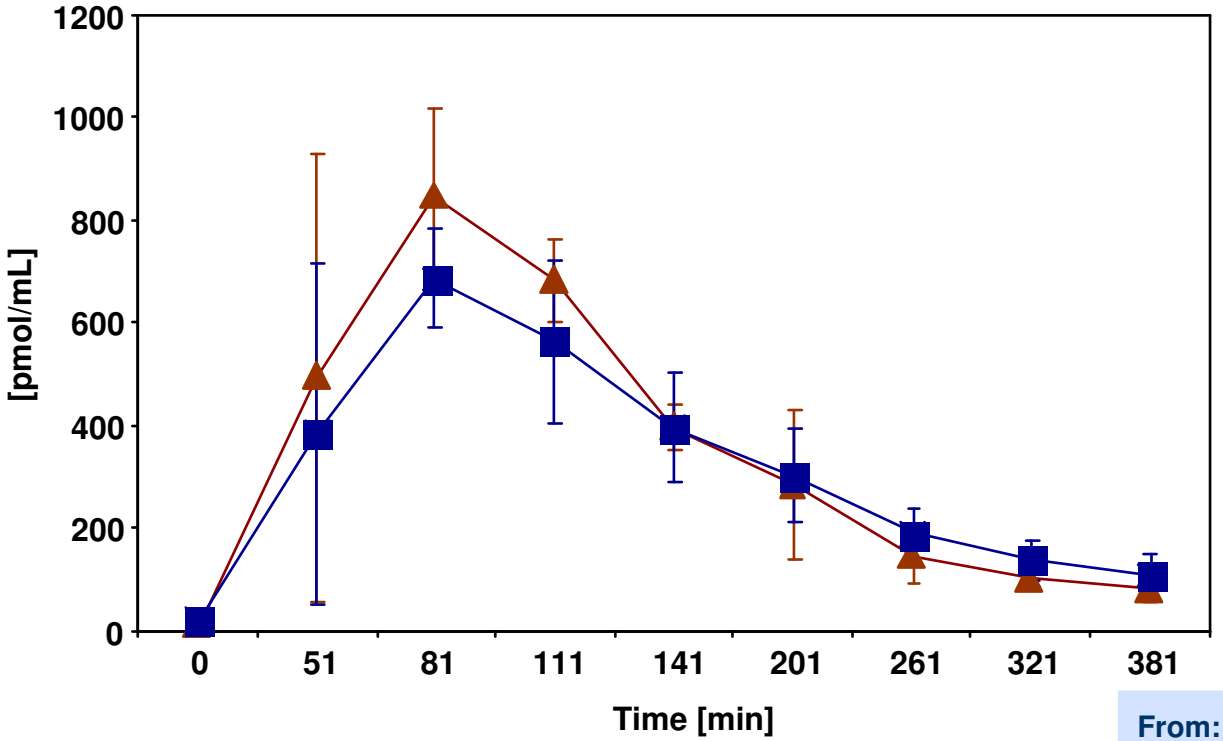
Blood concentrations in four male subjects after oral administration of 5 mg d_{16}-bisphenol A



(♦) d_{16}-bisphenol A glucuronide determined by LC-MS/MS (mean ± SD)

(■) total d_{16}-bisphenol A determined by GC/MS after glucuronidase treatment

From: Voelkel et al., Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. *Chem Res Toxicol.* (2002) 15:1281-1287.

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Conclusions

- Bisphenol A exposures from food, even when using a conservative exposure assessment, are well below the conservative TDI