Submitted on 13th October 2022

HEAL comments - SVHC identification proposal for 4,4'-sulphonyldiphenol (Bisphenol S; BPS) as a SVHC

Reasons for proposing:

- **Toxic for reproduction (Article 57(c))**
- **Equivalent level of concern having probable serious effects on the environment due to endocrine properties (Article 57(f))**
- **Equivalent level of concern having probable serious effects on human health due to endocrine properties (Article 57(f))**

The Health and Environment Alliance (HEAL) thanks the Belgian Competent Authority for its proposal to identify Bisphenol S (BPS) as a substance of very high concern (SVHC) due to its reprotoxic properties (article 57(c)) and its endocrine disrupting properties relevant for human health and the environment (article 57(f)). We fully support this proposal.

BPS is manufactured and imported into the EU at ≥ 10 000 tonnes per annum. It is used in many different production processes and products like food contact materials, personal care products, textiles, thermal paper, dental cements, water pipes, and medical devices.

Introduction

BPS is a good example of a regrettable replacement as it is being used in lieu of BPA, a candidate list substance with similar use profiles and hazard properties. BPA has been classified as a 1B reproductive toxicant under Annex VI under CLP and identified as endocrine disruptors under article 57(f).

Reproductive Toxicity

In February 2022, BPS was added to the Annex VI of CLP as a category 1B reproductive toxicant. Therefore, we consider the identification of the substance as a SVHC due to its reproductive properties under REACH article 57(c) to be unequivocal.

Endocrine disruption

Based on the scientific literature applying the Weight of the Evidence Approach, the dossier concludes that BPS can be identified as an endocrine disruptor for human health as per WHO/IPCS' definition and meets the criteria of Equivalent Level of Concern (ELoC). HEAL agrees with this conclusion. There is strong evidence from *in vitro and in vivo* studies showing estrogenic activity linked to BPS exposure. Further, studies demonstrate the link between estrogenic potency and BPS exposure at even low doses, as well as during different windows of

exposure, demonstrating that low-dose effects and timing are both relevant to the complex hormonal effects observed. [1]

Mode of action (MoA)

The Belgian Competent Authority provides a thorough summary of the different MoAs with consistent *in vivo* and *in vitro* evidence of estrogenic activity and steroidogenesis.

In humans, consistent evidence of estrogenic activity and steroidogenesis as the main MoA's was highlighted in the dossier, meeting the criteria for estrogenic, androgenic, thyroidal, and steroidogenic (EATS)-mediated effects. In *in vitro* studies, oestrogen binding assays demonstrated BPS' capability to bind with the ER in rat and human cells. In *in vivo* studies using rat uterotrophic assays, investigators determined estrogenicity resulting in increases in uterine weight. EATS-mediated effects also resulted in observed outcomes including disturbance of the estrous cycle, reduced sperm count and motility from low dose exposure and high incidence of mammary gland multifocal atrophy in male rodents. In *in vitro* assays, steroidogenesis was also observed after BPS exposure leading to trends in decreased testosterone and increases in testis aromatase expression. Several *in vivo* studies in rodents saw serum testosterone levels decrease as well. Other MoAs that are sensitive to, but not diagnostic of, EATS observed outcomes include decreased female fertility and number of pups via a decrease in the number of embryo implantation sites and post-implantation loss. [2]

Regarding the environment, the dossier also provides clear scientific evidence of EATS-mediated effects derived from estrogenicity and steroidogenesis resulting in adverse effects (e.g. reduced sperm count and a trend towards feminisation in zebrafish). Other MoAs that are sensitive to, but not diagnostic of, EATS also stemming from ER binding and steroidogenesis result in such outcomes as reduced fecundity and hatching rate, and oocyte maturation in fish were also observed [3]. We strongly agree with the dossier's assessment that overall impacts on endocrine function leading to adverse effects on development and reproduction are concerning at a population level.

Adverse effects

As mentioned in the dossier, male and female reprotoxic effects have been linked to BPS' endocrine disrupting properties, with similar developmental and reproductive outcomes seen in vertebrates and fish alike. Importantly, the dossier notes significant concerns pertaining to interactions between MoAs, due to the complexity of the effects sensitive to, but not diagnostic of EATS-mediated effects. Research suggests that the effects seen in male rodent's mammary glands indicating endocrine disruption may influence outcomes such as the development of tumours. Several studies also suggest the biological plausibility of estrogenic activity related to BPS exposure and adverse effects seen in mammals and fish. The dossier also notes that brain neurogenesis and behaviour alterations were seen in fish.

Epidemiological and biomonitoring evidence:

The dossier provides a comprehensive list of studies, which detected BPS in biomonitoring samples (e.g. urine, blood serum, cord blood, placenta, amniotic fluid, etc) in the general

population and in workers throughout Europe and other parts of the world. [4] Studies looked at concentrations in children, pregnant women, and cashiers and found detectable concentrations, indicating that vulnerable populations are exposed. Exposure during vulnerable windows of development in utero and during childhood pose permanent and long-term adverse health threats at the individual and general population levels.

Based on current evidence, the dossier was not able to verify a safe threshold for exposure due to resulting low-dose effects, which suggests no currently known safe level of exposure to BPS. Furthermore, studies have shown that low-dose exposures are associated with adverse outcomes such as increased risk of type 2 diabetes. Human studies have also found exposure to BPS is likely to alter the ovarian cycle, which has been associated with increased risk of infertility, spontaneous abortions, and chronic diseases such as breast and ovarian cancer, uterine fibroids, diabetes, obesity and cardiovascular disease. [5] [6] [7]

Thus, epidemiological and biomonitoring evidence further establishes the linkage between BPS' oestrogenic activity and reprotoxic and endocrine disrupting endpoints seen in humans.

Equivalent level of concern

There is strong evidence of irreversible, adverse impacts to human health and the environment including impaired reproduction and population stability as a result of developmental exposures to BPS. In addition, many substances are commonly used together, creating the potential for additive and synergistic adverse effects in real life exposures. [8]

Therefore, HEAL supports the dossier's conclusion that due to BPS' endocrine disrupting properties, it is considered to be of equivalent level of concern to CMR Cat. 1, PBT or vPvB substances as listed in Article 57 points (a) to (e) of the REACH Regulation.

In summary, HEAL fully supports the Belgian Competent Authority proposal to identify BPS as a SVHC due to its scientifically well documented reprotoxic and endocrine disrupting properties for human health and the environment under REACH articles 57(c) and 57(f) respectively.

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[1] Belgian Competent Authorities.(2022). Identification of 4,4'-sulphonyldiphenol (Bisphenol S; BPS) as a SVHC. Pg. 10.

[2] Ibid. Pg. 10-11.

[3] Ibid. Pg. 13

[4] Ibid. Pg. 33-39.

[5] Duan Y., Yao Y., Wang B., Han L., Wang L., Sun H. and Chen L. (2018). Association of urinary concentrations of bisphenols with type 2 diabetes mellitus: A case-control study. *Environmental Pollution*. 243, 1719-1726. Doi: 10.1016/j.envpol.2018.09.093.

[6] Thoene, M. et al. (2020). Bisphenol S in Food Causes Hormonal and Obesogenic Effects Comparable to or Worse than Bisphenol A: A Literature Review. *Nutrients.* 12(2): 532. Doi: 10.3390/nu12020532.

[7] Belgian Competent Authorities. Pg 73

[8] Ibid.Pg. 13