Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

4-phenylbenzophenone

EC Number: 218-345-2
CAS Number: 2128-93-0

CLH-O-0000007379-62-01/F

Adopted

30 November 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 4-PHENYLBENZOPHENONE

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: 4-phenylbenzophenone
EC number: 218-345-2
CAS number: 2128-93-0
Dossier submitter: Germany

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2023	Sweden		MemberState	1

Comment received

Reproductive toxicity:
The Swedish CA supports the proposed classification of 4-Phenylbenzophenone as Repr. 1B (H360FD).

Fertility
The Swedish CA supports the proposed classification of 4-Phenylbenzophenone as Repr. 1B for effects on sexual function and fertility (H360F) based on the OECD 422 study. This study reported a reduced mean number of implantation sites per pregnant female by 27% in the highest dose group of 1000 mg/kg bw/d, in the absence of adverse parental toxicity.

Development
The Swedish CA supports the proposed classification of 4-Phenylbenzophenone as Repr. 1B for effects on development (H360D) based on the OECD 422 study. There was clear evidence of treatment-related death of the developing organism, including increased post-implantation loss (post implantation survival index was 89, 82, 78 and 3% at 0, 100, 300 and 1000 mg/kg bw/d, respectively), and complete litter loss in the highest dost group. Furthermore, the post-natal growth was reduced at 300 mg/kg bw/d, demonstrated by reduced body weight at PND 7 (-15.7%) and PND 13 (-17.5%).

Dossier Submitter's Response

Thank you for your comment.

RAC's response
Thanks for the comment and support.

Date	Country	Organisation	Type of Organisation	Comment number
25.05.2023	France		MemberState	2

Comment received
FR agrees with the proposed classification for effects on sexual function, fertility and development as Repr. 1B – H360FD, based on the reduction in mean number of implantation sites with no live offspring at 1000 mg/kg bw/d and on death of developing organisms at 1000 mg/kg bw/d and altered pup growth (body weight decreases) at 300 mg/kg bw/d, in the OECD 422 study. There is an absence of severe maternal toxicity. However, in the high-dose group of females, thyroid and adrenal glands were identified as target organs that may point to an endocrine disrupter effect. Effects on reproduction and development may also suggest a possible underlying genotoxic mode of action. Germ cell mutagenicity was not assessed due to the existing data gap. Based on the two available positive Ames tests, it cannot be excluded awaiting the follow-up studies. It should have been interesting to assess the observed effects on reproduction and development with regard to mutagenicity. There are no data adequately assessing the effects on or via lactation. FR agrees that no classification is justified based on the lack of data.
Dossier Submitter's Response
Thank you for your comment. Indeed, it would be interesting to assess the observed effects on reproduction and development with regard to mutagenicity. So far, in the absence of *in vivo* mammalian mutagenicity data, it can only be speculated, whether the developmental toxicity of 4-phenylbezophenone was caused by genetic damage. A comparative MoA analysis is not required for the purpose of a CLH classification for the identified hazard of reproductive toxicity. Therefore, we have focused on identification and characterisation of the adverse effects in dams and foetuses in the current dossier.
RAC's response
RAC agrees with the DS response. Without further analysis on mutagenic effects, the MoA is not relevant for the classification for reproductive toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2023	United Kingdom	Health and Safety Executive	National Authority	3
Comment received				

Reproductive Toxicity – Sexual Function and Fertility Regarding adverse effects on sexual function and fertility, classification in Category 1B is proposed based on a reduction in the mean number of implantation sites at the limit dose (1000 mg/kg bw/d). In the absence of a full corpora lutea count, it is difficult to determine whether the reduction in implantation sites was a result of a decrease in the number of eggs produced or a failure of the implanted blastocyst to progress. Given the uncertainty as to whether the reduced mean number of implantation sites is a result of an effect on fertility or development, we question whether there is sufficient evidence to support category 1B for fertility effects.
Dossier Submitter's Response
Thank you for your comment. Based on the available data one cannot exclude with full confidence that female reproductive performance was not affected. Indeed, the observed reduction in the number of implantation sites may be interpreted as an embryotoxic effect, at the same time it may result from effects on the ovaries or the uterus. A set of the studies which would cover investigations of the effects of 4phenylbenzophenone on early pregnancy could be imagined, for example a decidual cell response technique would be a suitable method to distinguish between substances acting as embryotoxic vs. substances affecting the uterine environment. Similarly, it is still to be established whether 4-phenylbenzophenone is mutagenic to proliferating mammalian cells. If so, the cytotoxic effect could affect either the germ cell cycle (e.g. follicle development) or the proliferating cells of blastocysts, or both. Taken together, the available data demonstrate inhibition of the implantation rate of blastocysts in treated females leading to early pregnancy loss. In the context of human relevance, early subclinical pregnancy loss is viewed as a manifestation of reduced fertility. Thus, we consider that our proposal for classification to Repr. 1B (H360F) for the effects on sexual function and fertility is justified[1].
RAC's response
RAC agrees with the DS response.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
25.05.2023	France		MemberState	4
Comment received				
FR agrees with the proposed classification as Skin Sens. 1A based on the effective concentration of 25% inducing a stimulation index (SI) of 3 (rounded) in the LLNA test (EC3 > 2 %).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
RAC agrees with the DS response.				

1 https://www.ajog.org/article/0002-9378(95)90489-1/fulltext

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2023	United Kingdom	Health and Safety Executive	National Authority	5

Comment received

4-phenylbenzophenone (CAS: 2128-93-0)
We agree with the CLP proposal noting that the 0-72h ErC10 of 0.33 mg/L is the key relevant endpoint for chronic hazard classification. However, it would be useful if the DS could confirm the statistical method for significance analysis and we are unclear what the quoted 'NOErC <0.0066 mg/L based on statistical significance' represents.

Given a REACH Compliance Check Decision has requested long term toxicity information for fish and invertebrates, we note the classification may need updating when this information is available.

Dossier Submitter's Response

Thank you for your support for the key endpoint.
Concerning the 'NOErC <0.0066 mg/L based on statistical significance': At the lowest concentration (6.6 µg/L TWA), the effect was lower than 10% compared to the control. The statistical method was not reported in the RSS.
Concerning the REACH Compliance Check: We are aware that based CCH Decision long-term toxicity tests on fish and invertebrates will be conducted. As the deadline to submit the information is the 28th March 2025 and the proposed classification in this CLH dossier is Aquatic Acute 1 and Chronic 1, the results of the tests may only change the M-factor for chronic toxicity.

RAC's response

RAC agrees with the DS response. RAC notes that a potential refinement of the M-factor value could take place once the new information will become available.

Date	Country	Organisation	Type of Organisation	Comment number
25.05.2023	France		MemberState	6

Comment received

FR agrees with the proposed classifications as Aquatic Acute 1; H400 (M=10) and Aquatic Chronic 1; H410 (M=1) based on algae toxicity (OECD TG 201). Estimated bioaccumulation data (for example from EPIsuite) could be added to the document. However, experimentally derived Kow value is available and is preferred for classification purpose in the absence of bioaccumulation test data. Thus, this additional information would not change the conclusions.

Dossier Submitter's Response

Thank you for your support for our proposed classification and the hint concerning the bioaccumulation.

RAC's response

RAC agrees with the DS response.