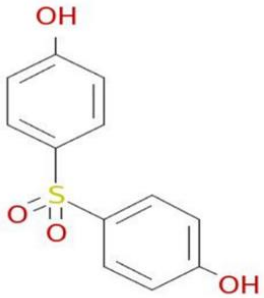
AGREEMENT OF THE MEMBER STATE COMMITTEE
ON THE IDENTIFICATION OF

4,4'-sulphonyldiphenol

AS A SUBSTANCE OF VERY HIGH CONCERN
under Articles 57 and 59 of Regulation (EC) 1907/2006
Adopted on 28 November 2022

This agreement concerns
4,4'-sulphonyldiphenol (bisphenol S, BPS)
EC number: 201-250-5
CAS number: 80-09-1
Molecular formula: $C_{12}H_{10}O_4S$
Structural formula:



The Member State Committee agreed that:

1. **4,4'-sulphonyldiphenol (bisphenol S, BPS) is a substance under Articles 57 (c) and 57 (f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with toxic for reproduction properties, and with endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health and environment which gives rise to an equivalent level of concern to substances listed under Article 57 (a) to (e) of REACH.**

2. **BPS must be added to the Candidate list of substances of very high concern**.

Annex 1: Scientific evidence for identification of a substance of very high concern

The information below is based on Support Document (Member State Committee, 28 November 2021)

4,4'-sulphonyldiphenol, referred to hereinafter as 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)[1] and it is classified in the hazard class toxic for reproduction category 1B (H360FD: 'May damage fertility. Suspected of damaging the unborn child'). Therefore, this classification of the substance in Regulation (EC) No 1272/2008 allows its identification as substance of very high concern in accordance with Article 57(c) of REACH.

In addition, BPS is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because of its endocrine disrupting (ED) properties for which 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 estrogenic, androgenic and steroidogenic (EAS)-mediated.

In addition, effects that are sensitive to, but not diagnostic of, estrogenic, androgenic, thyroidal and steroidogenic (EATS) (as potentially linked also 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 ED properties of BPS. These include EAS-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.

[1] COMMISSION DELEGATED REGULATION (EU) 2022/692 of 16 February 2022 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (18th ATP)

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 tumour 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 Zebrafish Extended One Generation Reproduction Test (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 EAS-mediated effects were observed at concentrations below general toxicity.

In addition, effects that are sensitive to, but not diagnostic of, EATS (as potentially linked also to other MoAs) 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 estrogen receptor (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 17β-estradiol /testosterone (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, respectively).

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 EAS-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 EAS-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.

There is a large degree of conservation of the endocrine system, implying large commonalities between non-mammalian and mammalian vertebrate species in regard to hormones, enzymes and receptors involved in the EATS modalities. All mammalian data provide substantial evidence that BPS can disrupt particularly estrogenic pathways. Therefore, those data were also considered in the Weight of Evidence approach for the assessment of the ED properties in the environment and thus wildlife species.

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 ED 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 4,4'-sulphonyldiphenol (BPS) fulfils the WHO/IPCS (2002)[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 estrogenic, androgenic and

[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.

steroidogenic (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.

Annex 2: Procedure

1. On 26 August 2022, Belgium presented a proposal under Article 59(3) and Annex XV of the REACH Regulation on identification of BPS as a substance which satisfy the criteria of Articles 57 (c) and 57 (f) of REACH.
2. On 2 September 2022, the Annex XV dossier was circulated to Member States and the Annex XV report was made available to interested parties on the ECHA website as required by Articles 59(3) and 59(4).
3. BPS received comments from both Member States and interested parties on the proposal.
4. On 16 November 2022, the dossier was referred to the Member State Committee (MSC) and agreed in the written procedure of the MSC with closing date of 28 November 2022.