Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

benzyl(diethylamino)diphenylphosphonium 4-[1,1,1,3,3,3-hexafluoro-2-(4-hydroxyphenyl)propan-2-yl]phenolate

EC Number: 479-100-5
CAS Number: 577705-90-9

CLH-O-0000006967-56-01/F

Adopted

18 March 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BENZYL(DIETHYLAMINO)DIPHENYLPHOSPHONIUM 4-[1,1,1,3,3,3-HEXAFLUORO-2-(4-HYDROXYPHENYL)PROPAN-2-YL]PHENOLATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: benzyl(diethylamino)diphenylphosphonium 4-[1,1,1,3,3,3-hexafluoro-2-(4-hydroxyphenyl)propan-2-yl]phenolate
EC number: 479-100-5
CAS number: 577705-90-9
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2020	Germany		MemberState	1
Comment received				
In table 5 in section 2.1 of the CLH report ("Proposed harmonised classification and labelling according to the CLP criteria") the CAS No. to identify the substance in the resulting Annex VI entry is missing. Please add the corresponding information.				
Dossier Submitter's Response				
Thank you for spotting this. This is a clear editorial mistake from our side. The CAS number should be added in table 5.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	France		MemberState	2
Comment received				
Considering that the substance contains 50% of BPAF, read-across to the classification proposal of BPAF is appropriate.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Netherlands		MemberState	3

Comment received

We agree with the proposed classification in Repr. 1B for adverse effects on sexual function and fertility, based on data on Bisphenol AF (EC 216-036-7). Clear effects on fertility were observed in the OECD 422 study, starting at the lowest dose, without marked systemic toxicity. The clear effects on fertility observed in this study alone is considered sufficient for classification as Repr. 1B H360F. The mechanistic studies indicate an endocrine-mediated mechanism is involved, further supporting the proposed classification,.

Regarding developmental toxicity, the following was noted:

- OECD 422 study, oral, 0-30-100-300 mg/kg bw/day, rats
o No significant effects on offspring treated in utero.
o No differences in sex ratio and body weights of offspring between treated animals and controls.
o Necropsy findings in offspring: no evident effects from BPAF treatment
o Note: no pups at all produced by animals in the high dose group treated with 300 mg/kg bw/day.

- In vivo study mammary gland, exposure GD 10.5-17.5, follow-up offspring until 16 months, CD-1 mice, 0, 0.05, 0.5, 5 mg/kg bw twice per day:
o BPAF exposure caused accelerated pubertal mammary development.
o By 14 months of age, a significant dose-related increase in non-neoplastic lesions was found in BPAF-exposed groups, including cysts, inflammation, lobuloalveolar hyperplasia and squamous metaplasia.

- In vivo study on effects on offspring, SD rats, exposure GD 3-19 and PND 3-19, 0 and 100 mg/kg/bw/d:
o Lactational exposure caused significantly increased levels of BPAF in serum and in testis, showing that BPAF was transferred via breast milk.
o Gestational and lactational exposure lead to increased testosterone and decreased Inhibin B levels in male offspring. Androgen receptor levels in testes increased following BPAF exposure.

- In vivo study on neurobehaviours in adolescent mice offspring, exposure GD 1-19, 0-0.4- 4 mg/kg bw/day.
o Fetal exposure to BPAF induced anxiety- and depressive-like behaviours in male adolescent offspring. In addition, BPAF exposure impaired memory formation in both sexes.
o Note: no exact numbers given in the research article, no information on parental toxicity.

Perhaps a discussion for classification as category 2 developmental toxicant would be possible, but it seems there is insufficient robust reporting to draw conclusions on possible developmental toxicity.

Overall, there are indications of treatment-related developmental effects, but the evidence is inconclusive for classification and we agree that the available information is insufficient for classification for developmental toxicity and for classification for effect on or via lactation.
Dossier Submitter's Response
Thank you for your support.
RAC's response
The feasibility of your proposal to consider classification for developmental toxicity has been checked. Finally RAC agrees with the DS on the lack of robust data and noting that a new 1-generation study is soon awaited.

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2020	Germany		MemberState	4
Comment received				
The substance addressed in the CLH-report contains ca. 50 % Bisphenol AF as anion. The classification with Repr. 1B, H360F based on the data from Bisphenol AF is supported (see comment on Bisphenol AF). The available data provide clear evidence of an adverse effect on both male and female sexual function and fertility and that the observed effects are considered relevant for humans.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				