Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

propyl 4-hydroxybenzoate

EC Number: 202-307-7
CAS Number: 94-13-3

CLH-O-0000007263-77-01/F

Adopted

16 March 2023

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: propyl 4-hydroxybenzoate
EC number: 202-307-7
CAS number: 94-13-3
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2022	Germany	German Chemical Industry Association (VCI)	Industry or trade association	1
Comment received				
VCI would like to make a general comment firstly on fundamental toxicological aspects during CLH evaluation and secondly on the evaluation of OECD TG 443 studies, which are still under discussion because of an ongoing ECHA project. Substance-specific comments are outside the scope of this consultation submission. Rather, VCI would like to provide the following key statements: - Adherence of scientific principles for toxicological evaluation considering all relevant data (statistically significance and biological relevance of effects, use of historical data, consideration of dose dependency). - Functional parameters related to observations for isolated values within the OECD TG 443 should be considered in order to evaluate the adversity of effects, evidence of adversity, evidence of causality. - Isolated evaluation of single biological parameters without consideration of the whole database and other toxicological OECD-conform studies is not scientifically justified and should be performed in a Weight of Evidence approach. - Relevance of toxicological observation for classification and labelling. - Results of the ongoing ECHA project assessing OECD TG 443 studies should be taken into account. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2022-06-10 VCI-Kommentar - CLH Report propyl 4-hydroxybenzoate - OECD 443.pdf				
Dossier Submitter's Response				
Your comment is noted.				

The ongoing ECHA project is not linked to this CLH process. Moreover, the OECD TG 443 is a validated OECD study and is included in section 3.7.2.5 of Annex I of CLP. As a consequence the results must be taken into account as well as all the results of other available studies.
RAC's response
RAC also notes the comment, and agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2022	Belgium	Cosmetics Europe	Industry or trade association	2
Comment received				
None ECHA note – An attachment was submitted with the comment above. Refer to public attachment ECHA Propylparaben CMR 2 public consultation - Final Contribution 09 06 2022.pdf				
Dossier Submitter's Response				
Your comment is noted.				
RAC's response				
RAC noted the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2022	Germany	<confidential>	Academic institution	3
Comment received				
<confidential> takes the opportunity to provide the attached scientific comments on the CLH report on propyl paraben provided by MS Belgium. The comments disconfirm the concern regarding the proposed classification of propyl paraben as reprotox Cat 2, H361 f,d. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Expert statement - CLH dossier - propyl paraben_CRL_2022-06.pdf				
Dossier Submitter's Response				
Your comment is noted.				
RAC's response				
RAC noted the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2022	Germany	Clariant Produkte (Deutschland) GmbH	Company-Importer	4
Comment received				
Clariant Produkte (Deutschland) GmbH does not agree with the position provided by the Belgium MS regarding classification of propyl 4-hydroxybenzoate as Repr. 2 H361d,f. For a detailed scientific evaluation and commenting on the CLH dossier please refer to the attached document. In addition to the comments provided by Clariant Produkte				

(Deutschland) GmbH this document includes a scientific statement on the Extanded One Generation Reproductive Toxicity Study (EOGRTS) done by the CRO BSL BIOSERVICE who performed the study as Belgium MS raised a concern regarding reproductive and developmental toxicity based on the results of the EOGRTS. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on CLH Dossier Propyl 4-hydroxybenzoate-Clariant_2022-06-09.pdf
Dossier Submitter's Response
Your comment is noted.
RAC's response
RAC noted the comment.

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2022	Germany		MemberState	5
Comment received				
In section 1.1, table 1 the "Degree of purity (%) (if relevant for the entry in Annex VI)" of propyl 4-hydroxybenzoate is given. If not relevant for the entry in Annex VI, the given purity should be deleted.				
Dossier Submitter's Response				
Thank you for your comment. In the Guidance on the preparation of dossiers for harmonised classification and labelling, it's mentioned in section 5.4.1.2. The technical dossier : "Substance identity: Information on substance identity is crucial for evaluation of the CLH dossier and for the entry in Annex VI to the CLP Regulation. Sections 1.1 and 1.2 of the substance dataset in IUCLID should always be filled in and should include the IUPAC name or chemical name, CAS number, EC number, registration number for the registration dossier which was used as a source of information (if available), molecular and structural formulae (if applicable), as well as the purity of the substance and any impurities (see Section 5.2.1) and the state and/or form(s); and…" Therefore the purity should not be deleted.				
RAC's response				
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Date	Country	Organisation	Type of Organisation	Comment number
08.06.2022	Belgium	EFfCI - The European Federation for Cosmetic Ingredients	Industry or trade association	6
Comment received				
The European Federation for Cosmetic Ingredients (EFfCI) is taking the opportunity to provide the following comments on the CLH report on propylparaben dated March 2022 provided by the MS Belgium. These comments express significant concerns regarding the proposed classification of propyl paraben (chemical name: propyl 4-hydroxybenzoate, CAS-No. 94-13-3) as reproductive toxic, category 2 with H361fd in that the rational for classifying propyl paraben is lacking compliance with fundamental scientific principles and				

regulatory requirements regarding the evaluation of substances in terms of toxicological significance and relevance of observed effects.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2022-06-07 CLH Dossier Propylbaraben - EFfCI comment.pdf

Dossier Submitter's Response

Your comment is noted.

- In your attached document, you mention *"Considering the CLH report provided by the MS Belgium it is our concern that a scientifically, and via CLP regulation required, balanced, transparent and objective assessment of all available data has not been carried out. Instead, it appears that negative data were not given equal weight with more weight being given to seemingly positive outcomes.*

For example, „reduced" AGD values are considered only from the F1 pubs despite the fact that these findings in F1 pubs did not occur in the F2 pubs, were not statistically significant after normalization to cube root of body weight, were not dose-dependent and – importantly – were all well within the range of historical control data."

BE CA wants to highlight that the data regarding the F1 pups were available in table 42 and the data concerning the F2 pups in table 45 of the CLH report.

- Furthermore, it's written in the document that *"With regard to the slight increase in post-implantation loss observed in the `extended one generation reproductive toxicity study`(EOGRTS), it is particularly remarkable that no discussion or mentioning takes place that this finding was statistically not significant, not confirmed / reproducible in cohort 1B of the EOGRTS, and – again – was well within the range of historical control data."*

BE CA wants to respond that the data regarding the post-implantation loss in the cohort 1B are available in table 18. Moreover, in section 10.10.6 Comparison with the CLP criteria, it is clearly mentioned "In the EOGRTS (Registration dossier (study report, 2021)), in the F0 generation, the percentage of post-implantation loss was increased at the highest dose, but the modification was not dose-related (5.99, 7.79, 4.76 and 8.98 %). This effect was not confirmed in the cohort 1B."

- Regarding Oishi's study, this study was available in the registration dossier and in the CLH and reported in both as a study with reliability 3. Moreover, in the registration dossier, even if the study is mentioned as 'disregarded', it is also indicated "acceptable, well documented publication which meets basic scientific principles".

Administrative data

Endpoint:	fertility, other
Remarks:	based on test type (migrated information)
Type of information:	experimental study
Adequacy of study:	disregarded due to major methodological deficiencies
Reliability:	3 (not reliable)
Rationale for reliability incl. deficiencies:	other: Acceptable, well documentated publication which meets basic scientific principles.
Remarks:	Control values outside normal range, not consistent with literature data and other Oishi studies, absence of dose-response for DSP, small group size, full study protocol and raw data not available.

RAC's response

RAC noted the comment.
In the RAC opinion, data on post-implantation loss from several studies is presented in an overview Table. With regard to AGD, all data available from the EOGRTS are presented in another overview Table. RAC conclusion on no classification warranted is based on all available data in a weight-of-evidence approach.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2022	France		MemberState	7

Comment received

FR welcomes this proposal and supports it. Nevertheless FR is wondering if BE has envisaged to propose a classification as Repro Cat.1B instead of Cat.2?
Indeed, based on the effects observed especially the coherent effects see on sperms (count and morphology) among the studies, including the EOGRTS. The fertility index was not affected in this study but it should be noted that, despite the effects seen in previous studies, the pre-mating index was reduced to 2-weeks. It is in line with the guideline, nevertheless, because of the effects associated with the substance, a longer pre-mating period of 10 weeks would have been more relevant. Particularly, regarding the CLP criteria, it seems that there is no mechanistic information raising doubt about the relevance of the effects to human, and no strong deficiencies were noted in the study which could have justify a classification in Cat. 2.
Additionally, since the effects are common to the family (at least methyl-, ethyl- and butyl-) could the effects seen with the other substances be also added in order to have a more global approach and strengthen the evidence?

Dossier Submitter's Response

Thank you for your comment and your support.

Regarding the family approach, currently no harmonised classification is available for another paraben (methyl-, ethyl- and butyl-).

RAC's response

RAC noted the comment.
With regard to the 2 instead of 10 weeks premating. This was decided by MSC.
"According to the ECHA guidance (Chapter R.7a), the pre-mating exposure duration shall be 10 weeks in order to cover the full period of spermatogenesis and folliculogenesis. However, due to the request of the extension of cohort 1B, ECHA is of the opinion that the pre-mating exposure period could be reduced to 2 weeks, as these development periods will be covered in the F1 generation."
No information is available in the CLH report on other parabens.

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2022	Belgium	Cosmetics Europe	Industry or trade association	8

Comment received

Comments on the CLH Report Proposal for Harmonised Classification and Labelling – Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Substance Name: EC number: 202-307-7 CAS number: 94-13-3; Dossier Submitter – Belgium (FPS Public Health, Food Chain Safety and Environment DGEM/ Department of Product Policy and chemical Substances / Management of Chemical Substances)

Headline summary

The Belgian REACH authorities submitted a classification proposal of Repr.2, H361fd for Propylparaben. This is mainly based on the results of an extended one generation reproductive toxicity study (EOGRTS) according to the OECD Test Guideline 443 after oral (gavage) administration at dose levels of 100, 300, and 1000 mg/kg body weight day to Wistar rats (2021). In the study report it was concluded that the NOAEL for developmental and reproductive toxicity, neurotoxicity and immunotoxicity was determined as 1000 mg/kg body weight/day. In contrast to that, the Belgian rapporteur defines a NOAEL of 300 mg/kg body weight/day based on changes in sperm motility and morphology. In addition to the proposed effects on sperm parameters in the EOGRTS, the rapporteur has cited decreased absolute anogenital distance (AGD) of male pups, and apparent increases in post implant loss as further reason for Repr.2 H361fd classification. However, examination of the toxicology database for propylparaben demonstrates there are no toxicologically relevant effects on sperm, AGD or post implantation loss.
Given the definite lack of toxicologically relevant effects on sexual function and fertility, or on development, it is the opinion of Cosmetics Europe (CE) reproductive toxicology experts that there is no justification for a Repr.2 classification for propylparaben.

Fertility

According to the submitted CLH report, the 2021 EOGRTS revealed a reduction in sperm motility in the high dose groups of both the F0 and F1 generations. The CLH also states that the total number of abnormal sperm was greatly increased in the high dose groups of both generations, primarily driven by increases in the number of 'tail only' sperm. The conclusions from the CLH contrast with that of the study report which states that 1000 mg/kg/day was a clear reproductive NOAEL. The CLH conclusions also differ from the conclusions of reproductive toxicology experts from CE who concur that a NOAEL of 1000 mg/kg/day was established in the EOGRTS due to a clear lack of significant and adverse effects on reproduction. Moreover, the SCCS evaluated this study in its recent opinion on propylparaben (SCCS/1623/20, adopted on 30-31 March 2021) and agreed that the results of the EOGRTS suggest a NOAEL of 1000 mg/kg/day.
In the F0 generation, mean motile sperm counts were reported as 77.05% and 72.67% in the control and high dose (HD: 1000 mg/kg/day) groups respectively. In the F1 generation, the mean motile counts were reported as 79.10% and 72.42% in the control and HD groups respectively. However, in the view of CE reproductive toxicology experts these small, statistically not significant, decreases are not toxicologically relevant when compared with the historical control data (HCD) for motile counts of the conducting laboratory, which range between 65.25% to 98.17% (mean -/+ 2SD). This view is supported by the recent SCCS opinion (SCCS/1623/20).
In addition, examination of the individual animal data (IAD) reveals one outlier in the HD group of the F0 generation. Animal 92 has no motility data across all recordable fields (motile, static, and rapid counts) and 74% of the 200 sperm counted from this animal had 'abnormal morphology', a clear outlier of the group. Due to the extreme results across several parameters, compared to the remaining animals of the same dose group, CE reproductive toxicology experts consider it appropriate to exclude this animal from further analysis on a weight of evidence basis. Exclusion of this animal changes the mean motile count from 72.67% to 75.17% for the F0 HD group. In conclusion, despite small incremental decreases in mean values between HD groups and concurrent control groups, CE reproductive toxicology experts do not agree these constitute significant or toxicologically relevant changes to sperm motility.
The CLH report also highlights increases in the total number of abnormal sperm in both the F0 and F1 males. In the F0 generation, the mean total of abnormal sperm is reported as 8.25% and 13.33% in the control and HD groups respectively. However, as previously mentioned there is a clear outlier (animal 92) within the HD group with unusually

divergent results across several parameters. Without this animal the total number of abnormal sperm is only 7.48% in the HD group, lower than the concurrent controls. In addition, the percentage of 'tail only' sperm are reported as 2.96% and 8.17% in the control and HD groups respectively, compared to only 2.96% and 2.83% when animal 92 is excluded.
Similarly, in the F1 generation when a clear outlier (animal 298) is excluded, the total number of abnormal sperm is 10.35% and 12.29% in control and HD animals compared to 10.35% and 19.06% when animal 298 is not excluded. In the 'tail only' analysis the values are 3.85% and 5% in control and HD groups without the outlier, compared to 3.85% and 11.17% including the outlier.
In summary, all the high dose values for total number of abnormal sperm are within the conducting laboratory HCD, which ranges between 0% to 19.30% (mean -/+ 2SD).
Therefore, in conclusion, despite small incremental changes of some mean values between the HD groups and concurrent control groups in the EOGRTS, CE reproductive toxicology experts do not agree these constitute toxicologically relevant changes of sperm morphology. It should also be noted that there were no changes in sperm parameters, fertility or development in the F0 parental or F1 cohort 1A. Moreover, the rapporteur use data from the study of Oishi (2002, incorrectly referred to in the CLH report as Oishi, 2012) to support their conclusions (see CLH Report, Table 34). But it has to be noted that the Oishi (2002) study was a non-GLP, non-guideline study with small group size. There were a number of control values in parameters that were well outside of the normal range. The data were not consistent with literature data and data from other studies of Oishi for daily sperm production (DSP), epididymal sperm counts and testosterone concentration, and there was no dose-response for the effect on DSP. In addition, a full study protocol and raw data are no longer available which makes the results irreproducible and thus, scientifically unreliable (Snodin, 2017).
The rapporteur should also have referred to three other good quality, reliable GLP studies, i.e., Hoberman et al. (2008), Sivaraman et al. (2018) and Gazin et al. (2013). None of these studies showed any evidence of adverse effects on the male reproductive system including sperm parameters and measurement of hormone concentrations. The NOAEL of all these well-powered GLP studies was 1000 mg/kg bw/day.

Development

According to the CLH report there were consistent effects on post implant loss across multiple studies, and a decrease in male AGD in the EOGRTS following treatment with propylparaben. The conclusions in the CLH contrast with that of both the OECD Test Guideline 414 and EOGRTS study reports which state 1000 mg/kg/day as a clear developmental NOAEL. The CLH conclusions also differ from the conclusions of CE reproductive toxicology experts who concur that a clear developmental NOAEL of 1000 mg/kg/day has been established due to a lack of significant and adverse effects on development. This view is supported by the recent SCCS opinion (SCCS/1623/20).
Male AGD, the distance between the anus and the external genitalia, is an androgen-sensitive endpoint of the masculinization. Regarding the AGD, all the evaluated values were in the range of historical control data and no dose dependency could be observed. Furthermore, the changes were not statistically significant and could not be revealed in both generations of the EOGRTS indicating that these effects are due to biological variability rather than test item related.
In the EOGRTS the AGD of the F1 males was 2.84mm and 2.71mm in the control and HD groups respectively, which looks like a statistically significant difference. However, the value of 2.71mm is well within concurrent HCD for this finding at the conducting laboratory (mean of 2.6mm from 2073 male pups) and therefore although statistically significant, there is no biological or toxicological relevance to this change. Furthermore, the relative AGD measurements were not statistically different and are also well within

HCD. This is similar in the F2 males, where the AGD was 2.98mm and 2.77mm in the control and HD groups respectively. Again, although this change is recorded as statistically significant there is no biological or toxicological relevance to it as the HD value (2.77mm) is well within the concurrent HCD for AGD. In conclusion, despite small incremental changes to some mean values between the HD groups and concurrent control groups, CE reproductive toxicology experts do not agree that these constitute toxicologically relevant changes on AGD or development.
A decrease in AGD in male offspring may be associated with genital malformations at birth and reproductive disorders in adulthood. A concern regarding the reduction of AGD in male and female pups was raised by the CLH-dossier submitter based on the data provided in the OECD Test Guideline 443. Based on the data from the EOGRTS in male pups from the parental generation, on PND 0 marginal shorter absolute but not relative AGD was observed only in the HD group (1000 mg/kg bw per day) when compared to the concurrent controls. It is important to note that AGD is influenced by the body weight of the animal and therefore, this needs to be taken into account when evaluating the data (OECD Guidance document No. 151) and a normalization using the cube root of body weight is recommended in Test Guideline 443. In case of propylparaben (parental generation) no statistically significant effect could be observed after normalization of AGD to cube root of body weight. More importantly, no dose dependency was observed in these effects and all the values were well within the range of historical control data revealing that this effect is not considered to be test item related but due to biological variation.
Due to the strong correlation between AGD and various reproductive disorders and malformations, an isolated consideration of AGD is not appropriate. Especially in the case of propylparaben, where changes in male AGD were only minimal, well within the range of historical control data and not dose dependent, the concurrent lack of any functional or histopathological impairment contradicts the assumption of an adverse effect. The results from the EOGRTS clearly demonstrate that in utero exposure to propylparaben up to the limit dose of 1000 mg/kg bw per day did not induce any morphological or histopathological abnormalities in male reproductive organs. Importantly, functional parameters such as fertility and mating index were also not affected after treatment with propylparaben up to 1000 mg/kg bw per day neither in parental, nor in F1 and/or F2 animals. The effects on nipple retention did not support a possible relationship of the AGD findings with an anti-androgenic mode of action as the nipple retention is upregulated in the parental but downregulated in the F1 generation. These deviating and, in particular, contradictory effects, scientifically support the view that an anti-androgenic mode of action can be excluded and that the minor changes on AGD (and nipple retention) can plausibly be regarded as being due to biological variability and possible impact of body weight changes and therefore, are not considered to be a toxicologically relevant effect.
With regard to post implant losses, in both the EOGRTS and OECD Test Guideline 414 studies the small incremental changes in these values were not dose responsive, not statistically significant and therefore, not considered toxicologically relevant. In two lower powered range finding studies, there was an apparent increase in what appears a dose responsive manner, however the values for post implant loss were all well within the conducting laboratory HCD for this finding. The CLH states for one range finding study that post implant loss of 12.4% at the HD is 'severely higher' than the concurrent control group (at 5.9%), however the mean post implant loss in historic control animals is comparable to the HD group at 10.1%, with a range of values from 0- 51.8% -/+ 2SD. In conclusion, despite small incremental changes to some mean values between the HD groups and concurrent control groups, CE reproductive toxicology experts do not agree that these constitute toxicologically relevant changes of post implantation loss or development.
For the purpose of weight of evidence, the CLH should have also referred to the study of

Sivaraman et al. (2018) which showed no evidence of adverse effects on development, including no increase in post implant loss. The NOAEL of this well-powered GLP study was 1000 mg/kg bw/day.

Other Relevant Information

Following oral exposure, propylparaben is very rapidly metabolised to p-hydroxybenzoic acid which is cleared within 4-6 hours via urinary excretion in humans. At the oral doses administered (up to 1000 mg/kg bw in rats and up to 2 mg/kg bw in humans) excretion is principally urinary and fast with more than 90% of the propylparaben dose excreted within 24 h post-dosing in both rat and human, confirming that propylparaben does not accumulate in the body (Shin et al., 2019). The rapid metabolism of propylparaben, particularly in the rat, substantiates that after oral administration no plasma levels are achieved which may be high enough to lead to adverse effects such as, e.g., reproductive toxicity.

Comparison with the CLP criteria

Substances suspected of being toxic for human reproduction are classified in category 2 for reproductive toxicity, i.e., when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development.
The CLH concludes that due to severe effects in sperm in the absence of clear general toxicity, a classification as Repr. 2 H361f is warranted. It also concludes that classification as Repr. 2, H361d is warranted based on AGD and post-implantation loss's modifications. However, examination of the toxicology data demonstrates there are no toxicologically relevant effects on sperm, AGD or post implant losses.
Given the definite lack of toxicologically relevant effects on sexual function and fertility, or on development, it is the opinion of CE reproductive toxicology experts that there is no justification for a Repr.2 classification for reproductive toxicity of propylparaben.

Conclusion

A classification for reproductive and developmental toxicity according to CLP is not justified based on the scientific evidence in the context of the regulatory criteria (REGULATION (EC) No 1272/2008). According Regulation (EC) 1272/2008 of the European Parliament and of the Council („CLP Regulation"), classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence which means that all available information that bears on the determination of reproductive toxicity is considered together in that both, positive and negative results are assembled together into a weight of evidence determination.
For an effect to warrant classification, CLP criteria primarily require, that the effect is adverse, which is furthermore characterized by several additional criteria including the assessment of the biological and toxicological significance, as well as the nature, severity, and incidence of the effect. Furthermore, conclusions on the inherent ability of a chemical to induce a specific adverse effect should be based upon the available data and an assessment of total weight of evidence which includes assembling together both positive and negative results. As already described, the extensive scientific evidence from animal studies involving oral exposure to propylparaben demonstrates a lack of adverse reproductive effects per the CLP criteria and therefore classification for development and fertility effects is not required. To conclude on a classification determination, there is a need to take into account the whole toxicological evidence for propylparaben in a robust weight of evidence approach to develop an informed regulatory decision that is commensurate and proportionate with all available data. Following these principles, the

following can be concluded with regard to the concerns brought forward by the CLH-dossier submitter: an isolated consideration of effects on single endpoints which are lacking statistical significance, and which are without any dose dependency, is not appropriate and/or justified for classification as developmental and reproductive toxicity. More importantly, all findings of concern discussed by the evaluating MS Belgium are well within the range of the historical control data and thus, represent biological variation rather than a substance-related true effect of toxicological relevance. Additionally, functional parameters which are correlated to single values need to be considered in order to assess the adversity of effects. When taking the complete set of available toxicological data into account, no adverse effect on all above mentioned functional developmental and reproductive parameters could be observed up to the limit dose of 1000 mg/kg bw per day and thus, a classification as Repr. Cat 2 is not justified.

[In the attachment the same input is provided with a friendly format for ease of reading]

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ECHA Propylparaben CMR 2 public consultation - Final Contribution 09 06 2022.pdf

Dossier Submitter's Response
Your comment is noted.
RAC's response
RAC agrees that classification should be based on an overall weight of evidence approach taking into account all data. RAC conclusion on no classification warranted is based on all available data in a weight-of-evidence approach.

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2022	Germany	<confidential>	Academic institution	9
Comment received				
The concern provided by MS Belgium is lacking scientific justifcation and does not take into account the scientific principles on toxicological evaluation (e.g. historical control data, biologcal variability, adversity of effects and dose dependency etc.). Thefore the classification of propyl paraben as reprotox Cat 2, H361 f,d is scientifically not justified, for more details please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Expert statement - CLH dossier - propyl paraben_CRL_2022-06.pdf				
Dossier Submitter's Response				
Your comment is noted.				
RAC's response				
RAC noted the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2022	Germany	Clariant Produkte (Deutschland) GmbH	Company-Importer	10
Comment received				
Clariant Produkte (Deutschland) GmbH does not agree with the position provided by the Belgium MS regarding classification of propyl 4-hydroxybenzoate as Repr. 2 H361d,f. Clariant Produkte (Deutschland) GmbH notes that an isolated consideration of effects on single endpoints which are lacking statistical significance, and which are without any dose				

dependency, is not appropriate and/or justified for classification as developmental and reproductive toxicity. More importantly, all findings of concern discussed by the evaluating MS Belgium are well within the range of the historical control data and thus represent biological variation rather than a substance related true toxicological significant effect. It is therefore concluded that the classification proposal for reproductive toxicity according to CLP is not justified based on an evaluation of the overall scientific evidence in the context of the regulatory criteria according Regulation (EC) No 1272/2008 of the European Parliament and of the Council), Considering the CLP Regulation, adverse effects on sexual function and fertility include effects on the onset of puberty gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence or modifications in other functions that are dependent on the integrity of the reproductive systems. Based on data from the EOGRTS and a weight of evidence approach taking all availabe data into consideration no adverse effect on functional developmental and reproductive parameters up to the limit dose of 1000 mg/kg bw per day could be observed and thus a classification of propyl 4-hydroxybenzoate as Repr. 2 H361d,f is not justified (for more details please refer to the attached document). In addition this result is supported by a statement done by the CRO BSL BIOSERVICE who performed the the EOGRTS. This statement is also included in the attached document (Annex II).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on CLH Dossier Propyl 4-hydroxybenzoate-Clariant_2022-06-09.pdf

Dossier Submitter's Response

Your comment is noted.

RAC's response

RAC agrees that classification should be based on an overall weight of evidence approach. RAC conclusion on no classification warranted is based on all available data in a weight-of-evidence approach.

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2022	Germany		MemberState	11

Comment received

There is evidence from animal studies that propyl 4-hydroxybenzoate negatively affects sperm counts, motility, and morphology. However, the study by Oishi (2002) has some shortcomings (see e.g. SCCS/1623/20), and the effects on sperm motility and morphology in the EOGRTS (OECD TG 443) study are statistically non-significant. In addition, it would be useful to take a closer look at the full study report, which animals and incidences are included in the published values, and again review corresponding HCD. Furthermore, the study by Gazin et al. (2013) and an OECD TG 422 study show no effects on sperm (although it is acknowledged that in the OECD TG 422 study compared with the EOGRTS, the top dose is slightly lower, and sperm of only 5 males per group was investigated). Therefore, classification as Repr. 2 H361f is proposed by the DS.

However, given the above mentioned contradicting data and the overall weight of evidence for sperm effects, the DE CA is of the opinion that this is a borderline case between Repr. 2 and no classification for fertility.

It should be mentioned that the lack of effects on fertility index is not an argument against classification (as stated in the CLH report on p28) since effects on sperm have to be very pronounced to induce reduced fertility in male rats. It might be considered to use the decreased male AGD/AGI (F1 and F2) in the EOGRTS as supporting evidence for

adverse effects on male fertility.

With regard to development, classification as Repr. 2 H361d is proposed based on increases in post-implantation loss and decreased AGD/AGI in males and females. It should be discussed whether the decreased AGD/AGI in males (as an anti-androgenic biomarker associated, among others, with reduced fertility) is used rather for classification for fertility than for development. In females on the other hand, it is unclear what type of adversity is associated with a decreased AGD/AGI and why this parameters should be used for classification.

Dossier Submitter's Response

Thank you for your comment. BE CA also agrees that this is a borderline case between cat. 2 and no classification.

Regarding the decreased male AGD/AGI, BE CA can agree that this modification can be used as supportive information for fertility classification proposal.

RAC's response

The CLH report does not contain information on HCD, however some information was attached in Comments 4 and 10. Some information is added to the RAC opinion.
With regard to the effect on AGD, this is not very pronounced. If this is a signal of a potential anti-androgenic mechanism, this is not supported by other parameters in the EOGRTS (like sperm count, fertility index).
RAC notes the relevant discussion on Category 2 or no classification. Classification should be based on an overall weight of evidence approach. RAC conclusion on no classification warranted is based on all available data in a weight-of-evidence approach.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2022	United Kingdom	Health and Safety Executive	National Authority	12

Comment received

The DS considered post implantation loss and anogenital distance (AGD) as signs of developmental toxicity leading to a classification of repr. 2. We note that in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Registration dossier (study report, 2012)), the registrant mentions historical control data (HCD). The effects on post implantation loss, according to the registrant, were in the range of the HCD. Furthermore, the AGD effects seen in the EOGRT study were also within the range of the HCD. We note that the CLH dossier does not refer to HCD for these effects – is it possible to obtain this HCD so it can be included in the assessment?

In addition, we note that the top dose used for both studies are at or above the limit dose specified by OECD (1000 mg/kg bw/d).

Dossier Submitter's Response

Your comment is noted.
Regarding the combined study, the HCD for the % post-implantation loss is :

HCD available in the full study report of the combined study

Study nb	1	2	3	4	5	6	7	8	9	10	11
Year	05/09	12/09	02/10	02/10	03/10	03/10	03/10	04/10	08/10	09/10	09/10

% of PI-loss	5.1	12.6	9.6	5.6	8.5	6.4	6.0	10.4	3.7	9.9	10.9

No HCD regarding AGD was available in the full study report.

RAC's response

RAC thanks the DS for providing HCD for one study on post-implantation loss.
RAC further notes that the HCD for AGD information in Comment 4 and 10 attachments was presented (data from the same laboratory, see Table in the RAC opinion).

PUBLIC ATTACHMENTS
1. 2022-06-10 VCI-Kommentar - CLH Report propyl 4-hydroxybenzoate - OECD 443.pdf [Please refer to comment No. 1]
2. ECHA Propylparaben CMR 2 public consultation - Final Contribution 09 06 2022.pdf [Please refer to comment No. 2, 8]
3. Expert statement - CLH dossier - propyl paraben_CRL_2022-06.pdf [Please refer to comment No. 3, 9]
4. Comments on CLH Dossier Propyl 4-hydroxybenzoate-Clariant_2022-06-09.pdf [Please refer to comment No. 4, 10]
5. 2022-06-07 CLH Dossier Propylbaraben - EFfCI comment.pdf [Please refer to comment No. 6]