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: exposure assessment

Background

On the 25th July, the European Food Safety Authority (EFSA) launched an open consultation on a draft assessment of consumer exposure to BPA performed by the EFSA's Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel). This was the Authority's first review of exposure to BPA since 2006 and the first to cover both dietary and non-dietary sources. Data from scientific literature was collected and considered in the exposure assessment.

EFSA will publicly consult on the second part of its draft opinion which focuses the assessment of the potential human health risks of BPA early next year.

This is Breast Cancer UK's formal position on the consultation and includes comments submitted directly to EFSA prior to the deadline date of 15th September 2013.

Breast Cancer UK Summary Position

Breast Cancer UK has always maintained 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 .

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.

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.

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 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.

This latest consultation from EFSA, which concludes that human exposure to BPA is likely to be 11 times lower than previously thought and therefore below the current TDI, does nothing to change this opinion. Notwithstanding the fact that even every low levels of exposure to BPA can cause harm, Breast Cancer UK also question EFSA's methodology and conclusions. EFSA has been selective in its use of measurements and data and has for unclear reasons dismissed key areas of exposure. This could mean that the overall measurement of human exposure to BPA falls far short of the reality. We also seriously question the use of flawed toxicokinetic studies which have been heavily criticized by scientists in the past, but yet again prioritized by EFSA to dismiss other independent bio-monitoring studies.

Given the number of studies which show that low levels of exposure to BPA can cause adverse health effects and particularly malformations of breast cells, Breast Cancer UK strongly advises caution. It will be important to ensure that EFSA's draft opinion does not to lead to complacency about human exposure to BPA and that it is not used to support any misconceived claims that current human use is perfectly safe.

Specific Comments submitted to EFSA

1. Irrational and Selective use of measurements (4.3.6/4.5.2/4.6.3/4.7)

Breast Cancer UK question EFSA's decision to base exposure calculations solely on an 'average' product whilst choosing to ignore products which contain higher levels of BPA. EFSA rightly provides information on the highest levels of BPA measured in products, but for most areas choose to calculate total exposure from a median or average number.

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.

E.g Cosmetics: In lines 1138-1153 it is stated that one study found up to 100 mg/kg of BPA in products such as shampoo and conditioner (Line 1341) and another up to 88 µg/kg is products such as shower gel and hair gel (Line 1339) but that for the purposes of calculating total exposure the measurement of 31 µg/kg was used based on the notion that this was found in body lotion. Yet most people will use shower gel, shampoo and conditioner on a daily basis – therefore why not consider the higher measurements found in these products? It is not safe to assume that consumers choose to buy a product with a notionally average amount of BPA. Ideally, calculations should be based on "average behaviours" as well as average products. Women in particular, are known to use a wide range of personal hygiene products, many of which could be at the higher end of the spectrum.

Indoor air: A similar decision is made which dismisses higher levels of BPA found in ' indoor air', (Line 1216 – 1234). The draft opinion states that concentrations of BPA have been found at an average of 1 ng/m3 and a high concentration of 5.3 ng/m3 but only the 1 ng/m3 value is used for the purposes of calculating exposure on the basis that there is only one study for Europe. It is difficult to understand why, when data is scare, wider data from the USA was ignored. Especially, since indoor air in one country in Europe is no more or less likely to be the same as the indoor air in France (the country of origin of the study used) as it is in the USA.

Dust: Similarly for dust (Lines 1255 – 1257), EFSA again seems to have chosen to prioritise a study which presented lower median concentrations. For unknown reasons the ANSES study which measured median concentrations of 4700 µg/kg, (lines 1244-1257) was ignored in favour of an older study which measured a media of just 1460 µg/kg.

Dermal Absorption: EFSA has for reasons unknown chosen to ignore data that indicates that dermal absorption for cosmetics can be up to 95-100% (Line 1454), yet throughout EFSA use a factor of 0.3 for most dermal exposures and 0.6 for cosmetic dermal absorption. This is particularly concerning as women and teenage girls tend to have high levels of exposure to both cosmetics and receipt paper and could therefore have far higher exposures to BPA than EFSA has calculated. Lines 90, 1449-1457, 1466-1470, 1895-1896, 1910-1911, 1956, 2666.

In summary, Breast Cancer UK has a fundamental concern that EFSA appears to have chosen to base their calculations on studies which identify lower "averages" without considering potential behaviour or data which indicates that exposure could be far higher. Ignoring the higher data found and the conditions in which they may have been found – e.g vacuuming less often, could skew calculations and lead to an under-estimated exposure calculation and undermine confidence in the study.

2. No provision for differences and uncertainty in human behaviour

EFSA has not made any provision or calculated for uncertainty for differences in human behavior. The fact is that people are not uniform in the way they vacuum or wash and dry PC bottles. They do not store products in the way they are meant to be stored or throw things out after 6 months. Many PVC products will be used over years if not decades. Many mums re-use plastic cups, dishes and cutlery, as well as old PC baby bottles etc.

For example in lines 993-997 the draft opinion reveals that two water carboys thought to have been stored at a higher temperature released significantly more BPA than water carboys stored at lower temperatures. EFSA has predictably chosen to use lower measurements in their overall calculation. There is no data however to support the assumption that this sort of storage is not actually quite commonplace. In the UK where many carboys are stored in offices which are centrally heated, it is highly possible that many carboys are stored close to radiators or in direct sunlight.

Another example: Whilst it is true that PVC should now no longer contain BPA (lines 678-685), PVC products are notoriously long lasting so there should be no assumption that exposures from such sources do not still occur.

EFSA should at least provide for such uncertainties when making the overall assessment.

3. Dismissal of whole areas of exposure. 4.3.6/4.6.3/4.8.3

Breast Cancer UK is also concerned to note that EFSA has chosen to ignore specific exposures entirely.

Dust in the workplace: For reasons unknown, the 2009 study measuring levels of BPA in dust (1248) identified higher measurements of BPA in the workplace but these were not included in calculations on exposure. With many adults spending more than a third of their time at work, this is a significant area of exposure which has not been measured.

Occupational handling of receipts: EFSA has also chosen to ignore occupational exposures like receipt handling? This is an important area of exposure which warrants further investigation by EFSA. See lines 270-275, 1298-1307, 1858-1863, 1890-1891.

Medical devices (Line 1354): Despite acknowledging that exposure to BPA from medical devices is likely to contribute to high circulating concentrations of unconjugated BPA (lines 2216-2218, 2553-2556, 2655-2657, 2704-2705, 2722-2723, 2728-2730, 2827-2828, 2889-2890.) EFSA has decided to ignore or discount exposure to BPA from medical devices "since they are used in specific sub populations only" (line 1361). This is a matter of serious concern to Breast Cancer UK. Excluding medical devices from assessment means that exposures experienced by significant numbers of men, women and children who undergo some sort of medical treatment every year, not to mention vast numbers of clinical personnel such as nurses, doctors, dentists etc. goes un-assessed. It also ignores potentially higher exposure amongst vulnerable sub-populations such as cancer patients, those on dialysis or premature babies and also those most at risk from potential damage from early exposure to BPA - pregnant women and their unborn children. Arguably far fewer people use PC kettles (lines 1614-1616) yet these exposures are still considered.

Dental Sealants: Breast Cancer UK also has significant concerns with regard to EFSA's decision to exclude exposures to BPA from dental sealants on the grounds that baseline measurements were very low and that exposure would only be "acute" (lines 1826-1831, lines 1837-1839). Yet EFSA cites one study which shows that levels did not return fully to baseline within 24 hours, which suggests that exposures may not be "acute" (see lines 1391-1395). A significant portion of the population has dental sealants and this number is increasing. Recent studies have found that the use of dental sealants in children could be linked to obesity and neurobehavioral problems. Therefore to ignore exposures to BPA from dental sealants is unsafe.

Outdoor Air: EFSA notes that BPA concentrations in outdoor air "vary widely and depend on regional factors" (lines 257-258) and uses this as a rationale for why exposures from outdoor air were not considered (lines 1213-1215). To exclude such areas from the total assessment can only mean that the final assessment figure for BPA exposure must be far lower than human exposure in reality.

Toilet paper and facial tissue (675-676) EFSA excludes exposure from toilet paper and facial tissue, which are known to contain relatively high concentrations of BPA.

4. Questions raised over BPA levels in meat (4.6.1)

There are areas of EFSAs draft opinion which raise further questions and potential concerns about BPA in the food chain. For example, EFSA suggests, without providing supporting evidence, that meat only

contains BPA as a result of exposure to BPA (rather than bioaccumulation in the animal) (see lines 571-574, 1113-1114, 4749-4750, 4759-4763, 5319-5320). Yet, in other data cited, high concentrations of BPA have been found in ***non-canned*** meat and meat products (up to 395 µg/kg) (lines 138-140, 1102-1104, 1110-1112, 3103-3108, 3321-3323, 5332-5336) and ***non-canned*** fish (up to 97.9 µg/kg) (lines 5352-5353). Similarly relatively high levels of BPA have been found in eggs (4.5 µg/kg and 10.45 µg/kg – see lines 5385-5387 and 5391-5392). If these levels of recorded BPA are as a result of food packaging (which is hard to believe especially in the case of eggs) then this is extremely concerning and warrants further investigation, as it suggested migration from food packaging is alarmingly high. If it is not as a result of food packaging, then it must indicate that BPA is bio-accumulating in the animal which is a conclusion which challenges EFSA's assumptions that BPA is efficiently metabolized in the body – again a conclusion which warrants further investigation. Or alternatively, that high levels of BPA in meat are a result of exposure from an as yet unidentified source – again warranting further investigation.

5. Limited and flawed toxicokinetic data – 4.8.1/4.8.3 Biomonitoring studies on serum levels

Breast Cancer UK supports concerns raised previously about EFSA's reliance on limited and flawed toxicokinetic data (see Vandenberg et al 2013). For example, Volkel 2002. (see lines 2492-2499, 2513-2524). Volkel et al can only provide a snap shot of metabolism of BPA after a one off oral dose – it does not reflect usual human exposure to BPA, via oral and non-oral sources over a whole lifetime. Other toxicokinetic studies from rodents (Doerge et al. 2010a) and intravenous injection exposures in non-human primates (Patterson et al. 2013) (lines 2504) are used but it is not explained why they might be considered appropriate comparisons.

A study by Teeguarden is also used to support the conclusion that "serum concentrations of conjugated or total BPA would only infrequently be expected to exceed a level of 1 µg/l" (line 2522 - 2523) But Teeguarden's (2011) study has also been heavily criticized as being flawed. 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. Therefore it seems unsafe to use the Teeguarden study to dismiss other independent bio monitoring studies. (lines 2591-2596).

One study apparently not used by EFSA in this assessment, but which looked at the metabolism of BPA in non-human primates found that adult primates fed a diet of 400 µg/kg of body weight per day (8 times the recommended human TDI) led to detection of BPA in serum levels similar to those found in human serum (Tharp, Maffini et al 2012). Therefore this suggests that human exposure to BPA via oral intake must be 8 times that of the current TDI of 50 µg/kg of body weight per day.

6. Concerns over measurements of BPA in non PC baby bottles

In lines 1028-1037, EFSA states that a small number of non-PC baby bottles were tested with "some polyamide baby bottles being found to have high concentrations of BPA". Breast Cancer UK have very serious concerns that despite a ban on the use of BPA in baby bottles, that any such testing should find BPA. It is not acceptable that the evidence is dismissed as being "limited" and "incidental". It raises the question whether further testing might reveal more examples of BPA contamination. Therefore rather than dismissing the findings, EFSA should carry out further investigations.