HEAL comments - SVHC identification of Isobutyl 4-hydroxybenzoate

Reason for proposing:

- **Equivalent level of concern having probable serious effects on human health due to endocrine properties (Article 57f)**

The Health and Environment Alliance (HEAL) thanks the Danish Competent Authority for its proposal to identify Isobutyl 4-hydroxybenzoate (or isobutylparaben) as an SVHC under REACH article 57(f) due to its endocrine disrupting properties relevant for human health giving rise to an equivalent level of concern to that of substances listed under REACH articles 57(a) to (e).

We fully support this proposal and congratulate the dossier submitter for their preparation of a well-structured, -reasoned and very transparent dossier.

Endocrine disrupting properties

Mode of action

In terms of endocrine mode of action, the dossier provides for strong evidence of estrogenic activity based on in vitro data, supported by moderate-strong evidence in vivo (uterotrophic assays).

Adverse effects

When it comes to adversity, as clearly detailed by the dossier submitter, there were few studies available for IBP in the registration dossier, with low reliability. The available studies provided low-moderate evidence of adverse effects on ovary and uterus, and no evidence investigated the effects of perinatal exposure on sperm quality. The overall data gap was rightly addressed by the dossier submitter through a read-across approach, taking butylparaben as a source substance.

Isobutylparaben is a close analogue to butylparaben, with only minor structural differences. Butylparaben was already identified as a SVHC due to endocrine disrupting properties for human health. The dossier submitter has provided a clear justification for using a read-across approach in order to close data gaps and proceed with the assessment, based on close structural similarity, similarity in mode of action (estrogenic), and the similar potency observed in vivo and in vitro.

The weight of evidence approach for existing IBP data, together with the read-across from BP, support the conclusion that exposure to both butylparaben and isobutylparaben can cause adverse effects on sperm count and quality.

Biologically plausible link

We support the dossier submitter's conclusion on the biologically plausible link between the ER activation during development and the adverse effects observed on the male reproductive system after exposure to IBP at perinatal stage.

The dossier offers transparent documentation of the supporting mode of action analysis, with clear detailing of the reasoning in the identification of the molecular initiating event (ER activation) and the different key events leading to the adverse effects.

Equivalent level of concern

It is well-known that the adverse effects at play (reduced sperm count and quality) are irreversible, affect individuals' wellbeing throughout their lifetime, and overall contribute to infertility - thereby making these effects relevant at population level over the long term. Infertility is a growing health concern worldwide, and medical treatments for infertility disorders, when available, are extremely costly [1].

By way of illustration, we recall that:

- A 2017 systematic review and meta-analysis on sperm counts (data collected on men from North America, Europe, Australia and New Zealand from 1973 to 2011), found a decline of more than 59%, with no sign of leveling off over time. This is all the more concerning as low sperm levels have also been linked with higher risks of hospitalization and death [2].
- The 2013 Berlaymont declaration already warned that: *"In some EU Member States large proportions of young men have semen quality so poor that it will seriously affect their chances of having children. At the same time, congenital malformations such as hypospadias (malformations of the penis) and non-descending testes are increasing or levelling off at unfavourably high levels."*[3]
- According to the WHO, "more than half of the countries that make up the WHO European Region have fertility levels which are defined as low or lowest-low" (WHO 2006). "In the Nordic countries up to 4% of all children born come from IVF treatments, another 2-3 % from other forms of infertility treatments, summing up to 6-7% of all children born". "In Europe one in six couples is affected by unwanted childlessness."[4] In 2013, HEAL already warned that the rate at which couples are seeking medical assistance due to infertility is increasing by a rate of more than 10% per year [5].
- The limited figures available to assess related economic costs of seeking infertility treatments suggest a high burden: the demand for assisted reproductive techniques (ART) such as in vitro fertilization (IVF) has risen over the last 40 years. In 2016, the contribution of EDCs to the costs associated with ART was already estimated at 4.7 billion euros [6].

Finally, we note that it was not possible to derive a safe concentration from the available data, which poses a practical challenge in terms of ensuring the safe use of the substance at risk-management stage.

Therefore, for all the reasons above, the criteria for equivalent level of concern can be considered to be met.

Conclusion:

Based on the above, the dossier submitter's proposal for the identification of IBP as a substance of very high concern due to its endocrine properties for human health under REACH article 57(f) is fully supported.

---

[1] Fertility Europe. 2017. A policy audit on fertility: Analysis of 9 EU countries. https://www.eshre.eu/-/media/sitecore-files/Publications/PolicyAuditonFertilityAnalysis9EUCountriesFINAL16032017.pdf

[2] Hagai Levine, Niels Jørgensen, Anderson Martino-Andrade, Jaime Mendiola, Dan Weksler-Derri, Irina Mindlis, Rachel Pinotti, Shanna H Swan, Temporal trends in sperm count: a systematic review and meta-regression analysis, Human Reproduction Update, Volume 23, Issue 6, November-December 2017, Pages 646–659, https://doi.org/10.1093/humupd/dmx022

[3] The 2013 Berlaymont Declaration on Endocrine Disrupters. Brunel University, May 24, 2013. https://www.brunel.ac.uk/__data/assets/pdf_file/0005/300200/The_Berlaymont_Declaration_on_Endocrine_Disrupters.pdf

[4] WHO Europe. 2006. Low fertility: The future of Europe? Entre Nous, the European magazine for sexual and reproductive health. No. 63. http://www.euro.who.int/__data/assets/pdf_file/0010/73954/EN63.pdf

[5] Health and Environment Alliance, "Health Costs in the European Union – How much is related to EDCs?", 2013, https://www.env-health.org/wp-content/uploads/2018/06/health_costs_report_edcs.pdf - Specific chapter on reproductive problems, http://env-health.org/IMG/pdf/reproductive_problems-2.pdf

[6] Trasande L, Zoeller T et al., "Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis", 22 March 2016, https://doi.org/10.1111/andr.12178