Verband Deutscher Schleifmittelwerke

Statement of the German Abrasives Association VDS on the CLH Report for Bisphenol F

29th September 2023

Executive Summary

The statement of VDS discusses the following issues:

- There is no clear justification given for a classification of Bisphenol F (BPF) as a category 1B reprotoxic substance.
- Only one of the cited studies is rated "reliable without restriction" (Klimisch 1) and this study shows no reprotoxic effects.
- 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.

1. Introduction

The German Abrasives Association (VDS) represents the abrasives industry in technical, economic, environmental and legal issues. The VDS was founded in Berlin in 1917 and is today the largest national association for the abrasives industry in Europe. It represents 61 member companies, including manufacturers in Switzerland and Austria, with over 7,000 employees and an annual turnover of around EUR 1.8 billion EUR.

On 22 June 2023, ECHA published a proposal for the harmonised classification and labelling of 4,4'-methylenediphenol (Bisphenol F, BPF) as Repr. 1B, H360F. VDS appreciates having the possibility to comment on the proposed restriction.

2. General Statement

Currently, BPF is not classified as hazardous, but self-classifications are noted in the C&L inventory of ECHA: Skin Irrit. 2, H315, Eye Irrit. 2, H319, STOT SE 3, H335 (respiratory irritation), Aquatic Chronic 3, H412. The CLH dossier submitted by the Swedish Chemicals Agency now 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 (Repr. 1B, H360F) and that a harmonised classification under CLP-Regulation

Article 36(1) (d) is therefore justified. The proposal 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.** The other studies were assigned "Klimisch 2" and "3" by ECHA. Most of them 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.

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 are rated as clear evidence and not just some evidence. To say "there is clear evidence" is correspondingly wrong because clear proof is missing as unreliable studies are being used.

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.

3. BPF in the abrasives industry

BPF can occur in phenolic resins that are used by the abrasives industry to produce resinoid-based abrasives. Not intentionally added, BPF is formed when phenol and formaldehyde react under acidic or basic conditions to form a phenol-formaldehyde polymer network through condensation reaction.

Resinoid-based abrasives represent 60 – 70 % of the manufactured and sold abrasive products in Europe. They are coated abrasive products like sandpaper, flap discs, or abrasive belts but also resin-bonded products like grinding or cutting-off wheels. Resins (phenolic, epoxy, urea resins) are used as binders for abrasive grains.

Abrasive products have enormous importance and leverage in almost all industrial manufacturing processes. They are indispensable both for securing basic needs and maintaining

system-relevant industrial productions. Material and product properties such as low roughness and mechanical toughness that can only be achieved by grinding processes, result in reduced friction and less wear, thus in reduced energy and resource consumption in nearly all industrial areas.

4. Evaluation of the CLH dossier

Justification for action at community level

The CLH report was submitted by the Swedish Chemicals Agency in June 2023. The authors of the dossier start displaying the substance identity and physicochemical properties followed by the composition and substance purity. The need for action at the community level is not clearly justified. The authors state that there is no necessity for a justification that action is needed at Community Level (p. 6 of the CLH Report). This statement is incomprehensible as a proposal on CLH should only be made if one of the following 3 situations occurs and new relevant information is available:

- If there is new evidence, that a substance is either CMR or a respiratory sensitizer.
- When it is justified that a classification for a substance at EU level is needed for other hazard classes than CMR or respiratory sensitizer.
- To add one or more new hazard classes to an existing entry (under the conditions mentioned before).

None of these requirements seem to apply here. **Therefore, the CLH proposal itself seems unjustified because no justification according to the CLP regulation was given**.

BPF is considered by the authors 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. The authors state that BPF is currently not registered under REACH and therefore no toxicity studies are available in ECHA's database. This means, that the substance is not placed as such on the European market in an amount above 1 t/a. In consequence, BPF can only be found as residue in certain articles.

The classification proposal is based on scientific studies from publicly available sources. According to the authors, the classification proposal is also supported by the so-called read-across from bisphenol A (BPA) to BPF, which can be generally questioned.

Further in the dossier, the physical, health, environmental and additional hazards are shown. The focus is clearly laid on the evaluation of reproductive toxicity and the read-across from BPA to BPF.

Assessment of reproductive toxicity

Scientific studies from open literature sources such as PubMed were used to evaluate the reprotoxic potential of BPF. The studies were assessed by ECHA and each study was classified based on the “Klimisch” criteria, which showed that only one study was rated as Klimisch 1 (“reliable without restriction”): Lee et al. 2022b. The other studies taken as a basis were assigned Klimisch 2 and 3 by ECHA. A total of 17 studies was classified in case of male effects and 12 studies in case of female effects.

In the reproduction and developmental toxicity study by Lee et al. 2022b (labelled as Klimisch 1) no reproductive toxic effects were found. Only an increase in saliva production and an increase in Cowper gland weight were observed at the highest dose. BPF had no effect on mating behavior, fertility or histopathology in rats. In the 28-day study by Higashihara et al. 2007, which is classified as Klimisch 2 ("reliable with restriction"), no histopathological effects were detected. Regarding reproductive toxic effects, no relevant effect could have been determined either apart from a slight body weight reduction at the highest dose, an increase in relative testicular weight and changes in serum T3 and T4 levels.

In contrast to that, in a study by Ullah et al. 2018, reprotoxic effects initiated by BPF are described. But this study was classified as unreliable by ECHA. Taking a closer look at this study, it is noticeable that data like the CAS number of the substance is missing. Furthermore, no information is available on what the control group received. Moreover, there is no further specification according to the method of oral administration. Besides, no statement on the mortality rate is made in the study results. All these factors do not speak for a reliable study, which is why we agree with the assessment as not reliable. The situation is similar for the other studies that have already been classified as not reliable by ECHA.

This 28-day study by Ullah et al., in which BPF was administered after dissolving in a saline solution with an ethanol content < 0.1-0.5 %, presents a diluted testicular epithelium with reduced height and reduced levels of testosterone in plasma and testes. Further, an increase in ROS in the testis is described. These effects could not be shown by Lee et al. 2022b.

Disagreements in studies

Besides the fact that only one of the referenced studies was classified by ECHA as Klimisch 1, the study results are also partly contradictory. The study by Ullah et al. 2018 described above for example refers to a decrease in testosterone concentration. In contrast to that, a 28-day study by Ijaz et al. 2020, which was also classified as not reliable, showed a strong increase in the testosterone level in plasma. This is not indicative of a clear effect direction triggered by BPF. Beside others, the study lacks on data about the chemicals and vehicles administered. The treatment of the control group is also questionable.

In addition, the solvents used in some studies are questionable. For example, in the study by Ullah et al 2018, a small amount of < 0.1-0.5 % ethanol was used in the solvent. Ethanol itself owns a developmental toxic and teratogenic potential[1]. In the study by Yang et al. 2017, a portion of dimethyl sulphoxide (DMSO) is used in the solvent. DMSO is known as a laboratory chemical and can penetrate cell membranes very well. It is known to have a cytotoxic effect[2]. In the zebrafish study by Mu et al. 2022, however, a solution with an acetone concentration of 0.005 mL/L was used. Here, an irritant effect is present that can also be triggered by cytotoxic processes[3].

If we combine the fact that only one reliable study rated Klimisch 1 is referenced in the CLH report with the fact that it does not show any relevant reprotoxic effects, the question arises as to what extent one can refer to the effects of the other cited studies (Klimisch 2 and 3). In addition, it is unclear to what extent the visible effects can actually be attributed to BPF, when

[1] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16105/7/9/3 (12.09.23)

[2] https://www.chemie.de/lexikon/Dimethylsulfoxid.html (12.09.23)

[3] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15460/1/1 (12.09.23)

other substances contained in the solvent (though sometimes in low concentrations) can also have an influence on the cells.

In conclusion, the mentioned studies do not provide a reasonable basis for assessing BPF as a category 1B reprotoxic substance.

Epidemiological studies and studies based on human material

As already seen in the reliable study by Lee et al. 2022b, where no evidence of a reprotoxic effect of BPF could be found, **there is also no clear evidence of a reprotoxic effect triggered by BPF when looking at the epidemiological studies**. In the study by Benson et al. 2021, no association between BPF and a change in sperm quality could be determined, and Jeseta et al., who performed a case-control study in 2022, could only detect in one test person per group; the other measured values were below the detection limit. For that reason, no further examinations were carried out.

The in vitro studies showed effects on sperm (reduced motility and viability, Castellini et al. 2021) as well as reduced testosterone levels (Desdoits-Lethimonier et al. 2017). However, it should be noted that both studies used a dilution containing DMSO, which can have a negative effect on the cells being tested. In addition, in the study by Desdoits-Lethimonier et al. no significant change in the testosterone level was found in the highest dosage, so that it is not possible to suspect a dose-dependent effect here, thus the question arises as to whether the change can be attributed to BPF or not.

Only one of the five epidemiological and human material-based studies (Chen et al. 2022) 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. This does also not support a clear correlation between reprotoxic effects and the exposure to BPF.

Assessment of the studies by the authors

The authors' assessment of the studies demonstrates some mistakes. In their summary, an explanation is sought for why only a few substance-related effects occurred in the studies by Lee et al. 2022b and Higashihara et al. 2017. The authors tried to address the oil used as a vehicle and underlined that the bioavailability of the substance used could be reduced this way, assuming that BPF is a water-soluble substance. As a response, BPF is said to have a moderate water solubility of 0.54 g/L and a relative hydrophilic property at a LogKow of 2.91-3.06 (p. 44 of the CLH report). Even though moderate water solubility might be present, the conclusion on the hydrophilicity of BPF at a LogKow of up to 3.06 is debatable. This is underlined by the assumption that a high bioaccumulation of lipophilic substances is already achieved at a LogKow of 4. This also becomes apparent when comparing the hydrophilic substance ethanol. Ethanol has a water solubility of 789 g/L, which is 1461 times greater than BPFs water solubility. In addition to that, ethanol has a LogKow of -0.35. The comparison with ethanol makes it clear that BPF cannot be a very highly water-soluble substance more than a lipophilic substance that would accordingly also dissolve sufficiently in an oily vehicle.

This misjudgment on the authors' part indicates an attempt to achieve greater acceptance of the unreliable studies with visible effects supposedly triggered by BPF. At the same time, the authors seem to be trying to attribute effects to the more reliable studies by Lee et al. and Higashihara et al. that these studies have not shown.

Comparison of BPA and BPF

Besides the studies on BPF from the open literature, a read-across was also conducted to assess the reprotoxic effect of BPF. For this purpose, the substance bisphenol A (BPA) was chosen. BPA, in contrast to BPF, is classified as Repr. 1B, Eye Dam. 1, STOT SE 3, Skin Sens. 1, as well as Aquatic Acute 1 and Aquatic Chronic 1. BPA is currently on the candidate list as a substance of very high concern (SVHC) due to its reprotoxic and endocrine disrupting properties. The authors chose to compare BPF and BPA because of their structural similarities, the physicochemical properties and the biological and toxicological properties. Both substances are included in the group of bisphenols and have a similar chemical structure due to the phenol rings.

The generic approach that all bisphenols trigger the same effects is fundamentally debatable. The studies that are listed in a table to compare BPA and BPF also show clear differences between the two substances in several cases. For example, the study by Gingrich et al. 2019, in which 0.5 mg/kg of both BPA and BPF were administered, shows that the urine concentrations of BPF were by far lower than the concentrations of BPA, and that BPA had a clearance that was about twice as low as BPF at the same time. In addition to that, all fetal BPA concentrations measured were higher than those of BPF. This toxicokinetic study already demonstrates clear disagreements between BPA and BPF, even though they have similar structural characteristics.

The comparison of in vitro studies dealing with hormone-like activity also showed clear differences between BPA and BPF (Table 17 of the CLH report). The IC50 values of BPF in some cases are several times higher than those of BPA, which indicates a significantly reduced potency of BPF compared to BPA (Molina-Molina et al. 2013, Liu et al. 2019, Blair et al. 2000).

It is also noticeable in the comparative studies that a high number of studies are used which are only “reliable with restriction” or “not reliable” according to the evaluation under Klimisch criteria. As already noted, when considering the BPF studies from the open literature, this also does not provide a sufficient assessment basis for the classification of BPF as reprotoxic by the read-across with BPA.

The authors of the report state that the read-across with BPA was performed to strengthen the weight of evidence for the harmonised classification (p. 51, CLH report). This holds only to a limited extent because the epidemiological studies and the studies using human material that are compared show a stronger effect for BPA than for BPF (Table 21, CLH report). For example, the effect on sperm motility and viability is much greater for BPA than for BPF (Castellini et al. 2021).

In summary, no clear reprotoxic effect triggered by BPF can be shown due to the read-across with BPA. In addition, a read-across is generally not justified if the substances differ too much from each other. As the tabular comparison of BPF and BPA has shown, there are some major differences in their kinetics and their potency. This makes a read-across with BPA for BPF questionable.

5. Conclusion

In conclusion, the CLH report by the Swedish Chemicals Agency does not provide a clear justification for a classification of BPF as a category 1B reprotoxic substance for the following reasons:

- The relevant criteria for a need for action at the community level are not fulfilled.
- In the reproduction and developmental toxicity study by Lee et al. 2022b – the only study that was rated “Klimisch 1” (reliable without restriction) – no reproductive toxic effects were found.
- There is no clear evidence of a reprotoxic effect triggered by BPF when looking at the epidemiological studies.
- The study results are partly contradictory.
- No clear reprotoxic effect triggered by BPF can be shown due to the read-across with BPA. The generic approach that all bisphenols trigger the same effects is fundamentally debatable.
- 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.

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