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**Risk Management Option Analysis Conclusion Document**

**Substance Name: 4,4’-sulphonyldiphenol (Bisphenol S; BPS)**

**EC Number: 201-250-5**

**CAS Number:** **80-09-1**

**Authority:** Belgian Federal Public Service Health, Food Chain Safety and Environment Risk Management service

**Date:** 12 September 2022

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# Foreword

The purpose of Risk Management Option analysis (RMOA) is to help authorities decide whether further regulatory risk management activities are required for a substance and to identify the most appropriate instrument to address a concern.

RMOA is a voluntary step, i.e., it is not part of the processes as defined in the legislation. For authorities, documenting the RMOA allows the sharing of information and promoting early discussion, which helps lead to a common understanding on the action pursued. A Member State or ECHA (at the request of the Commission) can carry out this case-by-case analysis in order to conclude whether a substance is a 'relevant substance of very high concern (SVHC)' in the sense of the SVHC Roadmap to 2020[[1]](#footnote-1).

An RMOA can conclude that regulatory risk management at EU level is required for a substance (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. Any subsequent regulatory processes under the REACH Regulation include consultation of interested parties and appropriate decision making involving Member State Competent Authorities and the European Commission as defined in REACH.

This Conclusion document provides the outcome of the RMOA carried out by the author authority. In this conclusion document, the authority considers how the available information collected on the substance can be used to conclude whether regulatory risk management activities are required for a substance and which is the most appropriate instrument to address a concern. With this Conclusion document the Commission, the competent authorities of the other Member States and stakeholders are informed of the considerations of the author authority. In case the author authority proposes in this conclusion document further regulatory risk management measures, this shall not be considered initiating those other measures or processes. Since this document only reflects the views of the author authority, it does not preclude Member States or the European Commission from considering or initiating regulatory risk management measures which they deem appropriate.

### OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

BPS has a harmonised classification under CLP for Repr.1B (H360 FD).

After evaluating of the new toxicity data (EOGRT with DNT and DIT cohorts, toxicokinetic study in rats) introduced following the substance evaluation under REACH EFSA concluded that the current Specific Migration limit (SML) of 0.05 mg/kg food is still appropriate (EFSA, 2020).

### CONCLUSION OF RMOA

This conclusion is based on the REACH and CLP data as well as other available relevant information.

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| --- | --- |
| **Conclusions** | **Tick box** |
| Need for follow-up regulatory action at EU level: |  |
| *Harmonised classification and labelling* |  |
| *Identification as SVHC (authorisation)* | X |
| *Restriction under REACH* | X |
| *Other EU-wide regulatory measures* |  |
| Need for action other than EU regulatory action |  |
| No action needed at this time |  |

### Need for follow-up regulatory action at EU level

### Harmonised classification and labelling

RAC adopted an opinion on harmonised classification for reproduction: Repr. 1B, H360FD (RAC opinion of 10 December 2020) in response to a CLH dossier submitted by BE CA. Consequently, BPS was included in the Annex VI of the CLP Regulation on 16 February 2022 (CLH entry: 604-098-00-1; EUR-Lex - 32022R0692 - EN - EUR-Lex (europa.eu) ).

### Identification as a substance of very high concern, SVHC (first step towards authorisation)

BPS is covered by index number 604-098-00-1 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3 (the list of harmonised classification and labelling of hazardous substances) and it is classified in the hazard class toxic for reproduction category 1B (H360FD).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for SVHC identification:

* Toxic for reproduction category 1B in accordance with Article 57 (c) of REACH.

Based on the conclusion proposed below , BPS is proposed to be identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) as there is scientific evidence of probable serious effects to the environment and human health which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of the REACH Regulation.

*Adverse effects*

**Human health:**

BPS consistently affects the estrous cyclicity in female rodents, at different windows of exposure. All the available studies show irregular cycles, linked in most of them to a prolongation of the diestrus phase. The disturbance of estrous cycle is considered as EATS (estrogenic, androgenic, thyroidal, and steroidogenic)-mediated.

In addition, effects that are sensitive to, but not diagnostic of, EATS (as potentially linked to other Modes of Action, MoA) were also reported regarding rodent female reproduction. A statistically significant decrease of the number of embryo implantation sites was observed in reproductive toxicity studies, resulting in decreased fertility and number of pups.

Other developmental and male reproductive adverse effects were observed in the available rodent studies supporting the endocrine disrupting properties of BPS. These include EATS-mediated effects such as reduced sperm count and motility at low doses and a high incidence of male rodent mammary gland multifocal atrophy. Additionally, adverse effects sensitive to, but not diagnostic of, EATS were observed including dose-dependent increased post-implantation loss in reproductive toxicity studies and higher adrenal glands weight, in particular in males, in several independent studies.

These adverse effects have been observed at doses showing neither maternal toxicity nor severe general toxicity. Moreover, since estrogen signalling is critical to reproductive success in all vertebrates including mammals, it is assumed that the observed adverse effects on fertility through disruption of estrogen signalling in rodents are relevant to humans.

The complexity of the effects sensitive to, but not diagnostic of, EATS observed following exposure to BPS suggests the interaction of multiple MoAs to produce the observed effects, increasing the concern for human health. For example, the consistent effects on the mammary gland in males in two rodent species provides an indication of hormonal disturbance and may have influence on e.g. human breast tumor development.

**Environment:**

There is evidence in literature that BPS affects sperm count and sex ratio in zebrafish (*Danio rerio*) after exposure in the µg/L range. In a ZEOGRT (OECD TG 240 adapted for zebrafish), the findings on sex ratio were not significant. However, a similar trend towards feminisation was observed with the number of males close to or even below natural variation at low concentrations. These EATS-mediated effects were observed at concentrations below general toxicity.

In addition, effects that are sensitive to, but not diagnostic of, EATS (as potentially linked to other Modes of Action) were also reported regarding reproductive effects: reduced fecundity, reduced hatching rate and altered oocyte maturation in fish.

Other important adverse effects on brain neurogenesis and behaviour were identified in fish. Experimental data on zebrafish demonstrated that these effects depend on BPS-induced changes in aromatase activity.

Effects on apical endpoints such as fecundity and altered sex ratio are considered to impair population stability and recruitment. Therefore, these effects are to be considered population relevant for the environment.

**BPS induces adverse effects on development and reproduction in rodents and fish.**

*Endocrine activity*

Bisphenols are known to target many endocrine pathways. Consistent *in vivo* and *in vitro* evidence is available on steroidogenesis and in particular on estrogenic activity.

* *Estrogenic activity*

*In vitro* ER binding assays demonstrate that BPS is capable of binding to the estrogen receptor, with IC50 ranging from 5.8 to 105 µM depending on the cell line used (rat and human). Several *in vitro* literature studies using different cell cultures showed a weak increase in the estrogenic activity (ER reporter gene assays, proliferative assays and ER-regulated gene expression assays). *In vivo*, the increase in uterine weight, observed in all rodent uterotrophic assays, is a parameter diagnostic of estrogenicity.

Vitellogenin, a biomarker of estrogenic activity in fish, was induced in embryonic and adult male zebrafish. Literature data also reported a change in steroidal hormone balance with decreased testosterone and increased estradiol levels and an increased E2/T ratio in zebrafish.

**BPS exhibits estrogenic activity.**

* *Steroidogenesis*

In a range of *in vitro* assays investigating steroidogenesis following exposure with BPS, a clear trend towards decreased testosterone was observed. Furthermore, an increase in testis aromatase expression was observed in several studies following exposure to BPS. Several, but not all, *in vivo* studies, showed decrease in serum testosterone level in rodents.

Moreover, the impact on the synthesis of steroid hormones (decrease of testosterone and increase of estrogen) was clearly shown in *in vivo* studies with zebrafish. These findings were accompanied by an increased expression of genes involved in steroidogenesis and specifically in aromatase (CYP19a, CYP19b in testis and brain resp.).

**BPS is shown to affect steroidogenesis.**

*Plausible link between adverse effects and endocrine activity*

**Human health:**

Considering the results of all available experimental studies, there is strong evidence that the adverse effects on fertility in female rodents are due to the estrogenic activity of BPS. The increase in uterus weight (as seen in the available uterotrophic assays) is a strong diagnostic parameter for estrogenicity. Furthermore, the prolongation of the estrous cycle was consistently observed in the majority of the studies. In addition, the number of implantation sites was decreased in three reproductive studies, resulting in a decrease of both fertility and number of pups. All of these parameters are considered as either EATS-mediated or sensitive to, but not diagnostic of, EATS modalities. The different effects of BPS, in particular on the female reproductive system, can be plausibly linked to the estrogenic activity of the substance and could therefore explain the adverse impacts seen on fertility endpoints.

Other modes of action than those involving estrogenic activity and/or signalling pathways are likely. For example, altered testosterone production is probably linked to adverse effects on the male reproductive system (reduced sperm count and motility) or the male mammary gland. Despite the fact that these data give further indications of the endocrine activity of BPS, they are considered as supportive adverse human health effects.

In conclusion, the effects on the female reproductive organs and functional parameters are consistent with an estrogenic mode of action of BPS. The adverse effects on the estrous cycle are EATS-mediated, therefore, in the absence of information proving the contrary, the biologically plausible link is already pre-established based on existing scientific knowledge. There is strong evidence that the **adverse effects on fertility and sexual function are plausibly linked to the estrogenic activity of the substance. BPS is therefore an endocrine disruptor according to the WHO/IPCS definition with regard to human health.**

**Environment:**

Based on the weight of evidence approach and considering the results of all available studies there is evidence that the adverse effects of BPS on sperm count and sex ratio in zebrafish are due to the estrogenic activity and to disrupted steroidogenesis.

Skewed sex ratio is recognised as an EATS-mediated effect. Altered gametogenesis as reduced sperm counts has been also observed. Based on the existing knowledge in mammals and the similarities with fish gametogenesis, reduced sperm count is considered as EATS-mediated also in fish. The estrogenic activity of BPS is demonstrated in mammals and is further evidenced by vitellogenin induction in fish. Altered steroidogenesis may lead to the observed decreased sperm counts and altered oocyte maturation which, in turn, may lead to impaired hatchability of the eggs. Increased aromatase activity is consistently observed and is clearly responsible for effects on fish brain and behaviour. Impaired social behaviour may also result in reduced reproduction.

All mammalian data were considered in a weight of evidence approach for the assessment of the ED properties in the environment, knowing that there is a large degree of conservation of the endocrine system. This implies large commonalities between non-mammalian and mammalian vertebrate species in regard to hormones, enzymes and receptors involved in the EATS modalities. Evidence of endocrine disruptive properties of BPS on mammalian vertebrate species therefore provides further support for similar properties in non-mammalian vertebrates, in particular with regard to disruption of estrogenic pathways.

**Considering all relevant and reliable information in a weight of evidence approach, it is concluded that BPS is an endocrine disruptor according to the WHO/IPCS definition with regard to environment.**

Equivalent level of concern:

The effects of BPS due to its endocrine disrupting properties are 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.

Based on the scientific evidence, the effects on organisms and populations are considered to be severe and irreversible as effects on estrous cycle, sex ratio, etc. are observed following developmental exposure. Such effects are considered to impair population stability and recruitment. Moreover, a wide range of taxa in different ecosystems may be adversely affected due to conservation of the endocrine system. However, the difference between taxa concerning specific hormones affected, binding affinities and modes of action makes it difficult to determine the most sensitive species and thus to quantify a safe level of exposure with regard to the endocrine mediated effects.

Bisphenols are widely used and can be found together in the environment. It has been already recognised that bisphenols can act jointly in the environment by sharing the same mode of action resulting in additive effects. Bisphenols can also act together with chemicals other than bisphenols (sharing the same and/or a different MoA) occurring in the environment, at comparatively low concentrations, displaying the same and/or additional effects. This supports equivalent level of concern as endocrine disruptors with similar MoA but also chemicals with different MoA can act additively or even synergistically.

**In conclusion:**

Based on all available scientific evidence, it can be concluded that BPS fulfils the WHO/IPCS (2002)[[2]](#footnote-2) definition of an endocrine disruptor:

* It shows clear reproductive adverse effect in rodents and fish. The reproductive endocrine system is highly conserved not only between mammals, but also between mammals and other vertebrates like fish.
* It has endocrine modes of action: clear estrogenic mode of action and alteration of steroidogenesis.
* The adverse effects, including the recognised EAS-mediated effects (e.g. on estrous cycle and sex ratio) and effects sensitive, but not diagnostic of EAS (e.g. fecundity, fertility, implantation sites and number of pups), are a consequence of the endocrine modes of action.

The assessment performed demonstrates that there is scientific evidence of **probable serious effects of BPS to the environment and human health due to its endocrine disrupting properties, which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of the REACH Regulation.**

Given the above, BE CA considers it appropriate to prepare and submit an Annex XV SVHC-dossier as a first step in the risk management of BPS. Addition of the substance to the candidate list for its ED HH (non-threshold) on top of the identification as reproductive toxicant entails additional information obligations (e.g. provide advice on safe use to downstream users) and may need stricter operational conditions and Risk Management Measures to minimize exposure to humans. Moreover the identification as ED ENV additionally to ED HH should lead to additional/different operational conditions and Risk Management Measures to minimize exposure to the environment.

Furthermore, identification as SVHC could also benefit other legislations (food contact materials, drinking water, integrated pollution prevention and control (IPPC), workers legislation, …). Indeed, although not detailed as such in the registration dossier, BPS can be found and used as a monomer and resin in the production of food contact material and adhesives (captured under the use as monomer). The use of BPS as a monomer in plastic food contact materials is authorized under Regulation n° 10/2011. A specific Migration limit (SML) of 0.05 mg/kg food was set and reconsidered by EFSA after evaluating of the new toxicity data (EOGRT with DNT and DIT cohorts, toxicokinetic study in rats) introduced following the substance evaluation under REACH. EFSA concluded that the current SML is still appropriate (EFSA, 2020). However in the Esteban cross-sectional study urine was monitored from 500 French children and 900 adults (age between 6 and 74) during 2 years. BPS was found in almost all samples and in a geometric mean concentration of 0.53µg/g creatine. The impregnation was higher in children than in adults. Although the conclusion of the causality of such cross-linking study should be treated with care, concentrations in children were found to increase with the consumption of pre-packaged fish and a less regular ventilation of the dwelling, while in adults the increase was found to be due to the consumption of pre-packaged foods.

Hence, identification of BPS as an endocrine disruptor for human health may have an impact and may lead to further assessments.

BPS can be found in several environmental compartments including water, sediment, sludge, indoor dust and air. However due to the difference in production, uses and sources of discharge in the different countries, different concentrations and detection frequencies of BPS are observed.

Moreover, although BPS can be adequately removed from a WWTP as shown by Česen *et al.* (2018), it still may be an important exposure source from the recycling process of paper as if BPS is removed from the paper matrix via the water used in this process it might end up in the environment.

Additionally, because of its structural similarity to BPA, BPS is considered by industry as a potential alternative to BPA. Therefore, the identification of BPS as an ED is recommended to control its use and import in Europe and to protect our industries from investing in unsustainable BPA alternatives. A grouping approach of bisphenols is considered relevant to avoid any regrettable substitution. The identification of BPS as an SVHC for HH and the ENV similar to BPA is a starting point in this process.

Depending on the scope of the intended restriction and the potential inclusion of the substance in the currently available restriction on BPA in thermal paper, authorization could be further considered as complimentary measure to avoid regrettable substitution and possibly regulate uses for which restriction may be considered not the appropriate tool (e.g. if it cannot be demonstrated that there is a community-wide risk for certain uses not adequately controlled).

### Restriction under REACH

Restriction can be introduced when there is an unacceptable risk to human health and/or the environment, arising from the manufacture, placing on the market (including imports) or the use of the substances, which needs to be addressed on a community-wide basis. A restriction may apply to any substance on its own, in a mixture or in an article. Restriction procedure also takes into account the socio-economic impact of the restriction, including the availability of alternatives. If it can be demonstrated that there is a Community-wide risk, which is not adequately controlled for certain uses of substances, a restriction process according to REACH Articles 69(1) and 69(4) should be started.

BPS is a potential candidate to be included in

1. the intended restriction of 4,4'-isopropylidenediphenol (Bisphenol A) and structurally related bisphenols (including derivatives) of similar concern for the environment restriction by DE CA with potentially following scope (expected submission date: 07/10/2022):

a) Restricting the use as an additive and the content in articles (0.02% by weight);

b) Restricting content of residues (unreacted monomer) in articles – also for imported goods (0.02% by weight);

c) Restricting the use of mixtures with content of 0.02% by weight for industrial and professional uses where strictly controlled conditions cannot be assured, e.g. in non-automated processes and for consumer uses.

d) Introducing release rates for BPA from articles (products and subassemblies) during service life (weathering, leaching due to cleaning action) preventing release into the environment and/or (direct) migration to organisms.

Additionally, alternative bisphenols with similar concern have increasingly been used as substitutes for Bisphenol A. Taking into account recent observations, it can be assumed that if the amount of Bisphenol A for a specific process decreases, the amount of alternative bisphenols increases at the same rate. Therefore, the scope of this restriction aims to also address bisphenols of similar concern for the environment.

BPS is expected to fall under the scope of the restriction proposal for BPA (ROI: [Registry of restriction intentions until outcome - ECHA (europa.eu)](https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e1853413ea)) however the exact scope and the outcome of this restriction proposal are still unknown.

### Other Union-wide regulatory measures

Not applicable.

### Need for action other than EU regulatory action

Not applicable.

### No action needed at this time

Not applicable.

### TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

Indication of a tentative plan is not a formal commitment by the authority. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

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| **Follow-up action** | **Date for follow-up** | **Actor** |
| Annex XV dossier for SVHC identification | August/ 2022 | BE CA |

1. For more information on the SVHC Roadmap: <http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/svhc-roadmap-to-2020-implementation> [↑](#footnote-ref-1)
2. An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, its progeny or (sub)populations. [↑](#footnote-ref-2)