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 16.08.2023

Substance name: piperonal; 1,3-benzodioxole-5-carbaldehyde
CAS number: 120-57-0
EC number: 204-409-7
Dossier submitter: Ireland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
10.08.2023	United Kingdom	IFRA UK	Industry or trade association	1

Comment received

IFRA UK CLP Consultation Response – piperonal CAS 120-57-0 – August 2023

Thank you for the opportunity to give feedback on the proposals to amend the classification of piperonal, also known as Heliotropine under Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. IFRA UK has some comments about this which we would like to set out.

About IFRA UK.
As a respected trade association, IFRA UK strives to support the development and advancement of the British fragrance industry and highlight the benefits of fragrance to health and well-being. IFRA UK actively works with legislators as an advisory body and influences legislation through advocacy and policy. The Association works to protect the industry's future by setting a strict requirement for its members to comply with current legislation and industry standards that ensure consumer safety.

IFRA UK does not support the Repr 1B classification that has been proposed by the HSA. IFRA UK supports the work that has been done by the Lead Registrant and the data presented is not conclusive.

Conclusion on classification
The data are not definitive on whether the effects seen in the OECD 422 study are direct reproductive or developmental toxicity, or secondary to effects in the parents. In the absence of an obvious mechanism of action, it may be concluded that there is a doubt about the relevance to humans. The reproductive toxicity occurs in the presence of parental toxicity and the effects are likely to be a non-specific consequence of the parental toxic effects. Furthermore, the human relevance of the effects is highly questionable.

Thank you for taking note of our feedback, we hope it is helpful and will aid constructive dialogue on the classification of piperonal.

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2023	Spain	UBE CORPORATION EUROPE SAU	Company-Importer	2
Comment received				
See attachment. Full review in attached file. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Heliotropine-CLH-Report-Opinion-Independent-PJ.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2023	France		MemberState	3
Comment received				
The assessment of maternal toxicity should not be limited to mortality, clinical signs, body weight changes and food consumption. Haematology, clinical chemistry, gross or microscopic pathological findings and organ weight data must be taken account for evaluating maternal toxicity. Since STOT RE is not evaluated, reporting general toxicity data of reproductive studies in this part is, in our opinion, lacking of consistency. We suggest to report these data in the tables of fertility and development part with other general toxicity data to have a better overview of the results.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2023	Spain	UBE CORPORATION EUROPE SAU	Company-Importer	4
Comment received				
See attachment. Full review in attached file. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Heliotropine-CLH-Report-Opinion-Independent-PJ.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2023	Germany		MemberState	5
Comment received				
The DE CA supports to classify the substance EC no. 204-409-7 as a reproductive toxicant Category 1B for effects on fertility, mainly based on the reduced mean number of implantation sites. This is based on a reliable study performed according to OECD TG 422 (Combined Repeated Dose Toxicity Study (90d) with the Reproduction/Developmental Toxicity Screening Test; dose 100, 300, and 1000 mg/kg bw/d) in which none of the couples treated at highest dose was able to produce healthy offspring. This is mainly due to a decrease in the mean number of implantation sites at 1000 mg/kg bw/day (mean value control: 12.4 and 1000 mg/kg bw/day: 2.3). This was accompanied by a decrease in the fertility index at 1000 mg/kg bw/day (fertility index: 40%), compared to controls (fertility indices of low and				

mid dose, 90% and 90%, respectively). The mating index was not affected. There were no effects on the oestrous cycle or spermatogenesis. Furthermore, at highest dose, there was a statistically significant increase of absolute (55%) and relative (86%) ovary weight as well as absolute (164%) and relative (208%) uterus weight, compared to controls, however without histopathological findings at necropsy.

At 1000 mg/kg bw/day, there was a statistically significant lower female mean body on GD 17 and 20 (93% and 84% of the controls, respectively) and reduction in mean body weight gain on GD 20 (22 g compared to 44 g in controls). There was no test item-related mortality up to 1000 mg/kg bw/day, however, one female at 1000 mg/kg bw/day was sacrificed on day 1 of lactation because of a total litter loss. The DS hypothesises that the reduced mean body weight is explained by an intrauterine effect (no foetuses present) rather than maternal toxicity; 4/4 pregnant females at highest dose had abnormal pregnancies (three females with implantation sites only and one female with total litter loss on PND 1). Data on corrected female mean body weight were not available, because only females that gave birth were weighed (only one high dose female gave birth).

Absence of maternal toxicity is supported by the fact that females at 1000 mg/kg bw/d did not show any changes in mean body weight or mean body weight gain, relative to controls, during the pre-mating or mating periods or the pregnancy before GD17. Furthermore, there were no significant clinical observations reported.

Altogether, the DE CA supports to classify the substance EC no. 204-409-7 as a reproductive toxicant Category 1B for effects on fertility, mainly based on the reduced mean number of implantation sites.
Some comments for improved reading of the dossier:

- Percentages of body weight reduction in text and tables
- Details on pregnancies of females at highest dose would make maternal toxicity discussion much more clear (e.g. 4/4 pregnant females at highest dose had abnormal pregnancies; three females with implantation sites only and one female with total litter loss on PND 1; intrauterine effect = no foetuses present)
- Comments on histopathology of other organs could support lack of maternal toxicity

Developmental effects:

The German CA supports to classify the substance EC no. 204-409-7 as a reproductive toxicant Category 1B for effects on development.
This is mainly based on an increase of post-implantation loss (14.9% at 1000 mg/kg and 4.3% in controls) observed in a study conducted with test substance according to OECD 414 TG. Furthermore, at 1000 mg/kg bw/d there was a significantly reduced percentage of viable foetuses per litter (≥10% decrease), significant reduced mean foetal body weight (26% decrease) and an increase of 15% in total skeletal malformations, compared to controls. Effects occurred in the absence of maternal toxicity (decrease in body weight gain of 8% compared to controls).
Since most effects on fertility and development occurred at 1000 mg/kg bw/d, we recommend to place the substance in the low potency group of reproductive toxicants.

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2023	France		MemberState	6
Comment received				

FR agrees with the proposed classification for effects on sexual function, fertility and development as Repr. 1B – H360FD, based on: the modifications of reproductive organs weight, the decrease in fertility index, in gestation index, in mean number of implantation sites with no live offspring and on the decrease in the number of litters, mean litter size and number of viable pups on PND 1 at 1000 mg/kg bw/day and on the post-implantation survival index at ≥ 300 mg/kg bw/day, in the OECD 422 study.

Additionally, data from the OECD 414 study (increase in early and late resorptions and post implantation loss, decrease in foetal weight, in mean litter size and viable foetuses per litter at 1000 mg/kg bw/day as well as increased incidence of visceral and skeletal at ≥ 300 mg/kg bw/day and increase incidence of skeletal malformations at 1000 mg/kg bw/day) allowed to classify as Repr. 1B – H360FD.

Regarding the decrease of body weight in the high dose group at gestation days 17 and 20: we suggest to calculate the corrected mean maternal body weight of the controls and compare the results with the mean body weight of non-gravid animals in the high dose group. This would give indication whether the decrease of mean body weight is consecutive to a maternal effect in the high dose group.

Please clarify the table 12. The first column is untitled gestation period but is not clear what days 27 and 34 correspond to.

Please clarify the data about mortality and clinical signs in the OECD 422 between text in 10.10.2 and text in 10.12.1.

FR suggests to attempt to calculate specific concentration limits.

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.

Date	Country	Organisation	Type of Organisation	Comment number
10.08.2023	United Kingdom	IFRA UK	Industry or trade association	7

Comment received

IFRA UK CLP Consultation Response – piperonal CAS 120-57-0 – August 2023

Thank you for the opportunity to give feedback on the proposals to amend the classification of piperonal, also known as Heliotropine under Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. IFRA UK has some comments about this which we would like to set out.

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IFRA UK does not support the Repr 1B classification that has been proposed by the HSA. IFRA UK supports the work that has been done by the Lead Registrant and the data

presented is not conclusive.

Conclusion on classification
The data are not definitive on whether the effects seen in the OECD 422 study are direct reproductive or developmental toxicity, or secondary to effects in the parents. In the absence of an obvious mechanism of action, it may be concluded that there is a doubt about the relevance to humans. The reproductive toxicity occurs in the presence of parental toxicity and the effects are likely to be a non-specific consequence of the parental toxic effects. Furthermore, the human relevance of the effects is highly questionable.

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OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2023	Spain	UBE CORPORATION EUROPE SAU	Company-Importer	8
Comment received				
See attachment. Full review in attached file. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Heliotropine-CLH-Report-Opinion-Independent-PJ.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2023	Germany		MemberState	9
Comment received				
The DS concluded to classify the substance EC no. 204-409-7 as skin sensitiser without sub-categorisation (Category 1, H317). This is mainly based on a reliable guinea pig maximisation test (GPMT, similar to OECD TG 406), in which 40% (4/10, 48 hour reading) of the animals showed positive reactions using 1.5% test substance for intradermal induction and 80% for topical challenge. Other studies to evaluate the skin sensitisation property of EC no. 204-409-7 showed positive and negative reactions in tested animals, however studies were of limiting reporting concerning the methods and results and are therefore judged as not reliable for evaluation. The result of the GPMT fulfils the criteria for classification of the test substance as skin sensitiser with sub-category 1B (≥30% responding at >1% intradermal induction dose). However, lower concentrations of the test substance for intradermal induction were not tested and therefore sub-category 1A cannot be excluded (≥30% responding at ≤0.1% intradermal induction dose). Therefore, the DE CA supports to classify the substance EC no. 204-409-7 as skin sensitiser without sub-categorisation (Category 1).				

Date	Country	Organisation	Type of Organisation	Comment number
27.07.2023	France		MemberState	10
Comment received				
FR agrees with the proposed classification as Skin Sens. 1 (without sub-categorisation) based on the available guinea pig maximisation test that showed a positivity rate of 40% with an intradermal dose of 1.5 % while positive reactions described as ‘faint pink’ were				

described from 0.1 % without any further information on the severity of these reactions.

PUBLIC ATTACHMENTS
1. Heliotropine-CLH-Report-Opinion-Independent-PJ.pdf [Please refer to comment No. 2, 4, 8]