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Policy submission

CHEM Trust's Comments on the Annex XV Restriction Dossier for Bisphenol A (BPA)

Comments in support of the proposal by France to restrict the use of BPA in thermal paper

Gwynne Lyons, 9th October 2014

CHEM Trust supports the proposal by France to restrict the use of BPA in thermal paper (ubiquitously used for visa till receipts and lottery tickets). This is because several studies, from different research groups working in different laboratories, have shown that BPA, often at very low dose levels, can cause effects on mammary tissue.

The changes reported include increases in terminal end buds, 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 rodent studies, but also a 2012 monkey study by Tharp et al., reported advancement of developmental parameters in the mammary gland of primates, with increased epithelial density of terminal end buds. All these studies together should surely be considered relevant for human health risk assessment. Indeed, given our knowledge of the role of oestrogen in breast growth, and the known oestrogenic action of BPA, such consistency of findings of low dose effects on the mammary should perhaps not be surprising.

A study published in 2007 by Murray et al, noted that Wistar Furth rats that were exposed in utero to 2.5, 25, 250 and 1000 micrograms BPA/kg body weight/day had significantly increased rates of ductal hyperplasia and additionally, those exposed to the two highest doses developed ductal carcinoma in situ at post natal days (PND) 50 and 95.

If all the studies which have since concluded that BPA can lead to cancerous changes in the mammary gland are scrutinised, we can see a lot of concordance which adds weight to these findings. Of course, these need to be evaluated alongside those which do not report effects, but the reported effects on mammary tumour growth are a particular concern given the increase in mammary tumours in the EU population.

The 2009 Jenkins et al study, was the first *oral* study which indicated BPA-induced enhancement of sensitivity of the mammary gland to carcinogen-induced breast tumour formation in rat offspring following lactational BPA exposure of pups. This study supported the earlier concerns raised by Ana Soto's team. Further studies by Ana Soto's team (eg Acevedo et al) heighten the concern that developmental exposure to environmentally relevant levels of BPA during gestation and lactation may induce mammary gland neoplasms in the

absence of any additional treatment with a known carcinogen – such that BPA may act as a complete mammary carcinogen.

CHEM Trust considers that studies which show increase susceptibility to cancer, by evaluating an animal's response to a subsequent exposure to a known carcinogen should certainly be considered relevant for human risk assessment, as this will mirror the situation for the public at large, who will be exposed, albeit at low levels, to known carcinogens in the environment.

Although there are differing views on this, CHEM Trust considers that there are certainly sufficient grounds for concern that the proliferative / developmental advancement changes induced by BPA in mammary tissue may lead to enhanced susceptibility to mammary tumours in later life. Moreover, when extrapolating from animal studies to effects on humans, there is always an element of what it is reasonable to deduce, rather than absolute proof of what will occur in humans. **Given all the available evidence, it is certainly reasonable to deduce that BPA exposure increases susceptibility to mammary cancer.**

A recent study by Dhimolea et al published in July 2014 highlights that BPA can change how genes function in the mammary glands of Wistar-Furth rats. This study examined the impact of foetal exposure to BPA on the DNA of their mammary glands as they age. It found that BPA can change how genes express themselves in the mammary gland. BPA's effects on gene expression in the mammary gland have also been reported by other scientists in other laboratories (eg. see Moral et al.,2008).

BPA exposure appears to trigger changes in the postnatal and adult mammary gland epigenome and alters gene expression patterns. Dhimolea et al. conclude that these events may contribute to the development of pre-neoplastic and neoplastic lesions that manifest during adulthood. The dose was 250 micrograms of BPA/kg bw/day, and the exposure route of the rats was subcutaneous via osmotic pumps. This route is relevant because the researchers measured plasma levels and found that the free or un-metabolized BPA concentrations were within the range of those reported in humans. These scientists have suggested that BPA acts through the oestrogen receptors which are detected exclusively in the mesenchyme during this exposure period, by directly altering gene expression.

CHEM Trust considers that understanding all the steps in cancer is a long way from our grasp, and waiting for complete clarity on mechanisms of action and the precise relationship between an increase in terminal end buds and breast cancer is not feasible. However, the available scientific data are sufficient to conclude that the mammary gland changes reported after BPA exposure are an adverse effect. **Studies have reported an increased risk of mammary tumours due to BPA exposure and it is reasonable to conclude that BPA exposure from thermal paper may pose a risk**.

We do not consider that all the studies which have reported low dose effects on the mammary gland have such shortcomings that they should all not be used in the risk characterisation and risk assessment. It is the sheer number of studies reporting similar effects at similar low dose levels that should lead to a weight of evidence approach that includes these studies. Given that similar results have now been reported in many laboratories, it is very unlikely that these results are spurious. **Based on all the studies which have reported low dose effects on the mammary gland, it would seem appropriate to consider that BPA should be treated as a non-threshold substance, and substituted with safer alternatives wherever possible**.

The US FDA/NCTR sub-chronic 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. Mammary gland duct hyperplasia was also reported in the high dose female BPA groups examined at PND 90. In addition, the study reported many other effects at high doses which were noted to be consistent with estrogenic activity.

However, it is crucial to exercise caution in the weight given to the conclusions reached by Delclos et al. with regard to lack of low dose effects. 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. This contamination is clearly admitted in Churchwell study (attached here) and noted in the Delclos study, "*Despite our efforts to minimize the unintentional exposure of animals to BPA and the precautions taken to physically separate vehicle dosing from the BPA and EE2 doses (see Materials and Methods), BPA-glucuronide was detected in the serum of vehicle and naïve control animals at levels similar to those detected in animals dosed with 2.5 µg BPA/kg bw/day*."

The conclusions drawn by Delclos et al. that low doses of BPA do not have an effect are therefore unfounded due to the lack of adequate negative controls. It is just not scientifically sound to draw any conclusions about no low dose effects because there is nothing to compare with. Moreover, it is not justified to suggest that just because the control rodents of these FDA studies were contaminated with BPA, all controls used in laboratories elsewhere are also likely contaminated.

Many independent scientists have been working with BPA for many years, and their laboratories have a lot of experience of preventing such contamination. We are aware of future publications which are heavily critical of the FDA (Delclos et al) study, and attach here a word document of the critique published in Environmental Health News. See: http://www.environmentalhealthnews.org/ehs/news/2014/feb/bpa-low-doses

The 2014 EFSA *"Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs"* noted methodological weaknesses in all these studies showing BPA enhanced mammary proliferation "with the exception of the U.S. FDA/NCTR sub-chronic toxicity study, which was a detailed guideline study conducted in accordance with GLP". **This clearly shows that this panel put undue weight on the Delclos GLP study, which was in-fact the study which was undoubtedly flawed due to contamination of the controls.**

Nevertheless, the EFSA panel did conclude that "the effects on the mammary gland (duct hyperplasia or changes in differentiation) were - **likely**- using a weight of evidence approach. However, when taking these findings forward for risk assessment they considered they could not be used to derive a point of departure. **Given the EFSA Panel also conclude that a possible role of BPA in increasing the susceptibility to mammary gland carcinogenesis cannot be ruled out, CHEM Trust considers that it is unacceptable, not to take into account in the final risk assessment, the studies reporting low dose effects on the mammary gland.**

Exposure levels

With regard to assessing internal exposure from handling thermal paper there are considerable uncertainties. As noted in a recent RIVM report (September 2014) at this time "it is very difficult to reliably calculate internal BPA exposure as a result of external inhalation and dermal exposure, because of the lack of route-specific kinetic data. As a result,

it is also very difficult to reliably assess the health risks associated with external dermal exposure, since route-specific systemic toxicity data are not available." See: http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2014/september/Bisphenol_A_Part_1_Facts_and_figures_on_human_and_environmental_health_issues_and_regulatory_perspectives

Exposure to BPA from thermal paper may be much higher than expected. A recent paper has underlined the likely added transfer of BPA when hand-care products are used and when a subsequent greasy meal is eaten by hand (vom Saal & Welshons, 2014). **Dermal exposure may result in free BPA in the blood stream due to metabolism in the gut being bypassed.** This difficulty in accurately assessing exposure to BPA argues for the use of greater uncertainty factors, which would tend to increase the predicted risk.

The difficulties in assessing safe exposure levels with respect to effects on the mammary gland and the difficulties in assessing BPA exposure due to thermal paper underline the need for a policy response which aims to reduce exposures where practicable.

Substitution of Bisphenol A

ECHA has noted that the substitution of BPA by BPS or other bisphenols is likely, should the restriction be adopted, and that BPS might cause very similar adverse health effects as BPA. It is highlighted therefore that the estimated health benefits due to the restriction of BPA in thermal paper could be lower than estimated by France. **CHEM Trust considers that a decision to give notice of a forthcoming restriction in the use of BPA in thermal paper should not be held up due to a lack of sufficient toxicity data on the alternatives.**

Such a decision would create the necessary stimulation of the development of safer alternatives, particularly if issued alongside an intent to further investigate other bisphenols, including BPS. Industry should be urged to take responsibility and ensure that safer alternatives are found. CHEM Trust notes that it has been reported that a substitute based on corn might be a possible option, however we have no further data. See: http://www.fastcompany.com/1682423/coming-soon-corn-based-bpa-replacement

The US EPA report on "Bisphenol A alternatives in thermal paper" which was finalised in January 2014 provides much information on alternatives. See: http://www.epa.gov/dfe/pubs/projects/bpa/bpa-report-complete.pdf

CHEM Trust would be very concerned if BPS was used as an alternative. This is because there are growing concerns about its toxicity. For example, according to an animal study reported in June 2014, Bisphenol S (BPS) appears to be just as potent as BPA in altering brain development and causing hyperactive behaviour (Endocrine Society, 2014a). See: http://www.sciencedaily.com/releases/2014/06/140623103933.htm

Another recent study has also reported that BPS has similar toxic effects on the heart as previously reported for BPA (Endocrine Society 2014b). See: http://www.sciencedaily.com/releases/2014/06/140623103935.htm

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