Breast Cancer UK response to the Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs – Part 2: health risks

Introduction

Breast Cancer UK maintains that there is a significant amount of scientific evidence that shows that even low level exposure to the chemical Bisphenol A (BPA) has an adverse effect on the development of breast tissue and that dietary exposure is the main route of human exposure to BPA.

Whilst we welcome The European Food Safety Authority's (EFSA) acknowledgement that the chemical, BPA, is "likely" to have effects on the mammary gland, we are very concerned that its overall conclusion is that the health concern for BPA is low at current levels of exposure (line 25-26).

Numerous scientific studies have come to light in recent years which show that BPA has the ability to transform normal breast cells into cells of a more cancerous or overall malignant nature, that it can trigger DNA strand breaks, interfere with cell division and interfere with chemotherapy, making it less effective against breast cancers.

EFSA's decision to temporarily reduce the so-called Tolerable Daily Intakes (TDIs) for BPA at best draws a veil of safety over the chemical but at worst could be used to justify its continued use in food and drinks packaging and other products.

Scientific evidence suggests that BPA has an adverse effect on the mammary gland

Laboratory experiments show that BPA has the ability to transform normal breast cells into cells of a more cancerous or overall malignant nature[1,2,3]. Animal studies show that exposure to BPA in the womb, or during early life, can increase breast density, cell growth and increase susceptibility to tumours[4,5,6]. BPA has also been found to trigger DNA strand breaks and to interfere with cell division[7,8] and it has been found to interfere with chemotherapy, making it less effective against breast cancers[9].

1 Fernandez, M. F., J. P. Arrebola, et al. (2007). 'Bisphenol-A and chlorinated derivatives in adipose tissue of women.' Reprod Toxicol 24(2): 259-264.
2 Fernandez, S, V et al. (2012). 'Expression and DNA methylation changes in human breast epithelial cells after bisphenol A (BPA) exposure.' Int J Oncol. 2012 July; 41(1): 369–377. Published online 2012 April 20. doi:10.3892/ijo.2012.1444.
3 Goodson, W. H., 3rd, M. G. Luciani, et al. (2011). 'Activation of the mTOR pathway by low levels of xenoestrogens in breast epithelial cells from high-risk women.' Carcinogenesis 32(11): 1724-1733.
4 Tharp, A. P., M. V. Maffini, et al. (2012). 'Bisphenol A alters the development of the rhesus monkey mammary gland.' Proc Natl Acad Sci U S A 109(21): 8190-8195.
5 Jenkins, et al. (2012). 'Endocrine-active chemicals in mammary cancer causation and prevention.' Steroid Biochem Mol Biol.
6 Durando et al. (2011). 'Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling rats.' J Steroid Biochem Mol Biol. 2011 Oct; 127(1-2):35-43. Epub 2011 Apr 14.
7 Iso, T., T. Watanabe, et al. (2006). 'DNA damage caused by bisphenol A and estradiol through estrogenic activity.' Biol Pharm Bull 29(2): 206-210.

As well as being linked to breast cancer, BPA is also linked to a range of other conditions including obesity[10], heart disease and cardiovascular problems[11,12], infertility[13], diabetes[14] and recurrent miscarriage[15]. It was due to concerns about the harmfulness of the exposure of infants to BPA that the European Commission decided to ban its use in baby bottles in March 2011[16]. Whilst this overdue step was welcome, it did nothing to reduce the exposure of pregnant women and other young children to the harmful effects of BPA.

Whilst proponents of BPA claim that it is safe to use because human levels of exposure are low, evidence suggests that BPA is harmful even at very low levels of exposure[17]. BPA also gives rise to 'non monotonic' dose responses, which means that it has varying effects at different doses. Therefore, the application of so-called Tolerable Daily Intakes (TDIs)[18] of BPA, predicted from higher doses, to permit its continued use in products may be unsafe for the consumer.

The EFSA Review

EFSA have asserted that they have carried out a "thorough and extensive literature search" and reviewed studies released in recent years which have examined the various effects of BPA on different ends points. Using a 'Weight of Evidence Approach', EFSA concluded that BPA is "likely" to have an effect on the mammary gland, liver and kidney, but is "unlikely" to have cardiovascular or metabolic effects or be carcinogenic. Moreover EFSA's draft opinion concluds that current levels of exposure fall below thresholds considered to be safe and whilst recommending a temporary reduction in the Tolerable Daily Intake (TDI) to 5µg per kilogram of body weight per day have asserted that current levels of exposure fall below this level in any case.

BPA effects on the Mammary Gland (lines 5499-5670)

Breast Cancer UK has significant and fundamental concerns relating to EFSA's dismissal of evidence and research relating to low dose exposures and non monotonic dose response curves (e.g lines 989/1023/1048). History teaches us that a "lack of consensus" as to the "relevance" or "existence" of an effect does not necessarily make it less likely. However, it is particularly concerning given mounting evidence that BPA has been found in numerous studies to cause adverse effects on the development of the mammary gland at doses below EFSA's identified benchmark.

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8 George, O., B. K. Bryant, et al. (2008). 'Bisphenol A directly targets tubulin to disrupt spindle organisation in embryonic and somatic cells.' ASC Chemical Biology.

9 LaPensee, E. W., C. R. LaPensee, et al. (2010). 'Bisphenol A and estradiol are equipotent in antagonizing cisplatin-induced cytotoxicity in breast cancer cells.' Cancer Lett 290(2): 167-173.

10 Shankar, A., and Teppala, Srinivas. (2012). "Urinary Bisphenol A and Hypertension in a Multiethnic sample of US Adults." Journal of Environmental and Public Health 2012: 5.

11 Melzer, D., N. J. Osborne, et al. (2012). "Urinary bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women." Circulation 125(12): 1482-1490.

12 Shankar, A., S. Teppala, et al. (2012). "Bisphenol A and Peripheral Arterial Disease: Results from the NHANES." Environ Health Perspect.

13 Salian, S., Doshi, T. and Vanage G. (2011). "Perinatal exposure of rats to Bisphenol A affects fertility of male offspring--an overview." Reprod Toxicol 3: 359-362.

14 Shankar, A. a. T., S. (2011). "Relationship between urinary bisphenol A levels and diabetes mellitus." J Clin Endocrinol Metab 96(12): 3822-3826.

15 Mayumi, S.-O., Yasuhiko, Ozaki., Shin-ichi, Sonta., Tsunehisa, Makino., and Kaoru, Suzumori. (2005). "Exposure to bisphenol A is associated with recurrent miscarriage." Human Reproduction 20(8): 2325-2329.

16 European Commission (2011) 'Ban of Bisphenol A in baby bottle' Health & Consumer Voice - March - 2011 Edition http://ec.europa.eu/dgs/health_consumer/dyna/consumervoice/create_cv.cfm?cv_id=716

17 Vandenberg, L.N. Colbourn, T. et al. (2012). Op.cit.,

18 The Tolerable Daily Intake (TDI) is an estimate of the amount of a substance expressed on a body weight basis, which can be ingested daily over a lifetime without appreciable risk.

EFSA cites a number of studies (e.g lines 5372, 5499) including one examining the non-human primate (Tharp et al 2012) (line 5576) which show the developmental effects of low dose exposures to BPA on the morphology of the mammary gland but finds them either irrelevant, inappropriate or cannot agree with the conclusions. We find this eagerness to dismiss independent studies which have found low dose effects or non monotonic dose response curves extremely worrying.

A recent study by Vandenberg using a weight-of-evidence approach (Vandenberg 2012) found strong support for low dose effects. Low doses were found to alter mammary gland morphology at many life stages, and other studies revealed that low doses increase the incidence of preneoplastic and neoplastic lesions, as well as increase the response to chemical carcinogens. ANSES concluded that these studies indicated "proven" effects of BPA on the mammary gland. The draft opinion itself identifies numerous studies which show effects at or below 500 micrograms/kg/day (reviewed in EFSA's table 15; line 5934). Therefore, we find it difficult to understand how and why such studies can be ignored without robust scientific reasoning in this draft opinion.

Moreover such a general dismissal can do nothing to help protect future generations from vulnerability to diseases like breast cancer.

Dismissal of specific studies

Breast Cancer UK has concerns that EFSA appears to criticise and/or dismiss a number of individual studies erroneously. As a result some important studies have been excluded from the draft opinion. This eagerness to dismiss or criticize certain data is problematic and potentially serves to undermine the credibility of the "weight of evidence" approach that EFSA has set out to achieve.

- For example, in the review of Tang et al. (line 18451) EFSA identifies that qPCR data were collected from resorbed embryos (18466-18467) but in fact this endpoint was not included in that study.

- EFSA criticize and dismiss a longitudinal epidemiology study (D Melzer, line 14090) because the urine collection bottle material was not specified (line 14123). Whilst BPA can migrate, it is irrelevant to the findings of the study unless migration levels were different in the individuals studied – which would be unlikely.

- EFSA criticise another study (line 15599) Angle et al (2013) as having discrepancies and "insufficient study reporting" (line 15623) whereas the study has some extremely detailed statistical analysis.

EFSA has set out to use a weight of evidence approach but its dismissal of well conducted, independent studies serves to undermine the credibility of its conclusions.

Toxicokinetics

Part 1 of EFSA's investigation into human exposure to BPA relied in Breast Cancer UK's opinion too heavily on a single study by Teeguarden et al. 2011 (Line 8961). Similarly, for reasons that continue to remain unclear, the second part of EFSA's investigation also use this study as a benchmark for other data to the extent that other studies are dismissed if they do not match the results. It appears that the Teeguarden study endorses a view (Line 9006) already held by EFSA even though it does not replicate levels of BPA generally found in members of the public by independent bio monitoring studies.

Teeguarden's 2011 study has been heavily criticized as being flawed (vom Saal et al. 2012). For example, the food and drink used in the study were not tested for BPA, participants were isolated from other sources of exposure to BPA and large amounts of water were included in the diet, with no method to account for dilution (yet and care was taken to ensure that the water did not contain BPA). Only 49% of urine samples collected from these individuals between breakfast and lunch and only 74% of the 385 urine samples collected throughout the day had detectable levels of BPA which is a marked difference from numerous bio monitoring data which identify that over 90% of the US population have measurable levels of BPA in their urine.

There are now more than 40 studies that have examined BPA and/or BPA metabolites in human blood/serum. Some of these have gone to extensive lengths to control for contamination. Many of these studies have measured BPA and/or BPA metabolites in some, but not all, samples, typically at levels below 0.5 ng/ml.

It seems unscientific and alarming that EFSA appears once again to rely on one single study which has been criticised as being flawed in order to dismiss other independent bio monitoring studies.

Conclusions

EFSA's "thorough and extensive literature search" (line 78) and lengthy review of the studies that examine adverse health effects of BPA belies the fact that in the end many of the studies reviewed by EFSA were dismissed and ultimately excluded from their final opinion that current levels of exposure to BPA are safe.

Breast Cancer UK fundamentally disagree that current levels of exposure to BPA are safe based on mounting scientific evidence and independent studies which show that BPA has low dose effects on the mammary gland and has been found in numerous scientific studies to have non monotonic effects.

This draft opinion from EFSA is quick to dismiss independent studies which must necessarily undermine the credibility of its conclusions. In its report EFSA has ignored or dismissed evidence which shows that BPA gives rise to 'non monotonic' dose responses and is quick to dismiss much of the evidence which points to low dose effects. As such Breast Cancer UK strongly maintain that the application of TDIs of BPA, predicted from higher doses to permit its continued use in products, is likely to be unsafe for the consumer.