

The European Federation for Cosmetic Ingredients (EFFCI) is taking the opportunity to provide the following comments on the CLH report on propylparaben dated March 2022 provided by the MS Belgium. These comments express significant concerns regarding the proposed classification of propyl paraben (chemical name: propyl 4-hydroxybenzoate, CAS-No. 94-13-3) as reproductive toxic, category 2 with H361fd.

The classification proposal for propyl paraben as Repr. 2, H361d,f is viewed as warranted by the CLH-dossier submitter based on the following observations:

- A slightly lower anogenital distance (AGD) in F1 (but not F2) pups and a slight but not statistically significant increased post-implantation loss as postulated adverse effect on development
- Slight but not statistically significant effects in sperm motility and morphology in the absence of clear general toxicity as postulated adverse effect on fertility

Considering the proposal provided by the CLH-dossier submitter, it must basically be stated that the rationale for classifying propyl paraben is lacking compliance with fundamental scientific principles and regulatory requirements regarding the evaluation of substances in terms of toxicological significance and relevance of observed effects.

### Preliminary remarks

According Regulation (EC) 1272/2008 of the European Parliament and of the Council („CLP Regulation“), classification as a reproductive toxicant has to be made on the basis of an assessment of the **total weight of evidence**, which means that all available information that bears on the determination of reproductive toxicity needs to be considered together in that both, positive and negative results, are assembled together into a weight of evidence determination.

Considering the CLH report provided by the MS Belgium it is our concern that a scientifically, and via CLP regulation required, balanced, transparent and objective assessment of all available data has not been carried out. Instead, it appears that negative data were not given equal weight with more weight being given to seemingly positive outcomes.

For example, „reduced“ AGD values are considered only from the F1 pubs despite the fact that these findings in F1 pubs did not occur in the F2 pubs, were not statistically significant after normalization to cube root of body weight, were not dose-dependent and – importantly – were all well within the range of historical control data. With regard to the slight increase in post-implantation loss observed in the `extended one generation reproductive toxicity study` (EOGRTS), it is particularly remarkable that no discussion or mentioning takes place that this finding was statistically not significant, not confirmed / reproducible in cohort 1B of the EOGRTS, and – again – was well within the range of historical control data.

What is striking in this respect is that the CLH-dossier submitter apparently saw no need to take historical control data into account to assess the range of natural variation and thus the biological relevance of the above findings. On the contrary, good quality data from an OECD TG and GLP conform EOGRT study are „mixed“ with data from a historical non-OECD and non-GLP study (published by Oishi and coworkers already in 2002) without pointing to the existing limitations and shortcomings inherent to the methodological design and results of the Oishi study. However, such obvious deficiencies in study design clearly impact the quality and reliability of the evidence and thus should not be overlooked in any assessments.

What is also striking is that additional data from guideline conform tests carried out under GLP are only mentioned in passing, if at all, like a `three-month oral developmental toxicity study` carried out by Bristol-Myers Squibb Company (BMS Reference No. DN12004, included in the REACH registration dossier) which found no reproductive effects following administration of propyl paraben to juvenile rats for 8 weeks starting on PND21. In this study there were no propyl paraben-related findings on the number of corpora lutea, implantation sites, live embryos, dead embryos, early resorptions and pre and post-implantation losses for naive females mated with treated males.

Likewise, results from additional OECD and GLP conform higher tier studies, i.e. 90-day oral toxicity according OECD TG 408, prenatal developmental toxicity according OECD TG 414 and/or a reproductive screening study according OECD TG 422, which all did not show any toxicity and revealed NOAELs of 1000 mg/kg body weight per day like in the OECD TG 443 study, have also not been sufficiently weighed in the assessment performed by the CLH-dossier submitter.

The apparent lack of a structured, transparent and balanced approach to data assessment as performed by the CLH-dossier submitter results in the appearance of greater certainty and weight in support of a „hazard“ than the database scientifically actually warrants.

To conclude on a classification determination, there is a need to take into account the whole toxicological evidence for propylparaben in a robust weight of evidence approach to develop an informed regulatory decision that is commensurate and proportionate with all available data. In this respect, a balanced appreciation of all of the following, but apparently missing, facts according to scientifically accepted core principles is required:

- Proof of adversity of claimed effects which is defined according to WHO/IPCS (2004) as a change that results in impairment of functional capacity
- Proof of the existence of a dose-response as fundamental descriptor of a cause-effect relationship
- Proof of biovariability of claimed effects by comparing effect levels with concurrent and historical control data for the same effect to take the range of natural variation into account
- Proof of biological plausibility by considering inter alia whether effects are statistically significant and reproducible
- Proof of consistency/reproducibility of effects with findings from other studies

None of the findings brought forward by the CLH-dossier submitter meet the above requirements. The findings generally are only marginal or minor, and, moreover, all values are well within the range of historical control values. Based hereupon the CLH-dossier submitter apparently is discussing biological variation rather than substance related effects. However, even if the only effects recorded are considered to be of low or minimal toxicological significance, classification may not necessarily be the outcome according to the CLP Regulation (CLP, section 3.7.2.3.3). Consistency and toxicological significance of observations impacts the weight of the evidence and should thus be considered in a classification determination. For propyl paraben, the above observations are of no toxicological significance and therefore do not provide any convincing evidence to warrant a Repr. 2, H361d,f classification.

2022-06-07