COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 06.10.2023

Substance name: 4,4'-methylenediphenol; bisphenol F
CAS number: 620-92-8
EC number: 210-658-2
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2023	Germany	Gesamtverband Textil und Mode e.V.	Industry or trade association	1
Comment received				
The German Textile and Fashion Association (Gesamtverband Textil und Mode) submits the enclosed EUDICO statement "Statement concerning the proposed classification and labelling of 4,4-methylenediphenol (bishenol F/BPF)". We agree with the conclusion of the statement, that, taking into account the unreliable studies, the partly contradictive effects, the misinterpretation of basic physical properties and the differences shown between BPA and BPF a clear evidence for the harmonized classification of BPF as reprotoxic 1B is not given by the authors of this CLH report. For the further assessment see the full statement in the attachment. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BPF_CLP classification_Statement EUDICO for t+m_V1.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2023	Germany		MemberState	2
Comment received				
BPF is not registered according to REACH and therefore no registration data is available. There are several studies in the scientific literature, including studies according to OECD TGs, to describe the endpoints assessed in this CLH dossier (toxicokinetics, reproductive toxicity) on which a weight of evidence approach for reproductive toxicity is based. It is acknowledged that the DS performed a reliability assessment of the literature studies and assigned Klimisch scores. As it is not clear on which criteria the scoring is based, it would be favourable to describe the deficiencies of the single studies to put the respective results in perspective. For classification the DS proposes a read across to the structurally similar and extremely data rich substance BPA. BPA is an extremely well-studied substance. A wide variety of effects have been described. So, it is not surprising that "Many of the abovementioned adverse effects [i.e. effects described for BPA] are similar to those reported in the studies of the current CLH proposal for BPF." as has been stated by the DS with respect to male and				

female fertility. In our view it might have been sufficient to base the proposal on studies that have been performed with BPF only. A statement could be added why only BPA is used as source substance and not further substances structurally related to BPA or BPF and we suggest to elaborate a bit more according to ECHAs RAAF framework.
The references provided for BPA originated from the RAC opinion which dates back to 2014. It is recommended that more recently published studies on BPA are considered (e.g. those reported in the assessment report prepared by the German Federal Institute for Risk Assessment https://www.bfr.bund.de/cm/349/bisphenol-a-bfr-proposes-health-based-guidance-value-current-exposure-data-are-needed-for-a-full-risk-assessment.pdf or a re-evaluation performed by the European Food Safety Authority (EFSA) https://www.efsa.europa.eu/en/efsajournal/pub/6857.

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2023	Germany	EuDiCo GmbH	Academic institution	3
Comment received				
EuDiCo Experts have evaluated the CLH dossier of ECHA and assessed the proposed classification as reproductive toxicant category 1B. It is presented that BPF is considered to meet the criteria for classification as toxic for reproduction (Repr. 1B, H360F) and that a harmonised classification under CLP-Regulation Article 36(1) (d) is therefore justified. No other justification is given. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Gu_20230925_Stellungnahme_BPF_VersionECHA.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	European Chemistry for Textile and Leather AISBL (EUCTL)	Industry or trade association	4
Comment received				
The association European Chemistry for Textile and Leather (EUCTL) represents companies producing and putting on the market chemicals for the textiles and leather value chains in Europe. The EUCTL membership covers more than 70% of chemicals for textiles and leather produced in Europe, including Switzerland. EUCTL wants to comment the CLH intention on bisphenol F as this substance occurs as impurity in synthetic leather retanning agents and less important in synthetic aftertreatment agents for polyamide dyeing processes to increase color fastness. EUCTL ask ECHA to thoroughly assess the CLH proposal as EUCTL thinks that some inaccurate conclusions were made by the dossier submitter and insufficient evidence was provided for its reasoning. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-09-29_CLH-report-BPF_EUCTL-comment.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Germany	European Phenolic Resins Association	Industry or trade association	5

Comment received
The European phenolic resin industry, represented by the European Phenolic Resins Association (EPRA) welcomes the opportunity to comment on the submission made by the Swedish Chemicals Agency with respect to the harmonised classification and labelling of 4,4'-Bisphenol F (4,4' BPF, 4,4'-methylenediphenol, CAS 620-92-8, EC 210-658-2). Please refer to our comments in the attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EPRA response to ECHA Consultation on 4,4 BPF Dossier Submission by Sweden - FINAL.pdf

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Germany	Verband Deutscher Schleifmittelwerke VDS	Industry or trade association	6

Comment received
The CLH dossier submitted by the Swedish Chemicals Agency proposes a harmonised classification of BPF as Repr. 1B, H360F, without giving a clear justification. It is just stated that BPF is considered to meet the criteria for classification as toxic for reproduction. No justification is given. Indeed, only one of the considered studies was rated "Klimisch 1" (reliable without restriction): Lee et al. 2022b. This study shows no reprotoxic effects. The other studies - assigned "Klimisch 2" and "3" - describe reprotoxic effects, but at the same time they are contradictory: While in one study testosterone levels are increased, they are decreased in another one. In some of the mentioned studies there were solvents like DMSO, ethanol and acetone used to dissolve BPF although they can have confounding effects on the outcome of the studies and show reprotoxic effects at certain levels themselves. These findings do not provide a reasonable basis for assessing BPF as a category 1B reprotoxic substance. In addition, most of the epidemiological studies did not show any reprotoxic effects. Only one out of five epidemiological studies was able to identify a correlation between urinary BPF levels and an increase in sperm head abnormalities and an increase in reduced progressive sperm motility. Therefore, the lack of scientific findings does not give clear evidence to establish a link between reprotoxic effects and the exposure to BPF. Furthermore, the authors' argumentation is partly incorrect. They misinterpret physical properties like the partition coefficient to achieve greater acceptance of the unreliable studies with visible effects supposedly triggered by BPF. To strengthen the weight of evidence for the harmonised classification, a read-across of BPA to BPF was conducted. In general, the generic approach that all bisphenols might trigger the same effects is fundamentally questionable. In some cases, the comparative studies also show clear differences between the two substances. Not only do the toxicokinetic parameters differ, the IC50 values partly differ by a factor of 5 and the authors use unreliable studies. In summary, the unreliable studies in the CLH Report, the partly contradictive effects, the misinterpretation of basic physical properties and the differences shown between BPA and BPF in total do not represent clear evidence for the harmonised classification of BPF as Repr. 1B. Therefore, the VDS asks to reject the CLH report and the proposed classification of BPF as Repr. 1B. More details are described in the attached position paper. ECHA note – An attachment was submitted with the comment above. Refer to public

attachment CLH-Report_BPF_VDS-Statement_290923.pdf

Date	Country	Organisation	Type of Organisation	Comment number
28.09.2023	France		MemberState	7
Comment received				
We would like to ask whether you plan to propose an ED classification for the substance?				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2023	Germany	Gesamtverband Textil und Mode e.V.	Industry or trade association	8
Comment received				
see attachment "Statement concerning the proposed classification and labelling of 4,4-methylenediphenol (bishenol F/BPF)" (EuDiCo GmbH) ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BPF_CLP classification_Statement EUDICO for t+m_V1.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2023	Germany		MemberState	9
Comment received				
In studies performed with BPA, in particular in studies administering (extremely) low doses, particular attention is given to control the test animals' food for phytoestrogen content and their housing for contamination with endocrine-active/disruptive substances i.e., bisphenols. May we ask to add information on whether the presented studies on BPF consider this aspect. It is unclear why studies are sorted according to the OECD conceptual framework (CF) for Testing and Assessment of Endocrine Disrupters without considering a classification for the endpoint endocrine disruption (ED). The use of data from non-mammalian species such as zebrafish for classification of effects on sexual function and fertility in humans is uncommon, in particular, since ED as a hazard class is not considered. Furthermore, the way of presentation of non-mammalian studies implies equivalent relevance as mammalian data. The term “non-rodent” could be replaced by “non-mammalian” throughout the dossier. It is suggested to flag these data more clearly as additional information. The majority of the presented rodent studies (CF level 4) show clear and consistent adverse effects of BPF on male sexual function and fertility (i.e. sperm parameter in Fatai & Aribidesi 2022, Li et al. 2022, Ullah et al. 2018b, 2019a, 2019b, Gao et al. 2022) and female sexual function and fertility (folliculogenesis/oocyte morphology, GSI in Ijaz et al. 2022, implantation sites, number of born pups in Lee et al. 2022b). This would be generally sufficient to propose to classify the substance as Repr. 1B for fertility, although the weight of evidence is lowered as several studies come from the same lab (Ullah et al., 2018a, b, 2019a, b, c) and/or were rated as “not reliable/not assignable” by the DS (Ullah et al., 2018a, b, 2019a, b; Ijaz et al., 2020). Furthermore, it should be noted that the only Klimisch 1 study in males (Lee et al., 2022b) does not show relevant adverse effects in males, despite similar doses and even longer exposure compared to other studies with same vehicle (using oil instead of water). In our opinion it is not plausible why a higher volume of the vehicle (oil) lowers the bioavailability.				

Based on the information provided, the adverse effects on female fertility seen in Lee et al., 2022b could be considered for classification as Repr. 1B, provided that more detailed information on maternal toxicity (body weight etc.) and on the extent of decrease in implantations and litter size is available in the dossier.
Supporting information in favour of classification is described in three positive uterotrophic assays as well as several in vitro studies indicating ED activity.
DE CA tends to support the proposed classification of BPF as Repr. 1B, H360F awaiting that additional quantitative data on females will strengthen the evidence and noting the weight of evidence approach for the adverse effects in males.

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2023	Germany	EuDiCo GmbH	Academic institution	10
Comment received				
Only one study (Lee et al.2022b) was rated as Klimisch 1 and showed no reprotoxic effect. At the same time some of the effects described in other studies are contradictory.These factors do not provide a reasonable basis for assessing BPF as a category 1B reprotoxic substance. In addition to that most of the epidemiological studies and studies with human material didn't show any reprotoxic effect. Furthermore the authors' argumentation is partly incorrect. They misinterpret physical properties like the partition coefficient to achieve greater acceptance of the unreliable studies with visible effects supposedly triggered by BPF. In reference to the read across of BPA to BPF the generic approach that all bisphenols might trigger the same effects is fundamentally questionable. . In some cases the comparative studies also show clear differences between the two substances. Not only do the toxicokinetic parameters differ, the IC50 values partly differ by a factor of 5 and the authors once again use unreliable studies. According to the dossier submitters, the classification of BPF as Repr. 2 is not appropriate because the evidence for adverse effects on sexual function and fertility from the existing experimental data on BPF and the read-across of BPA is rated as clear evidence and not just some evidence. To say there is clear evidence is correspondingly wrong because clear proof is missing while using unreliable studies. In summary, the unreliable studies, the partly contradictive effects, the misinterpretation of basic physical properties and the differences shown between BPA and BPF in total do not represent a clear evidence for the harmonised classification of BPF as Reprotoxic 1B in this CLH Report. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Gu_20230925_Stellungnahme_BPF_VersionECHA.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	European Chemistry for Textile and Leather AISBL (EUCTL)	Industry or trade association	11
Comment received				
The CLH report on Bisphenol F (BPF = 4,4'-methylenediphenol, CAS 620-92-8, dated 22-6-2023) concludes in a proposal for harmonised classification and labelling that „based on a weight of evidence assessment including read-across from bisphenol A (BPA) that BPF fulfils the criteria as reproductive toxicant category 1B (Repr. 1B, H360F) as it exhibits adverse effects on male and female sexual function and fertility in the absence of marked general toxicity.				

As no REACH registration exists for BPF, the CLH intention is mainly based on literature data and read-across to BPA. The used studies are rated according to Klimisch criteria. One study was rated Klimisch 1, the others are rated Klimisch 2 and 3.

It is obvious that in comparison with BPA the data on BPF is rather limited and there exists in particular no one or two generation toxicity study to fully assess fertility and developmental toxicity for the test substance.

The available information on reproductive toxicity following BPF exposure, gathered from scientific studies in the open literature, seems not sufficiently robust to conclude on clear evidence for adverse effects on sexual function and fertility since in vivo and in vitro data altogether only give some indication of BPF reproductive toxicity.

Below, some selected studies were described to exemplify the limitation of the data base.

Page 38: In the CLH assessment much weight was given to a 48-week oral repeated toxicity study in male rats (Ullah et al 2018 b) in which several findings suggest a substance related effect on the male reproductive organs:
At the top dose level (50 µg/L) a small but significant decrease in gonadosomatic index (-7%), relative epididymis (- 4 %) relative seminal vesicle weight (-7%) were reported. Effect on relative prostate weight, absolute seminal vesicle weight, absolute prostate weight and absolute paired testis weight were not statistically different from control animals. The authors of the study conclude that „ these results suggest that exposure … for chronic duration can induce structural changes in testicular tissue". The study did not include treatment of female rats or a mating procedure. Moreover, the study was classified by ECHA as unreliable.

Page 45 + 75: Very recently a reproduction/developmental toxicity screening test with BPF according to OECD TG 421 has been reported by Lee et al.,2022 (Klimisch: Reliable without restriction). The study covered a broad dose range, (Dose levels: 1, 5, 20 and 100 mg/kg bodyweight, dissolved in 4ml/kg of corn oil. Exposure: Oral gavage, daily for 2 weeks prior to mating and throughout the day before sacrifice in males (total 62days) and through lactation day (LD) 13 in females (total at least 41 days).
No significant BPF-related changes were observed in the male rats. A decrease in bodyweight and food consumption was observed in the female rats treated with BPF at 20 and 100 mg/kg/day. Ovarian weight decrease was reported, and number of implantation sites were decreased at 100 mg / kg/day. Based on the results of this study, the no-observed-adverse-effect levels (NOAELs) of BPF for general systemic and reproductive effects were 5 and 20 mg/kg/day, respectively. Thus, no specific reprotoxic effects were seen with BPF below a general systemic toxic effect.

Page 36: In a 28-day study (Higashihara at al. 2007; reliable with restriction) no relevant reproductive toxic effects and no histopathological effects could be determined.

This should be kept in mind when effects on fertility are interpreted in other studies where dose levels were chosen that are above a general toxicity level.

In vivo studies on sexual function and fertility following BPA and BPF exposure were presented in the CLH report to underline a read across argumentation.
Most comparative in vivo study however have significant shortcomings due to the fact that they were judged as Klimisch not reliable, not assignable or reliable with restriction, which limit a meaningful comparison.
In addition, studies which may describe a reprotoxic effect are contradictory. For example, in one study it is reported that the testosterone levels decreased in another study the levels

increased. Moreover, in some of the studies describing a reprotoxic effect solvents like ethanol, acetone or DMSO are used to dissolve BPF. These solvents themselves may cause reproduction toxicity at a certain level.

Despite the similar structure between these substances and some similarity in physicochemical properties, significant differences between the two substances have not been fully acknowledged in the CLH report:

1) Significant differences in the metabolic detoxification exist between the two substances. Whereas BPF is mainly metabolized in rats to the BPF-sulfate (> 50%) the main metabolite of BPA is a BPA-glucuronide.

2) The comparative toxicokinetic study by Gingerich (2019) reports on a series of maternal and foetal kinetic data after subcutaneous injection of BPF and BPA:

At comparable dose levels cmax plasma levels in female sheep and in foetus were significantly lower for BPF. Total body substance clearance for BPF in females was more than two times higher than for BPA. Similarly, the AUC for maternal and foetal data show that the values for BPF were about only 50 % of the values for BPA. The authors concluded on toxicokinetic differences among the bisphenols and that toxicokinetic differences call for a more careful approach when extrapolating kinetic information from one bisphenol chemical to another.

3) The summary table of a study by Castellini et al (2021, effects of Bisphenol S (BPS) and BPF on human spermatozoa: an in vitro study in the CLH is somewhat misleading, documenting a „trend" of adverse effects on sperm motility, sperm viability and sperm mitochondrial function. This is in contrast to the authors summary: „In conclusion, BPS and BPF seem to be safer alternatives to BPA for sperm biology, as they do not affect mitochondrial functions, sperm motility and viability. "

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-09-29_CLH-report-BPF_EUCTL-comment.pdf

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Germany	Verband Deutscher Schleifmittelwerke VDS	Industry or trade association	12
Comment received				
The proposal for a harmonised classification of BPF as Repr. 1B, H360F, is based on scientific studies. There is only one study that was rated "Klimisch 1" (reliable without restriction): Lee et al. 2022b. This study shows no reprotoxic effects. In addition, most of the epidemiological studies did not show any reprotoxic effects. Therefore, there is no clear evidence that the proposed classification is justified. More details are described in the attached position paper. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH-Report_BPF_VDS-Statement_290923.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
28.09.2023	France		MemberState	13
Comment received				

Based on a weight of evidence assessment of BPF experimental data and the read-across from BPA, we agree with the proposal to classify BPF in Category 1B as it exhibits adverse effects on male and female sexual function and fertility in absence of marked general toxicity.

Page 52. In the section dedicated to the summary of the effects on female fertility (see paragraph 10.10.3 Hypothesis for read-across), it is mentioned that " The adverse effects are supported by alterations in plasma hormone levels (i.e., increased levels of testosterone and decreased levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol and progesterone) and cytotoxicity in the ovarian tissues (i.e., decreased levels of catalase and superoxide dismutase and increased levels of reactive oxygen species and thiobarbituric acid reactive substance)." However most of the rodent studies at the exception of the study from Ijaz et al., 2020 show an increase of the estradiol level. Thus, the summary of the effects should be amended accordingly.

PUBLIC ATTACHMENTS
1. 2023-09-29_CLH-report-BPF_EUCTL-comment.pdf [Please refer to comment No. 4, 11]
2. EPRA response to ECHA Consultation on 4,4 BPF Dossier Submission by Sweden - FINAL.pdf [Please refer to comment No. 5]
3. CLH-Report_BPF_VDS-Statement_290923.pdf [Please refer to comment No. 6, 12]

CONFIDENTIAL ATTACHMENTS
1. BPF_CLP classification_Statement EUDICO for t+m_V1.pdf [Please refer to comment No. 1, 8]
2. Gu_20230925_Stellungnahme_BPF_VersionECHA.pdf [Please refer to comment No. 3, 10]