COMPILED COMMENTS ON CLH CONSULTATION

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Substance name: Reaction mass of 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]diphenol and benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis[phenol] (1:1)
CAS number: -
EC number: -
Dossier submitter:

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05.05.2020	Germany		MemberState	1
Comment received				
In the CLH Report no EC-number is given for the substance. However, on the ECHA-dissemination site an EC-number of 947-368-7 is assorted. In the dossier (section 6 Data sources) it is stated that the data sources are the ECHA dissemination page and those of the Bisphenol AF (BPAF) (EC no. 216-036-7), since this is up to 90 % contained in the reaction mass. But the physico-chemical data from the ECHA dissemination page for the reaction mass is only a copy of the data for "benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl) ethylidene] bis[phenol] (1:1)" (EC no. 278-305-5). It seems that no studies on PC-data for the reaction mass itself are available. Therefore, it would be appropriate and more transparent to state the physical-chemical data for both constituents.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Netherlands		MemberState	2
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.

Date	Country	Organisation	Type of Organisation	Comment number
05.05.2020	Germany		MemberState	3

Comment received

The reproductive toxicity of reaction mass of 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]diphenol and benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis[phenol] (1:1) 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 performed screening study in rats used 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 Reaction mass of 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]diphenol and benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis[phenol] (1:1) 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 Reaction mass of 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]diphenol and benzyltriphenylphosphonium, salt with 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis[phenol] (1:1) as developmental toxicant is not indicated.

Date	Country	Organisation	Type of Organisation	Comment number

08.05.2020	France		MemberState	4
Comment received				
Considering that the substance contains ≥ 20% - ≤ 80% of BPAF, read-across to the classification proposal of BPAF is appropriate				