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EDITORIAL

Highlight report: the bisphenol A controversy

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Over the last 10 years, the scientific and journalistic controversy over whether bisphenol A (BPA) causes adverse effects in humans has attracted a lot of attention. Despite more than 5,000 published articles on BPA, the never-ending and sometimes emotional debate on possible human health hazards remains open. To give a well-founded and balanced resolution of the dead-locked situation, the Advisory Committee of the German Society of Toxicology has published a comprehensive review discussing key questions of the controversy on BPA (Hengstler et al. 2011). The Advisory Committee is elected by the members of the German Society of Toxicology; the largest toxicological Society in Europe with more than 1,000 members. Since BPA (Drozdz et al. 2010; Yang et al. 2009; Schmidt et al. 2006; Moors et al. 2006) and endocrine disruption (Romano et al. 2010; Umano et al. 2010, 2009; Wang et al. 2010; Asp et al. 2009) represent cutting-edge topics in our journal, we have summarized some key messages of the Advisory Committee (Table 1). The review is a must-read for everybody interested in the evaluation of the health hazards caused by exposure to BPA.

The review article of the Advisory Committee demonstrates again that with more than 5,000 published studies on BPA, an excellent database is available, which is better than for many other potentially more critical chemicals. In this context, a "funding bias" has recently been addressed (Bolt 2011). BPA appears to represent a typical example of a compound with a huge discrepancy between perceived and real toxicological risk.

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References

Asp V, Lindström V, Olsson JA, Bergström U, Brandt I (2009) Cytotoxicity and decreased corticosterone production in adrenocortical Y-1 cells by 3-methylsulfonyl-DDE and structurally related molecules. Arch Toxicol 83(4):389–396

Bolt HM (2011) Publications in toxicology: the current situation. Arch Toxicol 85(1):1–2

Drozdz K, Wysokinski D, Krupa R, Wozniak K (2010) Bisphenol A-glycidyl methacrylate induces a broad spectrum of DNA damage in human lymphocytes. Arch Toxicol 29 Sept 2010. (Epub ahead of print)

Hengstler JG, Foth H, Gebel T, Kramer PJ, Lilienblum W, Schweinfurth H, Völkel W, Wollin KM, Gundert-Remy U (2011) Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. Crit Rev Toxicol 41(4):263–291. Review

Melzer D, Galloway T (2011) Bisphenol a and adult disease: making sense of fragmentary data and competing inferences. Ann Intern Med 155(6):392–394

Moors S, Diel P, Degen GH (2006) Toxicokinetics of bisphenol A in pregnant DA/Han rats after single i.v. application. Arch Toxicol 80(10):647–655

Romano RM, Romano MA, Bernardi MM, Furtado PV, Oliveira CA (2010) Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. Arch Toxicol 84(4):309–317

Schmidt S, Degen GH, Seibel J, Hertrampf T, Vollmer G, Diel P (2006) Hormonal activity of combinations of genistein, bisphenol A and 17beta-estradiol in the female Wistar rat. Arch Toxicol 80(12):839–845

Umano T, Shiraishi K, Minobe Y, Yamasaki K (2009) Uterotrophic assay, Hershberger assay, and subacute oral toxicity study of 3-amino-1,2,4-triazole based on the Organization for Economic Co-operation and Development draft protocols. Arch Toxicol 83(5):459–467

Table 1 Key messages of the recently published comprehensive review article of the Advisory Committee of the German Society of Toxicology (Hengstler et al. 2011)

A tolerable daily intake value (TDI) of 50 μg/kg body weight/day has been established by the European Food Safety Authority (EFSA). The TDI is based on an overall no observed adverse effect level (NOAEL) of 5 mg BPA/kg bw/day and an uncertainty factor of 100
The NOAEL is mainly based on body weight changes in two- and three-generation studies in rats and mice. Recently, the latter studies have been criticized. However, the Advisory Committee concluded that the criticism was not justified. One of the published points of critique was that too many animals per group have been tested. This is an unusual argument, because if the study was overpowered (which in fact is not the case), this would not lead to incorrect conclusions
The Advisory Committee addressed the question whether oral doses of BPA below 5 mg/kg bw/day cause adverse health effects in laboratory animals. Similar to previous expert panels, the Advisory Committee concluded that it has repeatedly been impossible to reproduce the initial positive effects. Furthermore, recently published large and well-designed studies were negative for doses below 5 mg/kg bw/day
Published toxicokinetic studies have shown that orally administered BPA leads to maximum concentrations approximately 80 min post-administration to human volunteers. The half-life is less than 2 h. Importantly, the administered doses were completely recovered in urine as BPA-glucuronide. This is relevant for biomonitoring and allows precise exposure assessments
Using data on urinary concentrations of BPA, total daily doses of BPA well below 1 μg/kg bw/day have been derived for the general population. This is clearly below the TDI of 50 μg/kg bw/day
The Advisory Committee carefully considered if there are susceptible subpopulations. Newborns are at higher systemic BPA exposure due to lower glucuronidation activity. Pharmacokinetic modelling considering the reduced glucuronidation capacity and the already established BPA sulfation pathway concluded that threefold higher plasma concentrations can be expected in newborns and 1.6-fold higher concentrations in 3-month-old children compared to adults. Using worst-case estimations, an exposure of 11 μg/kg bw/day BPA has been derived for a 3-month infant who was fed with a polycarbonate bottle. It should also be considered that the TDI has been derived using an uncertainty factor of 100, including 10 for interspecies differences. This can be considered conservative as there is no evidence that humans are more susceptible to BPA than rodents. Specific exposure conditions are known for patients of neonatal intensive care units, where exposure to BPA may exceed the TDI although this occurs for only a limited period of time
Besides its estrogenic activity, BPA also activates other receptors, usually at higher concentrations. This is not surprising because hormonally active chemicals and also drugs usually interact with several receptors with different affinities. It should be noted that current risk assessment is based on a large number of adverse end points in animal experiments, including contributions by mechanisms other than activation of estrogen receptors, where relevant
Epidemiological studies have reported associations between urinary BPA levels and diabetes, cardiovascular disease, liver disease, semen quality, serum testosterone, estradiol sex hormone-binding globulin, and further end points. However, it is difficult to exclude unmeasured confounding factors in such studies (Melzer and Galloway 2011), and association studies can at best raise hypotheses but not demonstrate causal relationships

Umano T, Miyata K, Minobe Y, Yamasaki K (2010) Enhanced OECD TG 407 in detection of endocrine-mediated effects of 4,4'-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol. Arch Toxicol 84(3):175–182

Wang H, Wang Q, Zhao XF, Liu P, Meng XH, Yu T, Ji YL, Zhang H, Zhang C, Zhang Y, Xu DX (2010) Cypermethrin exposure during puberty disrupts testosterone synthesis via downregulating StAR in mouse testes. Arch Toxicol 84(1):53–61. Erratum in: Arch Toxicol. 2010 48(1):83

Yang M, Ryu JH, Jeon R, Kang D, Yoo KY (2009) Effects of bisphenol A on breast cancer and its risk factors. Arch Toxicol 83(3):281–285