Comments on the proposal for harmonized classification and labeling of Bisphenol A.

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General comments

- For many of the studies summarized in the proposal, it is not clear whether the studies are well performed and/or reported (how many animals were used, which analyses were performed, if GLP or guidelines were followed etc) and therefore how reliable these studies are. In addition, in most cases the quantity of effects and historical control range is not included, making it difficult to conclude whether observed effects are toxicologically relevant.
- Some of the studies included in the CLH proposal have used very high dose levels (sometimes at 6% in diet corresponding with 68 mg/mouse according to Berger et al, 2007, but 180-240 mg/mouse according to our calculation corresponding with approximately 9000 mg/kg bw). It should be discussed whether effects observed only at these dose levels would warrant classification as described in paragraph 3.7.2.5.7 of Annex I of CLP.
- Many studies were performed using subcutaneous injection or implanted time release pellets (bypassing the first pass effect). The relevance of these studies compared to humans and/or animal studies using relevant routes of exposure should be discussed based on the available toxicokinetic data in line with paragraph 3.7.2.5.6 of CLP. This should determine whether these studies can be used to support the proposed classification. The current chapter on toxicokinetic does not address this important question and in most studies using this exposure route, it is not or only very limited justified. Therefore, the relevance of these routes should be justified before using them for classification. The relevance could be dose dependent as sometimes a high dose is used subcutaneously which could result in very high exposure levels which may not be relevant as discussed under the previous bullet. The provided summaries focus mainly on the observed effects on development or fertility. However, information on maternal / other toxicity is often lacking. It is considered important to assess whether the observed reproductive effects are a direct effect of BPA or a secondary non-specific consequence of other toxicity. Further, it is unclear whether additional parameters have been determined in the studies which were not affected. This information is important for assessing the consistency between studies of effects observed in other studies.
- For all effects, it can be discussed whether these are effects on fertility or effects on development. Basically, effects on fertility (or the reproductive system) that are caused by developmental changes of the fertility system are primarily caused by an altered development and should therefore be seen as developmental effects. When fertility effects (or changes in the reproductive system) are observed in animals that are only exposed in utero, it can be concluded that these effects have arisen during development. If they are considered relevant for classification, they are relevant for classification for developmental effects, not fertility effects. Effects induced by post-natal exposure would not justify classification for development as described in Chapter 3.7.1.4 of the criteria. However, they could be considered as reprotoxic effects in general without differentiation as allowed in 3.7.1.1. It is suggested to first discuss which window of exposure would contribute to which differentiation of the classification for reproductive toxicity. Then the available studies could be split into those windows of exposure as a start before discussing the classification.

Reproductive toxicity

Effects on oocytes

- Effects on chromosome segregation could be considered induction of genetically based heritable effects on the offspring. According to chapter 3.7.1.1 it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

Effects on the male reproductive tract

- When adult male rats were exposed to BPA, via gavage or subcutaneously, a decreased sperm count and an increased ventral prostate weight were observed. This might decrease reproductive performance and may be considered as an effect on sexual function. This effect was however not reported in the multigeneration studies. Because of the short study descriptions, it is not clear whether the studies that report these effects can be considered as reliable.
- The summary of the study by Sakaue et al, 2001 contains an error as fertility was not determined in this study.

Effects on reproductive performance

- The reduced number of litters/pups in the 3-generation study in rats without an effect on resorptions (also in F0) and the reduced number of litters/pups in the continuous breeding study in mice suggests an adverse effect on fertility. This effect is observed in two species and in multiple studies (i.e. the secondary effect of reduced litters/pups). However, summaries of the available developmental studies could further substantiate whether this is an effect on fertility or development. No reductions in offspring were observed in the developmental studies by Stump (2010) and Ryan (2010). This further justifies that the effects in the multigenerational studies are due to an effect on fertility instead of post-implantation loss.

Human data

- Two epidemiological studies suggest a relationship between BPA and endometriosis. However, both studies have a poor methodology and are therefore not reliable.
- Some epidemiological studies indicate that higher urinary or plasma BPA concentrations are related to reduced implantation, increased miscarriages, premature birth or ovarian response following ovary stimulation. Also these studies have serious methodological flaws with regard to confounders, population size etc.
  Because human exposure to BPA largely comes via food intake and spot urine samples only reflect the last meal (Teeguarden et al, 2011), caloric intake should be included as confounder to exclude the possibility that the correlation is due to higher BPA intake due to higher food intake, in particular higher food intake via canned food (e.g. soft-drinks or beer). Only in some incidental epidemiological studies this possible confounding is mentioned but even in these few studies, the influence of this confounder was not taken into account.
- The methodology of the human data is insufficient, therefore these studies cannot be used for classification purposes. Not even as supportive evidence.