Chemistry & Industry — 4 April 2005 Page 14 - 15

Comment

Low-dose BPA: confirmed by extensive literature

Frederick S. vom Saal

The Association of Plastic Manufacturers adopted the tobacco Industry's 'sound science' strategy to deny findings about low doses of BPA, according to Frederick S vom Saal of division of biological sciences, at the University of Missouri, Columbia, Missouri

BPA dose: Bisphenol A (BPA) is the monomer used to manufacture polycarbonate plastic, the resin lining of cans, and other products, with global capacity in excess of 6.4bn pounds (2.9m tonnes) annually. 'Low doses' are lower than the doses used in toxicological studies to examine the health effects of chemicals for regulatory purposes. For BPA, this is 50mg/kg/day,2 and in the US this dose remains as the 'lowest adverse effect level' or LOAEL. This presumed LOAEL value (based on studies published in the 1980s) is important in that it was used to estimate a 'safe' or 'reference dose' for BPA in humans. The reference dose is supposed to be at least 100-fold lower than a dose that causes no adverse effects (the NOAEL) in animals. A very large number of studies published over the past eight years now contradict these prior assumptions.

There is a comprehensive document containing all BPA references at the author's website: http://endocrinedisruptors.missouri.edu/vomsaal/vomsaal.html

---

THE Association of Plastics Manufacturer's (APM) attempt to discredit scientific findings that threaten corporate products by invoking the concept of 'sound science' has failed in the past. The 'sound science' programme was a central part of the now discredited campaign by the tobacco industry to convince the public that secondhand smoke was safe. And research by independent scientists showing that secondhand smoke was a human health hazard was attacked as not being 'sound science' to block attempts to ban smoking in public places.1 Analysis of tobacco industry documents made public through litigation reveals that individuals and groups involved in the tobacco industry disinformation campaign are now involved in the campaign to promote chemicals such as Bisphenol A (BPA) as safe.1

The APM should be concerned that the low-dose issue could lead to 'a breakdown in trust in the science behind chemicals' by the public. Their recent commentary in *C&I* assured readers that 'extensive research conducted over more than 50 years provides strong reassurance that there is no basis for human health concerns from exposure to low doses of BPA'.2 A comprehensive review of published findings on the health effects of low doses of BPA reveals the opposite to be true.

The misinformation in the APM's commentary reveals an interesting tactic, which is to deny the published literature on low-dose effects of BPA, most of which was generated in the past three years. Acknowledging this research would mean having to explain how so many independent scientists found such a vast array of adverse effects. The APM has good reason to be concerned about a breakdown in trust in corporate-sponsored research, which for low-dose effects of BPA is uniformly negative, in contrast with the very large number of studies by independent scientists that find positive effects. The APM commentary, based on the premise that this huge scientific literature does not exist, adds fuel to the growing mistrust of industry. It appears that the APM assumed that *C&I* readers would not conduct a literature search and discover the truth.

Of 115 publications on low-dose effects (below the presumed lowest adverse effect level or LOAEL) of BPA in experimental animals accessed by a PubMed search at the end of 2004, 94 reported significant low-dose effects, and 31 of these reported significant effects below the predicted 'safe' dose.3

A critical issue is whether there is evidence of widespread human exposure to BPA at doses shown to cause adverse effects in animals. Because the ester bonds in BPA-based polymers are subject to hydrolysis, leaching of BPA has led to widespread human exposure; 95% of people in a recent study conducted by the US Centers for Disease Control (CDC) had measurable amounts of BPA in their urine.4 The prevalence and levels of BPA in the CDC study are consistent with blood and tissue levels of BPA detected in 100% of pregnant women and their foetuses in Germany and Japan.5,6 These findings suggest that humans are continuously exposed to BPA. Furthermore, these exposures result in blood levels of parent (unconjugated) BPA in humans that are above levels that cause adverse effects in mice.7

The APM implied that concern about exposure to low doses of BPA was based on 'a few small exploratory studies conducted with a limited number of animals'. However, among the 94 low-dose BPA studies showing positive results, our study in *Nature* reveals that feeding pregnant mice a very low dose of 2.4μg/kg/day BPA (20-times lower than the presumed 'safe' dose) for seven days has detrimental effects on their female offspring. 8 Control mice were fed just the vehicle, and a total of 186 females from 21 litters were examined per treatment group. Exposure even at this very low dose during foetal life significantly increased postnatal growth rate and accelerated puberty. This maternal dose of BPA results in levels of parent (unconjugated)

BPA in mouse foetuses,7 that are below levels found in human foetuses.5,6 Our findings have been replicated in a number of published studies by other investigators.3

The APM also said that large-scale, well-conducted research sponsored by both industry and government agencies, has found no evidence of health effects at doses relevant to human exposure. While none of the 11 industry funded studies published reported positive effects of low doses of BPA, in sharp contrast, 94 of the 104 (90%) government-funded studies reported positive effects of BPA at the same doses. The APM cites a recently published report funded by the American Plastics Council (APC) and prepared by the Harvard Center for Risk Analysis (HCRA). The report concluded that there was little evidence for effects of BPA in animals within the range of human exposure from products made from BPA. However, this report reviewed only 19 of the available published low-dose BPA studies as of April 2002, and they delayed releasing the report for two and a half years. The characterisation of this already outdated report as a 'comprehensive review' is clearly misleading.

The European Union's 2003 risk assessment for BPA relied on a literature search conducted in 1998, at which time there were only five publications showing low-dose effects of BPA.9 Since 1998, there have been 89 published articles reporting significant effects in animals caused by exposure to low doses of BPA. There were effects on rate of growth and sexual maturation, hormone levels in blood, reproductive organ function, fertility, immune function, enzyme activity, brain structure, brain chemistry and behaviour. A new risk assessment for BPA that includes these extensive new findings is now needed.

A single 1936 paper by Dodds, examining only one high dose of BPA does not justify the APM's statement that this study showed BPA to be a weak oestrogen. The further comment that 'only significantly higher doses of BPA — much higher than any realistic human exposure — have been shown to cause oestrogenic-type activity,' is not supported by the literature. There is now a large literature using cell culture demonstrating that BPA alters cell function by interacting with oestrogen receptors associated with specific genes. BPA also disrupts cell function by activating kinase cascades regulated by receptors associated with the cell membrane; this has been reported to occur at doses of BPA as low as 0.23 parts per trillion (ppt) in rat pituitary cells, similar to the effects caused by the same dose of oestradiol.10 BPA at the lowest dose tested (23ppt) also stimulated human breast cancer cells via a similar mechanism.11

The APM neglected to point out that the oestrogenresponse systems that mediate low-dose effects of BPA evolved to be regulated by very low concentrations of oestradiol (below one part per trillion) and to have tremendous amplifying capacity.

The APM also stated that: 'The fundamental principle of toxicology assumes that biological effects increase as the dose increases.' For BPA alone, there are 11 published studies reporting that a specific effect seen at very low doses can be reduced or disappear altogether at much higher doses.3

In rat pituitary cells, stimulation of calcium influx occurred at 0.23ppt BPA. The maximum response occurred at 230ppt BPA, but at 2300ppt BPA the response declined by about 50% relative to the response at 230ppt BPA.10 The APM ignored these findings and stated: 'The "low-dose hypothesis" asserts that health effects may be observed at extremely low doses, while higher doses do not have any effects.' This is misleading in that it is well recognised that as the dose of a hormone (or hormone-mimicking chemical) increases from very low to much higher doses, entirely different arrays of genes are activated and inhibited, leading to a unique set of responses at low and high doses.12 This is quite different to stating that the expectation is no effect at high doses. It is also well known that high doses of hormones can 'down-regulate' their receptors, and this phenomenon contributes to inverted-U dose–response curves.13 Thus, low-dose hormonal effects of BPA and other chemicals cannot be assessed by conducting studies that only examine very high toxic doses, which is discussed in detail elsewhere.13 Non-monotonic (inverted-U) dose–response curves are common in the endocrine literature, and this phenomenon is a consideration in the use of hormonally active drugs by physicians.

The APM's statement, that a specific effect that occurs at a high dose must always be greater in magnitude than the effect level at lower doses, would be to an endocrinologist equivalent to someone arguing with an astronaut that the Earth is flat.

Anyone interested in the facts can independently verify that there is an extensive literature reporting adverse effects of BPA in animals at doses, lower than the current reference dose; a high rate of leaching of BPA from food and beverage containers, leading to widespread human exposure; and, evidence that the median BPA level in human adult and fetal blood is higher than the level that causes adverse effects in mice. These published findings should be of concern to anyone interested in public health.

References

1 *Amer J Public Health* 2001, **91**, 1749
2 *C&I* 2005, **5**, 14
3 http://endocrinedisruptors.missouri.edu/vomsaal/vomsaal.html
4 *Environ Health Perspect* 2005, Online: 20 December 2004
5 *Human Reprod* 2002, **17**, 2839
6 *Environ Health Perspect* 2002, **110**, A703
7 *Environ Health Perspect* 2002, **111**, 309
8 K Howdeshell, A Hotchkiss, K Thayer, J Vandenbergh & F vom Saal, Exposure to bisphenol A advances puberty, *Nature* 1999, **401**, 763
9 European Chemicals Bureau, Bisphenol A: European Union risk assessment report (CAS no: 80-05-7) volume 37, Office for Official Publications of the European Communities, EINECS no: 201-245-8, 2003
10 *Environ Health Perspect* 2005, Online: 14 January 2005
11 *Mol Cell Endocrinol* 2005, **230**, 23
12 *Proc Natl Acad Sci USA* 2003, **100**, 13994
13 *Environ Health Perspect* 2003, **111**, 904