COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 22.11.2023

Substance name: 2-(4-tert-butylbenzyl) propionaldehyde; 4-tert-butylbenzoic acid; 3-(4-tert-butylphenyl)propionaldehyde [1] 4-tert-butyltoluene [2] 4-tert-butylbenzaldehyde [3] methyl 4-tert-butylbenzoate [4]
CAS number: 80-54-6; 98-73-7; 18127-01-0 [1] 98-51-1 [2] 939-97-9 [3] 26537-19-9 [4]
EC number: 201-289-8; 202-696-3; 242-016-2 [1] 202-675-9 [2] 213-367-9 [3] 247-768-5 [4]
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2023	Switzerland	Givaudan	Company-Manufacturer	1
Comment received				
Please find the comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Givaudan Response to CLH report Proposal for Harmonized Classification Bourgeonal_Sep 21_Final.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	France		MemberState	2
Comment received				
In the Background section, it is mentioned that the substances included in the present proposal are structurally similar to another group of substances forming the metabolite 4-isopropylbenzoic acid, 4-iPBA. The metabolites 4-iPBA and TBBA are only differing by a methyl group at the benzylic carbon. It is not clear why 4-iPBA is only cited in the present dossier without using these data for the proposed classification (4-iPBA and substances forming 4-IPBA being covered by an independent CLH report). If you want using data on 4-IPBA as supportive information in the category approach, it should be made more clear in this document. Toxicokinetics: The formation of the common metabolite TBBA is evident among all studies. However, quantitative species differences in the formation of TBBA have been reported especially in humans with lower concentrations than other species. FR questions the relevance of the clear formation of TBBA in humans.				

Date	Country	Organisation	Type of Organisation	Comment number

14.09.2023	Germany		MemberState	3
Comment received				
There is one note on the substance "4-tert-butylbenzoic acid". Index-No 607-698-00-1 in Table 3b: This substance has been harmonized with Regulation (EU) No 618/2012 (3rd ATP) in Annex VI of the CLP Regulation. The substance was classified as Acute Tox. 4, H302, among others. At that time, ATE values for classification as acute toxic were not yet included in CLP Annex VI. In the meantime, however, ATE values of substances to be included in Annex VI as acutely toxic are also included. It is therefore recommended to include a harmonized ATE value for this substance in Annex VI as well. However, this value, which is missing in this CLH dossier, can be added to the data from the RAC-Opinion, adopted in 21 February 2011, added to this CLH dossier and to Table 3b. The approach undertaken by the DS to form a category comprising several substances for classification purposes is supported and considered sound. Underlying hypothesis is that all the substances considered (apart from the critical metabolite itself) can be transformed into a critical metabolite responsible for the testicular and spermatotoxic effects. The selection of substances covered in the dossier is in part unclear. It is understood that it comprises substances that can be transformed into TBBA. However, there seem to be more substances that might give rise to formation of the TBBA as e.g. Study 26 of section 2.26 of confidential Annex I lists much more substances with structural similarities to the substance in focus of the CLH proposal. Were certain substances excluded and if so, why? Upon metabolism to TBBA, the substances covered (apart from TBBA itself) might form different additional metabolites. These metabolites, these differences and their potential impacts on toxicokinetics and toxicodynamics are missing. Based on chemical structures and differences in some physicochemical properties (e.g. water solubility, logPow) there might be differences in uptake/systemic absorption via the relevant uptake route(s) which could have an influence on differences in potencies between the substances.				

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	United Kingdom	IFRA UK	Industry or trade association	4
Comment received				
IFRA UK does not support the reproductive toxicity classification that has been proposed. ECHA note – An attachment was submitted with the comment above. Refer to public attachment IFRA UK CLP Consultation Response CAS 18127-01-0 as 3-(4-tert-butylphenyl)propionaldehyde – September 2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2023	Switzerland	Givaudan	Company-Manufacturer	5
Comment received				
Please find the comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Givaudan Response to CLH report Proposal for Harmonized Classification				

Bourgeonal_Sep 21_Final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	France		MemberState	6

Comment received

Fertility

3-(4-tert-butylphenyl)propionaldehyde
In the OECD TG 422 study, no effects were observed but the doses used were relatively low compared to other studies. Clear evidence of histopathological lesions in testes and seminiferous tubules as well as spermatotoxicity in rats were observed in the DRF study prior to OECD TG 422 study. Similar effects were reported in another screening toxicity test in rats.

4-tert-butyltoluene
In the OECD TG 407 study and in screening tests on testicular toxicity performed in several species (rat, guinea pig, mouse and dog), decreases of testes weight, damage to the germinal epithelium and adverse effects on sperm parameters were recorded. Similar type of reproductive toxicity is seen across different species, although most studies are conducted in rats and the degree of toxicity appears to differ between species (rats being the most sensitive species and the dogs being the less sensitive species). Do you have any opinion on which species is most relevant to humans for this substance?

4-tert-butylbenzylaldehyde
Screening tests on testicular toxicity with different species (rat, guinea pig, mouse and dog) showed a decrease of testes weight in rats and damage to the germinal epithelium with different degrees of severity across species.

methyl 4-tert-butylbenzoate
No toxicokinetics or experimental studies on reproductive toxicity is available.

Propionaldehyde (lysmeral) and 4-tert-butylbenzoic acid (TBBA)
These substances already have harmonised classification as Repr.1B (H360F).

Overall, four of the substances included in the proposal (lysmeral, 3-(4-tert-butylphenyl)propionaldehyde, 4-tert-butyltoluene and, 4-tert-butylbenzylaldehyde) have demonstrated to form in vivo tert-butylbenzoic acid (TBBA), which is considered responsible of the toxicity seen in male rats. Effects on the male reproductive system (testicular toxicity and spermatotoxicity) are reported for five of six substances in the category.

The available data provide, in a weight of evidence approach and using a read-across approach, clear evidence of adverse effects on sexual function and fertility justifying the Classification in Repr. 1B, H360F for the group of substances. We note that there is no toxicological study with methyl 4-tert-butylbenzoate. In the absence of toxicokinetics data, the read-across is only based on QSAR and structural and physico-chemical similarity.

Development

3-(4-tert-butylphenyl)propionaldehyde
In the OECD TG 422 study, reduced mean pup body weight was observed on days 9 and 12 postpartum.

4-tert-butyltoluene
In the OECD TG 421 study, there were decreases in number of offspring born and number of live pups born and increase in number of stillbirths. In this study and in a non-guideline prenatal developmental toxicity study in rats, lower pups body weights were also recorded.

2-(4-tert-butylbenzyl)propionaldehyde (lysmeral)
The substance already has a harmonised classification as Repr.2 for development (H360Fd) based on effects on post-implantation loss and reduced pup body weights consistently seen in several studies.

There are no substance-specific data available on developmental toxicity for 4-tert-butylbenzylaldehyde, methyl 4-tert-butylbenzoate and TBBA.

Overall, the available data provide, in a weight of evidence approach and using a read-across approach, some evidence of an adverse effect on development, which justifies the Classification in Repr. 2, H360d for the group of substances. France agrees that the substances present structural and physico-chemical similarities but it remains some uncertainties about the formation of TBBA in humans.

Lactation
Two studies (according to OECD TG 422 for 3-(4-tert-butylphenyl)propionaldehyde and OECD TG 421 for 4-tert-butyltoluene) showed reduced pup weight on LD 9-12 and on LD 4 and a tendency of reduced number of live offspring and viability index at LD 4 (4-tert-butyltoluene). France agrees that available data are not sufficient to determine whether the effects seen are caused by specific exposure via lactation. Thus, the comparison with the CLP criteria is inapplicable.

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2023	United Kingdom	Health and Safety Executive	National Authority	7
Comment received				
‘The DS has proposed a classification for developmental toxicity (repr. 2) for all substances within the group. The main concern comes from studies on lysmeral. Could the DS provide comment on why the other substances in the group should be considered as severe as lysmeral. Is there a read-across argument for developmental toxicity, not just a structural similarity? In the absence of developmental toxicity data on TBBA, or a proposed mode of action for TBBA-induced developmental effects, we would welcome clarification from the DS on their justification for using read-across to assess adverse effects on development for all substances in the group.’				

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2023	Germany		MemberState	8
Comment received				
1) Adverse effects on sexual function and fertility Available in vivo studies consistently report testicular and spermatotoxic effects fulfilling classification criteria Repr 1B. Based on the underlying hypothesis (formation of common toxic metabolite TBBA), application of this category to all members of the category is considered justified.				

2) Developmental toxicity

For developmental toxicity, the available data/the reported effects show a less consistent picture between the substances which might be due to the heterogeneity of the available study types. Qualitative differences in developmental effects might also be the consequence of other/additional pathways (e.g. independent from TBBA formation). Therefore, it might be sufficient to base the classification for that particular endpoint on weight of evidence only rather than read across.

PUBLIC ATTACHMENTS
1. IFRA UK CLP Consultation Response CAS 18127-01-0 as 3-(4-tert-butylphenyl)propionaldehyde – September 2023.pdf [Please refer to comment No. 4]
2. Givaudan Response to CLH report Proposal for Harmonized Classification Bourgeonal_Sep 21_Final.pdf [Please refer to comment No. 1, 5]