Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis[phenol] (1:1)

EC Number: 278-305-5
CAS Number: 75768-65-9

CLH-O-0000006966-58-01/F

Adopted

18 March 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BENZYLTRIPHENYLPHOSPHONIUM, SALT WITH 4,4'-[2,2,2-TRIFLUORO-1-(TRIFLUOROMETHYL)ETHYLIDENE]BIS[PHENOL] (1:1)

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: benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis[phenol] (1:1)
EC number: 278-305-5
CAS number: 75768-65-9
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05.05.2020	Germany		MemberState	1
Comment received				
BPAF-BTTP is a salt consisting of the benzyltriphenylphosphonium cation, with ca. 50 % bisphenol AF as anion. The use of toxicity information of BPAF for classification of BPAF-BTTP is plausible.				
Dossier Submitter's Response				
Thank you for your support.				
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
05.05.2020	Germany		MemberState	4
Comment received				
The reproductive toxicity of BPAF-BTTP was examined using data from the main constituent bisphenol AF. Fertility The evaluation of the reproductive toxicity of bisphenol AF was mainly based on a screening test according to OECD TG 422 and a 28-day study according to OECD TG 407 in rats with oral administration of the test substance. Supporting information from an uterotrophic assay and a Hershberger assay as well as several mechanistic studies are given. The screening study was performed in rats using dose levels of 0, 30, 100 and 300 mg/kg bw/day. BPAF caused a dose-dependent decrease in the fertility index down to 83 %, 64 %, and 0 % for 30, 100, and 300 mg/kg bw/day, respectively, compared to 100 % for the control group. In the highest dose group, no pregnancy was induced in any of the mated females. Pre- and post-implantation loss was increased in the low and mid dose compared to the control, this increase was however, not significant. The number of corpora lutea and implantations was lower in treated animals as compared to the control; this effect again was not significant. A high incidence of follicular ovarian cysts was noted in the non-pregnant high dose females (including the recovery group). Also in pregnant females of the other dose groups, ovarian follicles increased with dose. Absolute and relative weights of several reproductive organs (e.g. testes) were significantly decreased in the high dose males as compared to the control. In the 28-day study according to OECD TG 407 similar significant effects on male reproductive organs were detected at 100 mg/kg bw/day (e.g. prostate, seminal vesicles) including histopathological effects (e.g. Leydig cell atrophy in testes). A NOAEL of 30 mg/kg bw/day can be derived. In both tests irregular oestrus cycle was noted in some of the high dose females and atrophy of mammary glands in high dose males. The results indicate endocrine-mediated oestrogenic effects (effects on mammary glands, testes, oestrus cycle) that were underlined by the uterotrophic assay, where BPAF				

significantly increased the uterine blotted weight in all dose groups (8, 40, 100 mg/kg/day). Several other studies support the oestrogenic and anti-androgenic activity of BPAF (in vivo studies in zebrafish, in vitro studies). Comparative studies indicate a stronger oestrogenicity for BPAF as compared to BPA. With the dose-dependent significant decrease of the fertility index in the OECD TG 422 from the lowest dose (30 mg/kg bw/day), the significantly lower reproductive organ weights in males in the screening and the 28-day studies and the signs of oestrogenic/anti-androgenic activity clearly indicate an impairment of sexual function and fertility in both sexes. No marked general (parental) toxicity was seen in any study. Therefore, classification of BPAF as Repr. 1B, H360F is supported. Developmental toxicity: For the evaluation of developmental toxicity, a guideline study according to OECD TG 422 and few non-guideline studies are available. In the screening study no adverse effects on offspring were seen up to PND 5. However, it has to be noted that in the high dose group no offspring were produced, so developmental effects cannot be excluded at 300 mg/kg bw/day. In non-guideline studies, effects of BPAF on offspring were shown, such as accelerated pubertal mammary gland development in female mice, transfer of BPAF in breast milk and alteration of hormone levels in serum and testes of male rats, and impacts on behaviour (e.g. anxiety in males, impaired memory formation in both sexes) of mice. However, due to poor reporting of these studies and lacking GLP compliance these studies cannot be used for classification. Due to the lack of guideline-conform developmental toxicity data, the DE CA agrees that with the available information a classification of BPAF and consequently BPAF-BTTP as developmental toxicant is not indicated. Adverse effects via lactation In the screening study according to OECD TG 422 no effects of BPAF via lactation until PND 5 were found. A cross-fostering study in rats showed transfer of BPAF via breast milk and subsequent effects on inhibin B and androgen receptor levels as well as effects on body weight of offspring. However, the results of the study are not robust for classification due to poor reporting and lack of GLP-compliance.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.