COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Last data extracted on 10.02.2020

Substance name: 4,4'-sulphonyldiphenol; bisphenol S
CAS number: 80-09-1
EC number: 201-250-5
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	Germany	CHEM Trust Europe	International NGO	1
Comment received				
- CHEM Trust would like to thank the dossier submitter for their important work on the CLH report to classify BPS as a substance toxic to reproduction. - The similar substance Bisphenol A is already classified as Rep 1B and has been identified and included in the REACH Candidate List as a SVHC due to its endocrine disrupting properties. - An identification as endocrine disruptor may also be warranted for BPS as many studies have shown estrogenic activity like BPA (see e.g. https://academic.oup.com/toxsci/article/139/1/35/2338266). - Already in 2015 RAC highlighted that BPS has similar properties to BPA and still the substances was marketed without any information on its potential hazards despite indications for the damage on fertility (see insufficient self-classification by companies in the classification and labelling inventory, as summarized in the CHEM Trust report `From BPA to BPZ. https://www.chemtrust.org/wp-content/uploads/chemtrust-toxicsoup-mar-18.pdf) - At the same time BPS was increasingly used as a replacement for BPA in thermal paper, as has been found in an ECHA survey (https://echa.europa.eu/-/bpa-being-replaced-by-bps-in-thermal-paper-echa-survey-finds). - Use of BPS as a replacement for BPA may potentially lead to higher internal exposure to endocrine active substances as there may be a higher systemic bioavailability after oral ingestion of BPS compared to BPA as recently reported when studied in pigs (https://doi.org/10.1289/EHP4599). - In order to avoid replacing a harmful substance with one with similar properties we urge taking a group approach to bisphenols in the necessary subsequent risk management measures. - BPS has been included in ChemSec`s SIN list in 2014 as an endocrine disrupter based on its estrogenic properties. It has shown to be estrogenic in in vitro studies. In vivo studies have shown impaired reproduction in zebrafish and uterine growth in rat. (https://sinsearch.chemsec.org/chemical/80-09-1). - The need for classification due to other hazards e.g. acute toxicity should be scrutinised as a recent study in isolated mouse hearts may indicate a possibility for instant heart effects after exposure to BPS in amounts that mimicked typical human levels (https://www.news-medical.net/news/20200109/Study-Bisphenol-S-can-hinder-heart-function-within-minutes-of-exposure.aspx). - It is very concerning that there is widespread exposure of the general population to BPS. The substance has also been included as a priority in the ongoing Human Biomonitoring				

Initiative https://www.hbm4eu.eu/mdocs-posts/hbm4eu-ici-equas-report-bisphenols-in-urine-round-2/
- BPS is meanwhile already ubiquitous in the environment, and has been shown to affect the development of Zebrafish larvae (Wu et al. 2018). Wu L-H et al, 2018 Occurrence of bisphenol S in the environment and implications for human exposure: A short review. Sci Total Environ.615, 87-98; https://doi.org/10.1016/j.scitotenv.2017.09.194

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	Germany	BASF SE	Company-Manufacturer	2
Comment received				
Comments provided by the EU-REACH registrants ECHA note – An attachment was submitted with the comment above. Refer to public attachment 80-09-1_DHDPS_comments on CLH dossier_public consultation_clean.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2020	Denmark	DTU National Food Institute	Academic institution	3
Comment received				
We support that BPS is classified with Repr. 1B H360FD				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	Sweden		MemberState	4
Comment received				
The Swedish CA supports classification of bisphenol S (CAS No. 80-09-1) as Repr 1B H360 FD. SE agrees with the rationale for classification into the proposed hazard class and differentiations.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	Germany	CHEM Trust Europe	International NGO	5
Comment received				
- CHEM Trust supports the classification of BPS as a reprotoxic substance, category 1B (labelling GHS08 Dgr, H360FD) because: - A new EORGTS study from 2019 (OECD 443) supported by a reproduction/developmental toxicity screening test and further one combined with a repeated dose toxicity study (OECD 421 and 422) clearly show adverse effects on sexual function and fertility which cannot be related to a general toxicity. - A new EORGTS study from 2019 (OECD 443) supported by a prenatal developmental toxicity study (OECD 414) and a combined repeated dose toxicity study/reproduction/developmental toxicity screening test (OECD 422) clearly show adverse effects on development which cannot be related to a general toxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2020	Germany		MemberState	6

Comment received

For bisphenol S the classification Repr. 1B, H360FD is proposed. The proposal is based on effects seen in rats after administration of the test substance by gavage.

Fertility

In a reproductive toxicity study according to OECD 421 significant effects on fertility parameters were detected (Anonymous 12, 2000). In the highest dose group the mean oestrus cycle was significantly longer as compared to the control group. Also the fertility index was markedly lower in the high dose group (58 % as compared 92 % in the control group). A decrease in implantation sites was noted and the implantation index was significantly lower as compared to the control. In males a decrease of the relative pituitary weight and an increase of the weight of the seminal vesicles were observed in the highest dose group.
In an extended one generation reproductive toxicity study in rats similar effects were found (Anonymous 13, 2019). A significant longer oestrus cycle and a slight decrease of implantation sites were observed in F0 females at the highest dose level (180 mg/kg bw/d), as well as significant increased mean number and percentage of post implantation loss (also in Cohort 1B). A slight but significant decrease of sperm motility was noted in in all dose groups in F0 males; however, fertility was not affected. Additionally a significant lower number of liveborn and a higher number of stillborn pups were noted F0 females of the highest dose group.
Similarly a study according to OECD TG 422 in rats (Anonymous 14, 2017) observed a significantly increased oestrus cycle at the highest dose level (300 mg/kg bw/day) as well as a significantly lower mean number of implantation sites. Post-implantation loss (%) was significantly higher and the mean number of delivered pups was significantly lower at 300 mg/kg bw/d.
Maternal toxicity was not very pronounced, comprising slight effects on body weight, liver and kidney. No mortality was noted in any of the dose groups.
Because of absence of significant maternal toxicity and the increased length of oestrus cycle and marked reduction of implantation sites in three reproductive toxicity studies, the DE CA agrees that a classification as Repr. 1B, H360F is warranted.

Developmental toxicity

The classification of bisphenol S as Repr. 1B H360D is based on a significant increase of post-implantation losses in two studies in the absence of significant maternal toxicity. Indeed, post-implantation loss was significantly higher at the highest dose levels (300 mg/kg bw/d) in a combined repeated dose toxicity study with reproduction/developmental toxicity screening test (300 mg/kg bw/d; Anonymous 14, 2017) and an EOGRTS (60 + 180 mg/kg bw/d; Anonymous 13, 2019). In a prenatal developmental toxicity study according to OECD TG 414 (Anonymus 19, 2014) mean post-implantation loss is also noticeably increased at 300 mg/kg bw/d).
Maternal toxicity was minimal and thus, the classification of bisphenol S as Repr. 1B H360D is supported.

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2020	Denmark	DTU National Food Institute	Academic institution	7

Comment received

Arguments are provided below for support for a classification of Repr. 1B H360FD with reference to the CLP report and open literature.
Severe decreased number of implantation sites and severe higher estrus duration were observed in three different studies. These effects were more pronounced in the reproductive toxicity test (Anonymous 12, 2000) and in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Anonymous 14, 2017). In the EOGRTS (Anonymous 13, 2019), the highest tested dose was only 180 mg/kb bw/d (compared to 300 mg/kg bw/d in Anonymous 12 (2000) and Anonymous 14 (2017)). At this top dose, nearly absent general toxicity was observed. The DS wants to highlight that females exposed to 180 mg/kg bw/d exhibited already significant fertility effects, which would be more pronounced if the study would have been dosed higher as it is the case in the Anonymous 12 (2000) and Anonymous 14 (2017).
The setting of the top dose in Reproductive studies and Cancer studies is currently discussed in EU (incl. ECHA) and globally in OECD. In this EOGRTS study (Anonymous 13, 2019), the top dose might have been set too low, but still adverse reproductive toxicity effects (fertility) were seen. This supports a classification as with this low top dose no maternal toxicity or general toxicity is seen.
I strongly support that this also according to the CLP criteria leads to a classification as Repr. 1B for adverse effects on sexual function and fertility. This classification is warranted based on the above mentioned severe effects observed in the available studies, which cannot be related to a general toxicity (see also comment on top dose).

According to the CLP criteria a classification as Repr. 1B for adverse effects on development is warranted based clear evidence of an adverse effect on development in the absence of toxic effect. Severe higher incidence of post-implantation loss were observed in two different studies, which cannot be related to a general toxicity. I support that BPS is classified with Repr. 1B H360FD
Moreover, in the open literature, also several papers show similar effects on reproduction as BPA (Ahsan et al. 2018). The results in this study suggest that neonatal exposure to higher concentrations of BPS can lead to BPA like structural and endocrine alterations in female rats.
ANSES have made a report in 2013 entitled Substitution of bisphenol A: review of alternatives to BPA, identification of the hazards of potential substitutes for bisphenol A" (ANSES, 2013) Both the ANSES report and other previous studies have shown that most BPA analogous including BPAF share common mechanistic properties such as estrogenic activity.

Ref. Ahsan N, Ullah H, Ullah W, Jahan S. Comparative effects of Bisphenol S and Bisphenol A on the development of female reproductive system in rats; a neonatal exposure study. Chemosphere. 2018;197:336–343. doi:10.1016/j.chemosphere.2017.12.118

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2020	France		MemberState	8

Comment received

In relation to fertility, based on the data provided in the C&L dossier, an effect on female cyclicity is demonstrated with consistent findings in the 3 studies that investigate this parameter: increased cycle duration and prolonged dioestrus. Proper cyclicity is essential for a functional reproductive function in mammals and humans in particular. An effect on

implantation is also consistently observed. An impact on the fertility index is observed at the highest doses and the effect cannot be attributed to the modest general toxicity. A classification Repr 1B for fertility is fully supported on this basis.

In males, effects on the weight of reproductive organs are noted in several studies (effect on seminal glands in OECD 421 at 300 mg/kg, on prostate in the EOGRTS at 180 mg/kg, on prostate and seminal gland in the 28-day study, on testis and epididymis in the 90-day study). Atrophy of mammary gland is also consistently observed in males. Although it has no impact on the reproductive function, this effect may indicate sex hormone disturbance, together with increased pituitary weight in the OECD 421 study. No histological findings are reported in male reproductive organs. However, sperm parameters are very poorly investigated in the dataset. A decrease of sperm motility is reported in F0 in the EOGRTS and to our understanding this parameter has not been investigated in any other studies. An effect on male reproductive function is therefore suspected but is insufficiently characterised.

In relation to developmental toxicity, a significant effect in post-implantation loss in the OECD 422 study as well as in the EOGRTS is observed. The number of stillborn F1 pups was also increased in the EOGRTS and modifications of fetal weight are noted. The effects cannot be attributed to the modest maternal toxicity and a classification Repr 1B for development is fully supported on this basis.

In the EOGRTS, the DNT cohort gave a negative outcome and the DIT cohort was inconclusive. The results of the DNT cohort should have been reported with more details in Annex I to allow adequate analysis. In particular, data supporting the reliability and sensitivity of the test method (i.e. positive and historical control data) should be specified as well as statistical treatment of results, including statistical models used to analyze the data, and the results, regardless of whether they were significant or not (OECD TG 443). Lastly only means are reported in Cohort 2 without any indication on the standard deviation (SD) or the standard error of the mean (SEM). Moreover some published studies (see literature reference list below) show effects on the expression of maternal behavior and anxiety-related behaviour. Lastly the highest dose in this study is considered insufficiently high and prevent from any conclusion.

In conclusion, the proposed classification is supported for BPS.

It is also noted that the effects observed with BPS are similar to effects of its close structural analogue BPA, that is classified Repr 1B for fertility and identified as an SVHC for its endocrine disrupting properties relevant for health and environment.

In addition, it is noted that a number of studies have been published, in particular in the very recent years and relates to investigation of effects of BPS on reproductive function as well as developmental effects of BPS. A non-exhaustive list of publications is provided below. These data seem to :
- Provides further evidence that BPS affect female reproductive function as well as male reproductive function, in rats and mice
- Provides some indications that developmental exposure to BPS may alter metabolic function, behaviour and mammary gland development
- Provide indication about human impregnation including in pregnant woman
- Give some warnings about potential human health effects linked to BPS exposure but further investigations on its health effects in humans are warranted.

The data presented in the C&L dossier fully justify a classification Repr 1B for fertility and development and an in-depth assessment of published studies may not be necessary. But

these publications emphasise that the scope of the reproductive and developmental effects of BPS is not fully characterised yet. None of the published studies is in contradiction with the proposed classification.

We note that BPS is evaluated by Belgium (within the CORAP list). In this context, we recommends that these data should also be included in the registration dossier by registrants to provide an exhaustive evaluation of the effects of the substance

Editorial comment:
The OECD 407 study seems to be wrongly described on page 26 as a dietary study whereas BPS was given by gavage in this study.

Additional bibliographic references:
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2: Ullah A, Pirzada M, Jahan S, Ullah H, Razak S, Rauf N, Khan MJ, Mahboob SZ. Prenatal BPA and its analogs BPB, BPF, and BPS exposure and reproductive axis function in the male offspring of Sprague Dawley rats. Hum Exp Toxicol. 2019 Dec;38(12):1344-1365. doi: 10.1177/0960327119862335. PubMed PMID: 31514588.

3: Ijaz S, Ullah A, Shaheen G, Jahan S. Exposure of BPA and its alternatives like BPB, BPF, and BPS impair subsequent reproductive potentials in adult female Sprague Dawley rats. Toxicol Mech Methods. 2020 Jan;30(1):60-72. doi: 10.1080/15376516.2019.1652873. Epub 2019 Sep 13. PubMed PMID: 31424294.

4: Shi M, Whorton AE, Sekulovski N, MacLean JA, Hayashi K. Prenatal Exposure to Bisphenol A, E, and S Induces Transgenerational Effects on Male Reproductive Functions in Mice. Toxicol Sci. 2019 Dec 1;172(2):303-315. doi: 10.1093/toxsci/kfz207. PubMed PMID: 31532523.

5: Prokešová Š, Ghaibour K, Liška F, Klein P, Fenclová T, Štiavnická M, Hošek P, Žalmanová T, Hošková K, Řimnáčová H, Petr J, Králíčková M, Nevoral J. Acute low-dose bisphenol S exposure affects mouse oocyte quality. Reprod Toxicol. 2019 Dec 24. pii: S0890-6238(19)30692-6. doi: 10.1016/j.reprotox.2019.12.005. [Epub ahead of print] PubMed PMID: 31881267.

6: da Silva BS, Pietrobon CB, Bertasso IM, Lopes BP, Carvalho JC, Peixoto-Silva N, Santos TR, Claudio-Neto S, Manhães AC, Oliveira E, de Moura EG, Lisboa PC. Short and long-term effects of bisphenol S (BPS) exposure during pregnancy and lactation on plasma lipids, hormones, and behavior in rats. Environ Pollut. 2019 Jul;250:312-322. doi: 10.1016/j.envpol.2019.03.100. Epub 2019 Apr 9. PubMed PMID: 31003143.

7: Yin N, Liang X, Liang S, Liang S, Yang R, Hu B, Cheng Z, Liu S, Dong H, Liu S, Faiola F. Embryonic stem cell- and transcriptomics-based in vitro analyses reveal that bisphenols A, F and S have similar and very complex potential developmental toxicities. Ecotoxicol Environ Saf. 2019 Jul 30;176:330-338. doi: 10.1016/j.ecoenv.2019.03.115. Epub 2019 Apr 2. PubMed PMID: 30951980.

8: Meng Z, Wang D, Liu W, Li R, Yan S, Jia M, Zhang L, Zhou Z, Zhu W. Perinatal exposure to Bisphenol S (BPS) promotes obesity development by interfering with

lipid and glucose metabolism in male mouse offspring. Environ Res. 2019 Jun;173:189-198. doi: 10.1016/j.envres.2019.03.038. Epub 2019 Mar 21. PubMed PMID: 30921577.

9: Ullah A, Pirzada M, Jahan S, Ullah H, Khan MJ. Bisphenol A analogues bisphenol B, bisphenol F, and bisphenol S induce oxidative stress, disrupt daily sperm production, and damage DNA in rat spermatozoa: a comparative in vitro and in vivo study. Toxicol Ind Health. 2019 Apr;35(4):294-303. doi: 10.1177/0748233719831528. Epub 2019 Mar 14. PubMed PMID: 30871434.

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17: Pu Y, Gingrich JD, Steibel JP, Veiga-Lopez A. Sex-Specific Modulation of Fetal Adipogenesis by Gestational Bisphenol A and Bisphenol S Exposure. Endocrinology. 2017 Nov 1;158(11):3844-3858. doi: 10.1210/en.2017-00615. PubMed PMID: 28938450; PubMed Central PMCID: PMC5695840.

18: Shi M, Sekulovski N, MacLean JA 2nd, Hayashi K. Effects of bisphenol A analogues on reproductive functions in mice. Reprod Toxicol. 2017 Oct;73:280-291. doi: 10.1016/j.reprotox.2017.06.134. Epub 2017 Jul 1. PubMed PMID: 28676390.

19: Žalmanová T, Hošková K, Nevoral J, Adámková K, Kott T, Šulc M, Kotíková Z, Prokešová Š, Jílek F, Králíčková M, Petr J. Bisphenol S negatively affects the meotic maturation of pig oocytes. Sci Rep. 2017 Mar 28;7(1):485. doi: 10.1038/s41598-017-00570-5. PubMed PMID: 28352085; PubMed Central PMCID: PMC5428703.

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33. Philips, E. M., et al. (2018). "Bisphenol and phthalate concentrations and its determinants among pregnant women in a population-based cohort in the Netherlands, 2004–5." Environmental Research 161: 562-572.

34. Sakhi, A. K., et al. (2018). "Levels, variability and determinants of environmental phenols in pairs of Norwegian mothers and children." Environment International 114: 242-251.

35. Shen, Y., et al. (2019). "Bisphenol A analogs in patients with chronic kidney disease and dialysis therapy." Ecotoxicology and Environmental Safety 185.

36. Yang, Y., et al. (2019). "Assessment of bisphenol A alternatives in paper products from the Chinese market and their dermal exposure in the general population." Environmental Pollution 244: 238-246.

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Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	Germany	BASF SE	Company-Manufacturer	9
Comment received				
Please see the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment 80-09-1_DHDPS_comments on CLH dossier_public consultation_clean.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	Sweden	chemsec	International NGO	10
Comment received				
ChemSec strongly supports the classification of BPS as reprotoxic 1B. It is noted that aside from the references mentioned in the dossier, a very high number of supportive studies in different species are available, especially from the recent years. As is stated, there is a lack of studies in humans (for obvious reasons), but the following two studies can be of interest as they also support the classification on our opinion. Relationship between maternal exposure to bisphenol S and pregnancy duration, 2018 https://doi.org/10.1016/j.envpol.2018.03.057 Urinary bisphenol S concentrations: Potential predictors of and associations with semen quality parameters among men attending a fertility center, 2019 https://www.sciencedirect.com/science/article/pii/S0160412019313856				

PUBLIC ATTACHMENTS
1. 80-09-1_DHDPS_comments on CLH dossier_public consultation_clean.pdf [Please refer to comment No. 2, 9]