



11th March 2014

CHEM Trust's comments to the public consultation on the draft Scientific Opinion on the risks to public health related to the presence of Bisphenol A (BPA) in foodstuffs by the European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids.

<http://www.efsa.europa.eu/de/consultations/call/140117.htm>

This draft Scientific Opinion of EFSA's Panel to which our comments below refer is abbreviated in our submission and referred to as 'the EFSA report'. However it should be recognised that the EFSA report/opinion was drafted by the EFSA Panel with input from the Working Group on BPA Toxicology.

ABSTRACT

Lines 1-438

CHEM Trust considers that the overall transparency of the hazard and risk assessment is very poor. For example, although the EFSA report does not hide the lack of certainty, it does hide the implications of this. Thus, there is no clear indication of whether there is a margin of safety for the effects for which there is uncertainty.

Furthermore, the way EFSA has avoided taking effects on the mammary gland forward in the risk assessment is nothing short of a conjuring act. It certainly does not seem valid to exclude this data from the risk assessment, when the worth (importance and quality) of the studies reporting the effect has been accepted.

CHEM Trust concurs with the EFSA panel that BPA induced effects on the mammary gland of female animals exposed prenatally should be considered a likely effect. However, we are appalled that the mammary gland studies were not taken forward and actually used in the risk assessment. When so many studies have highlighted effects on the mammary gland at low levels of exposure, not to take this forward in the risk assessment is likely to leave the public insufficiently protected.

In addition, we have a grammatical comment relating to the following wording of the abstract "... reflects the current uncertainties surrounding effects of BPA on the mammary gland and other potential health effects, which the Panel considered less than "Likely"". This tends to suggest that the Panel considered the mammary gland effects less than likely, when that is not the case in that they concluded mammary gland effects were indeed likely. Thus, the clause 'which the Panel considered less than likely' relates solely to the other potential effects and not to the mammary gland

effects, but the sentence has been written in such a way as to be confusing to the reader.

SUMMARY

We strongly encourage EFSA to include a table in the summary, showing all the reported effects (including those considered unlikely or of unknown relevance to human health) and the dose levels in micrograms/kg bw/day these were reported in animals and the human equivalent dose (HED) to which this would equate. This would enable the reader to see whether indeed there was a margin of safety as compared to current human exposure estimates. A column in the table could be included showing EFSA's judgement on the studies, and whether or not the outcome was considered likely. By at least showing the dose level reported to cause such effects, this would enable the reader to consider the potential effects if, for example, the judgement of 'unlikely' was wrong, or if there was high uncertainty. The effects listed in the table should, for example, include developmental effects on the mammary gland, decreased female and male AGD, effect on the immune system, metabolic effects etc. and the dose levels causing these. Including such a table in the summary would greatly improve the clarity of the report.

The EFSA report merely dismisses a number of effects as not likely, but says that the reported effects add to the uncertainty which has been taken into account in the risk assessment. However, it is not clear exactly how this uncertainty has been taken into account in the risk assessment. If the only way this uncertainty has been taken into account is by determining it to be a temporary TDI, then this needs to be made clear.

Line 89

CHEM Trust considers that all 2013 studies should have been included where dose levels below a HED of 113 micrograms/kg bw/day have reported effects. If this has been done, this should be made clear.

Line 122

We cannot see the merit of scoring for 'likelihood' the human and animal and in vitro studies in isolation. It is the totality of these lines of evidence together that should be used to determine the likelihood of effects in the human population, and whilst this has been done, we consider that scoring them first independently is likely to lead to the overall conclusion of a lower likelihood.

Line 197

The statement that "Overall, the better powered, better conducted studies in animals found few effects of in-utero exposure to BPA on reproductive development at doses below 3.6 mg BPA/kg /day HED" is too dismissive. The GLP studies this refers to may be better reported and better powered, but if the studies followed OECD guidelines, they may not be measuring the most sensitive endpoints and therefore may miss important effects associated with health problems. Unfortunately, although GLP creates the semblance of reliable and valid science, it actually offers no guarantee of the reliability or validity of the results. GLP specifies nothing about the quality of the research design, the skills of the technicians, the sensitivity of the

assays, or whether the methods employed are current or out-of-date. GLP simply indicates that the laboratory technicians/scientists performing experiments follow highly detailed requirements for record keeping, including details of how the experiment was conducted.

Line 212

There is a need to specify more clearly how the uncertainties regarding the reproductive and developmental effects have been taken into account in the risk assessment.

Line 338

CHEM Trust concurs with the EFSA panel that BPA induced effects on the mammary gland of female animals exposed prenatally should be considered a likely effect. However, we are appalled that the mammary gland studies were not taken forward and actually used in the risk assessment. The argumentation for not including the data is incomprehensible and seems to be ill-founded. Such methodology tends to further obscure the usual inherent uncertainties in risk assessment. The outcome seems to be the on-going reluctance of EFSA to allow proper consideration of the hazards identified in non-OECD non-GLP studies.

Line 348

We do not agree with averaging the doses causing effects on the left and right kidney, but suggest instead that the lowest dose causing effects should be taken forward to give a HED of 109 micrograms leading to a TDI of 4 and not 5.

Line 361

CHEM Trust disagrees with the decision to not apply an additional assessment factor for the uncertainties related to the hazard identification.

CHEM Trust also has further comments on studies relating to brain function, anogenital distance (AGD), immune system, glucose regulation, mammary gland, epigenetic effects. We consider that these comments should also be reflected in a revision of the summary.

SECTION 3.3

3.3.2 Reproductive and Developmental effects

Lines 3238 and 10674 - 10721

The Delclos (FDA) et al study in rodents does report some interesting findings. We certainly consider delayed testis descent to be an adverse effect, as reported in 5% at the dose level of 260 micrograms. Similarly the increase in giant cells in the seminiferous tubule in males should be considered adverse. The study shows that BPA affects the male reproductive tract. However, it is very important to exercise caution in the weight given to the findings by Delclos et al. This is because both this study and the accompanying study by Churchwell et al. are of limited use because both studies lack negative controls since the naïve group and vehicle control group were contaminated with BPA. Conclusions drawn by the authors that low doses of BPA do not have an effect are unfounded due to the lack of adequate negative controls.

Lines 3257- 3264 & 10749 - 10787

The Christiansen et al study reports effects of BPA on anogenital distance (AGD). CHEM Trust considers that more weight should be put on the decreased AGD reported in males and that it should be considered an adverse effect, particularly as a recent study (Thankamony et al, EHP see <http://dx.doi.org/10.1289/ehp.1307178>) has highlighted the relevance of such findings for the human.

SECTION 3.4

Brain function

3.4.2

Line 3988

CHEM Trust concurs with the EFSA 2010 opinion which recognised BPA related biochemical changes (eg. altered receptor or protein expression) in different brain regions as potentially significant.

Line 4059

Moreover, we are very concerned that recent studies report similar changes suggesting effects on brain development (effects on neurogenesis and on gene expression, neuroendocrine effects, and effects on the morphology of certain brain regions etc.). We therefore do not agree that effects on human neurodevelopment should be considered as unlikely. EFSA's conclusion to try to further clarify whether such changes are mechanistically related to the reported neuro-behavioural effects following BPA exposure is likely to leave the public unprotected as more research takes time. Any biochemical change in the brain and changes in brain function and development should be considered adverse, and if reproducible, these should be taken forward in risk assessment. This is because it will not be scientifically possible to elucidate with certainty what these effects mean for the human brain. The uncertainty of extrapolating from either biochemical changes or behavioural effects in rodents to complex brain function over the entire human lifespan should lead to a more conservative approach in determining human relevance.

Section: 3.4.4 Conclusions on neurological, neurodevelopmental and neuroendocrine effects

Line 4104-4109

As noted above we cannot agree that effects on human neurodevelopment should be considered as unlikely given the wealth of animal data. It is the totality of the data which must be assessed to come to a decision as to whether BPA has the potential to perturb the neuroendocrine axis, and then whether such effects should be taken forward to risk assessment for humans.

The EFSA report should more clearly specify how the uncertainties regarding the neurological, neurodevelopmental and neuroendocrine effects have been taken into account in the risk assessment.

SECTION 3.5

Immune System

Line 4208

CHEM Trust notes that several studies have reported changes in cytokines, changes in T-cells and other aspects of immune modulation, including research suggesting that prenatal exposure to BPA may up-regulate immune responses in rodents. Furthermore, recent animal studies by Lee et al. (2012a), Kendziorzsky et al. (2012) and Nakajima et al. (2012) add to the concern with respect to immunotoxicity.

Section 3.5.5

Line 4291

CHEM Trust considers that taking the human and animal data together, we would not come to the conclusion that effects on the immune system are not 'likely'. We consider that some effects on immune system function should be judged likely. We therefore consider that it would be appropriate to consider these effects in the risk assessment.

SECTION 3.7 Metabolic effects

3.7.2.2. Evaluation of animal studies on effects of BPA on metabolism (lipogenesis, obesity) or effects related to glucose or insulin regulation (diabetes)

Line 4955

CHEM Trust considers that given the number of studies in rodents which now indicate BPA interferes with glucose or insulin regulation of lipogenesis, it is likely that 'something is going on' with respect to metabolism. However, given that some large studies do not report findings it is difficult to come to a clear conclusion. Nevertheless, the number of studies reporting metabolic effects certainly add to the uncertainty. We consider that effects which do not fit standard dose response curves should not be dismissed, but rather understanding and research needs to increase in this area.

As noted previously, we strongly encourage EFSA to include a table showing all reported effects at dose levels below the temporary TDI.

SECTION 3.9 Mammary Gland

3.9.2.3.

Line 5500

We note that since the previous EFSA review in 2010, several additional studies have reported proliferative effects on mammary tissue and/or effects on mammary tumour growth following administration of BPA (Jones et al., 2010; Ayyanan et al., 2011; 5500 Jenkins et al., 2011; Weber Lozada and Keri, 2011; ; Kass et al., 2012; Tharp et al., 2012; Acevedo et 5501 al., 2013; Vandenberg et al., 2013; ; U.S. FDA/NCTR, 2013).

The available data are very persuasive and CHEM Trust concurs that the effects on the mammary gland (duct hyperplasia or changes in differentiation) should be considered likely.

Line 5629 - 5736

The US FDA/NCTR sub-chronic (90-day) toxicity study on rats, conducted under the auspices of the NTP reported mammary gland duct hyperplasia in the female groups

examined at PND 21. The incidence of hyperplastic lesions was statistically significant in at least one of the three statistical methods used when compared with the vehicle control group in the 2,700 and 100,000 micrograms/kg bw/ day groups, but not in the 300,000 µg/kg bw/day group. This observation was considered possibly treatment-related by the study authors but not apparently by the original study pathologist. Mammary gland duct hyperplasia was also reported in the high dose female BPA groups examined at PND 90. We concur with the Panel who concluded that the observation of mammary hyperplasia in female rats in this study, is relevant for the risk assessment of BPA, given the findings in other studies reported above.

Line 5845

We do not agree, however, that the earlier studies that found effects on the mammary gland and particularly those examining the potential tumorigenesis properties of BPA should be judged to have shortcomings. The further data which confirms effects on the mammary gland vindicates this stand point. BPA has been shown to have a proliferative effect on mammary tissue at low doses (in some cases below the current TDI) in a number of studies published prior to the U.S. FDA/NCTR paper in 2013. The changes reported include increases in terminal end buds (TEBs), terminal ducts, and alveolar buds, accelerated differentiation, increased proliferation and reduced apoptosis, accompanied by changes in gene and protein expression related to the proliferative process (e.g. Markey et al., 2001, 2005; Munoz-de-Toro et al., 2005; Durando et al., 2007; Murray et al., 2007; Vandenberg et al., 2007, 2008; Moral et al., 2008; Jenkins et al., 2009; Betancourt et al., 2010; Jones et al., 2010; Jenkins et al., 2011; Weber Lozada and Keri, 2011; Ayyanan et al., 2011; Kass et al., 2012; Vandenberg et al., 2013, Acevedo et al., 2013) In particular, not only these rodent studies, but also the Tharp et al., 2012 study reporting advancement of developmental parameters in the mammary gland of primates, with increased epithelial density of terminal end buds, should surely be considered relevant for human health risk assessment. Although there are differing views on this, the proliferative/developmental advancement changes induced by BPA in mammary tissue may lead to enhanced susceptibility to mammary tumours in later life.

SECTION 3.10.4

Epigenetic effects

Line 6189

The EFSA report rightly acknowledges that mechanistic studies published since 2010 continue to support the hypothesis that BPA has effects on a number of receptor types in addition to other cellular targets resulting in effects on hormone homeostasis, on signal transfer and gene expression as well as cytogenetic and epigenetic effects. However, it then suggests that no single clearly defined MoA (mode of action) can be identified that can contribute substantially to the assessment of the risk for BPA. CHEM Trust considers that there is sufficient evidence that BPA has a complex ED MoA and that elucidating this further is not needed in order to factor this endocrine disruption into the risk assessment. Such an ED action with suggested epigenetic effects should require a more precautionary interpretation of the significance and likelihood of the reported effects.

SECTION 5 Risk characterisation

Line 6366

In our view not all relevant exposure situations and scenarios have been adequately included in EFSA's draft exposure assessment, such as exposure of children under 3 years old to thermal paper, e.g. via till receipts (dermal exposure). Please see respective earlier CHEM Trust comments in the context of EFSA's consultation on the draft exposure assessment. We have noted that children under 3 are sometimes given the visa receipts to hold while their mothers wheel the supermarket trolley to the car.

Line 6698

CHEM Trust disagrees with the decision to not apply an additional assessment factor for the uncertainties related to the hazard identification. With such a high number of uncertainties an additional assessment factor is merited. We feel that the EFSA report has adopted an element of political manoeuvring with respect to pragmatism about what exposures currently are and the difficulty of creating concern if exposure reduction was deemed necessary. We disagree that the derivation of the HED based on mouse data is already sufficiently conservative as to 'cancel out' any uncertainties in the hazard identification. This is a very unscientific approach which provides a smoke screen of accuracy by use of jargon and techniques that seek to hide the pervading uncertainty of the risk assessment.

Gwynne Lyons, CHEM Trust. March 2014