

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 3,4,5-trihydroxybenzoate

EC Number: 204-498-2

CAS Number: 121-79-9

CLH-O-0000007072-82-01/F

Adopted
18 March 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PROPYL 3,4,5-TRIHYDROXYBENZOATE

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 3,4,5-trihydroxybenzoate

EC number: 204-498-2

CAS number: 121-79-9

Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2021	France		MemberState	1
Comment received				
Environmental hazards FR supports the proposal to classify the substance propyl 3,4,5-trihydroxybenzoate (n° CAS: 121-79-9) Aquatic Acute 1 H400 (M-factor=1), Aquatic Chronic 2 H411. • We agree that based on the OECD 301F, propyl 3,4,5-trihydroxybenzoate is predicted to be not rapidly biodegradable. We note that Hydrolysis OECD 111 cannot be used in this context due to the specificity of the anaerobic compartments (Guidance on the Application of the CLP Criteria, July 2017, p.499). • We agree that all the validity criteria are met in the 72h-algae growth inhibition test using <i>Pseudokirchneriella subcapitata</i> (<i>Raphidocelis subcapitata</i>). However, it is unclear why the concentration of the test substance decreases rapidly below the LOQ. We are of the opinion that this decrease can hardly be explained based on the physico-chemical properties available (Koc, volatilisation, hydrolysis...). Moreover, as demonstrated by the OECD 301F study, the substance is considered as non-readily biodegradable. Can you please provide an argumentation on this topic if possible, as it will help to understand the uncertainties in the effect concentrations.				
Dossier Submitter's Response				
Thank you for your comment. Concerning the concentration decrease in the Algae test, there were no reasons obvious from the report (no undissolved test substance particles in the test solution...).				
RAC's response				
Noted. RAC does not understand the comment regarding the OECD 111 test. Maybe this was meant to refer to OECD 311 which is mentioned in the CLP Guidance on page 499.				

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Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Belgium		MemberState	2
Comment received				
<p>There is no field for giving comments on the aquatic environment which is also open for commenting: BE CA supports the proposed environmental classification of Aquatic Acute 1, H400, M-factor=1 for propyl 3,4,5-trihydroxybenzoate, based on the recalculated 72h-ErC50 value for algae of 0.22 mg/L. BE CA also supports the proposed environmental classification of Aquatic Chronic 2, H411 according to the most stringent outcome, based on the recalculated chronic 72h-ErC10 value for algae of 0.103 mg/L. BE CA would also like to point out that this chronic 72h-ErC10 value is very close to the cut-off value of 0.1 mg/L for Category Chronic 1.</p>				
Dossier Submitter's Response				
<p>Thank you for your support. Using the TWA method for calculating the mean measured concentration as commented by BE CA, the ErC10 value is with high probability below the cut-off value of 0.1 mg/L for Aquatic Chronic 1. Therefore, we agree that this classification should be used for the substance.</p>				
RAC's response				
<p>RAC supports the use of TWA method for calculating the mean measured concentration in this case. Please see the RAC opinion for more details.</p>				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Belgium		MemberState	3
Comment received				
<p>BE CA supports the WoE approach to modify the current classification of propyl-3,4,5-trihydroxybenzoate from acute tox. 4* to acute tox. 4 without the *. We acknowledge the lack of reliable studies but we support the use of the NTP 1982 results. While no effects were seen on the rat, the LD50 in mouse was determined at 1000 mg/kg bw since 1/5 and 3/5 males and females, respectively, died after being dosed with 2000 mg/kg bw. The remaining available, yet less reliable, studies on mice give LD50 equivalent to 1700, 2000, 2850 and 3500 mg/kg bw. Most reliable LD50 are 2000 and 1700 mg/kg bw from Boehl and Williams, 1943 and Karpyluk, 1959, respectively, both supporting the classification of the test substance in Oral acute toxicity, category 4. Therefore, a LD50 < 2000 mg/kg bw warranting a classification as Acute Tox. 4 is supported by BECA. Furthermore, an ATE of 1570 mg/kg bw (the most sensitive LD50, from one the most reliable studies, probably combined for both sexes) is supported.</p>				
Dossier Submitter's Response				
<p>Thank you for your comment and support for classification as Acute Tox. 4, H302. In the light of the comments received from BE CA and industry, a reassessment of the data was performed. As the cATpE (500 mg/kg bw) is not representative of the data available, the ATE value proposed (1000 mg/kg bw) represents the lowest value from the LD50 range of > 1000 to ≤ 2000 mg/kg bw in mice (NTP, 1982). However, the dose of 1000 mg/kg bw does not</p>				

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reflect the approximate LD50, as there was no mortality observed at this dose level. Besides, the 2000 mg/kg bw dose level represents the LD60 in female mice (3/5 females died) in the NTP study (1982). The lowest reliable LD50 value of 1700 mg/kg bw was determined in the study on mice by Karpyluk (1959), which indicates a good accordance with the NTP results. Therefore, we approve and endorse an ATE of 1700 mg/kg bw.

RAC's response

Thank you for your comment. Taking into account that it is not known how the LD₅₀ value of 1570 mg/kg bw was estimated RAC supports DS proposal (in above DS response) for the use of LD₅₀ value of 1700 mg/kg bw as ATE for acute oral toxicity for propyl gallate.

Date	Country	Organisation	Type of Organisation	Comment number
02.08.2021	Netherlands		MemberState	4

Comment received

Disagree with the proposal adaptation for C&L.
 Since the chronic algae effect concentration is bordering on the classification threshold between Aquatic Chronic 1 and 2 (0.01 mg/L), we performed an additional recalculation by non-linear regression using GraphPad based on the available information provided in the CLH report (the overview of the analytical results; using an LOQ/2 value of 0.1 mg/L for all n.d. and BLQ cases, and the inhibition growth rates). The 72-h ErC50 value was estimated to be 0.22 mg/L and the 72-h ErC10 was estimated to be 0.096 mg/L. Using 0.09 mg/L instead of 0.1 mg/L for the measured value in the 40.5 mg/L nominal series at the 72-h timepoint (as presented in the table of the analytical results), the ErC10 would be estimated to be 0.095 mg/L. If the 0.09 mg/L value were to be used for all 'n.d.' and 'BLQ' occasions, the ErC10 would be estimated to be 0.091 mg/L (ErC50 remaining in the >0.01 to ≤0.1 mg/L bracket).

Due to the unavailability of the raw cell density data in the report or the registration dossier, it is not possible to estimate a more substantiated chronic algal effect value. Nevertheless, our analysis highlights the effect of the choice of the mean measured concentrations on the final EC10 determined. Considering the rapid decline of the exposure concentrations, especially the geometric mean concentrations for the lower exposure seem to be an overestimation of the actual exposure concentrations. In this, it should also be noted that in Section I4.1 of the CLP guidance is stated that where concentrations are below the analytical detection limit such concentrations are considered to be half that detection limit. Therefore not LOQ/2 should be used in the calculations but LOD/2, this could affect the outcome as the LOD is generally lower than the LOQ. Alternatively the DS is requested to reflect on the use of a time weighted average concentration rather than geometric mean as this would be more applicable considering the rapid decline.

Based on the above, there is reason to believe that the 72-h ErC10 may be below the 0.01 mg/L threshold value which would trigger an Aquatic Chronic 1 classification for the substance. We would therefore like to ask the DS to re-evaluate their derivation of the effect values of the key algae study (in particular the 72-h ErC10 value) and clarify the calculation of the exposure concentrations used in their ECx derivation.

Dossier Submitter's Response

Thank you for your comments. We agree that the LOD/2 should be used, if concentrations decline this much in the test. Unfortunately, this was not possible, as the LOD was not reported but only the LOQ.

We also recalculated the effect values. As there were up to 72 % effect at 72h in the TWA-

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calculated concentration of 0.100 mg/L (4th concentration) and dose-dependent lower effects at the next lower concentrations, we agree that it may be that the 72-h ErC10 is below 0.1 mg/L.

Effects on Growth Rate

Tab. 53: Growthrate (G) and its inhibition relative to control (%) as computed from the raw data for test intervals selected; *nl with growth rate: nonlinear regression using the 3-param. normal CDF.

Treatment [mg/L]	0-24 h		0-48 h		0-72 h	
	G	%I	G	%I	G	%I
Control	0,960	0,0	1,372	0,0	1,520	0,0
0,100	1,187	-23,7	1,424	-3,8	1,387	8,7
0,100	1,157	-20,6	1,180	14,0	1,128	25,8
0,100	0,959	0,0	0,688	49,8	0,576	62,1
0,100	0,942	1,9	0,621	54,7	0,440	71,0
1,403	0,709	26,1	0,567	58,7	0,359	76,4
30,600	0,547	43,0	0,607	55,8	0,402	73,6

Using the TWA for mean measured concentration calculation it becomes obvious, that the classification should be Aquatic Chronic 1 based on the algae study.

RAC's response

RAC agrees with the use of LOQ/2 in absence of LOD. RAC also agrees to use the TWA method for calculating the mean measured concentration. RAC supports Aquatic Chronic 1 classification.

Date	Country	Organisation	Type of Organisation	Comment number
26.08.2021	France		MemberState	5

Comment received

France supports classification proposal in acute tox. 4 based on the results obtained in the most sensitive species (mice) in the most reliable study available. Moreover, France also supports the proposal for an ATE of 1000 mg/kg bw, considering, as the DS, that the cATpE is not representative of data.

Dossier Submitter's Response

Thank you for your comment and support.

RAC's response

Thank you for your comment. All the LD50 values summarised in table 11 of CLH report are well above 1000 mg/kg bw thus RAC supports DS proposal (in DS response to comment no 3, above) for the use of LD₅₀ value of 1700 mg/kg bw as ATE for acute oral toxicity for propyl gallate.

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2021	Germany	Ramboll Germany	Please select organisation type..	6

Comment received

We generally agree with the proposed adaption of classification as Acute Tox. 4 (H302) in line with relevant Regulation (EC) No. 1272/2008, which is supported by the results from an NTP study (1982) in mice as the most sensitive species. In general, and as pointed out in the CLH proposal, we want to note that there is an extensive data basis for the acute toxicity endpoint from studies in a variety of species, indicating extensive characterization of the acute toxicity endpoint. These data demonstrate very low toxicity, with the lowest LD50 values exceeding >2000 mg/kg bw in all species,

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except mice. For mice, two studies, the NTP study (1982) and a study by Karpliuk (1959), yielded the most sensitive LD50 values. Even from these studies, only low acute toxicity was observed which is reflected by the LD50 value of 1700 mg/kg bw that was determined in the study by Karpliuk (1959). As described by the dossier submitter, there were no mortalities in the NTP study (1982) at dose levels of 125, 250, 500 and 1000 mg/kg bw, while 3/5 females and 1/5 males died at 2000 mg/kg bw. Based on these findings, the lowest value (1000 mg/kg bw) from the LD50 range of >1000 to ≤2000 mg/kg bw was proposed as the ATE value by the German authority.

However, in our view, the basis for the selection of the ATE value is mainly defined by wider spacing of doses in the higher dose range in the NTP study (1982), rather than scientific justification. In this regard, the ATE of 1000 mg/kg bw does not reflect the LD50 from this study, as there was no mortality observed at this dose level. Considering that the 2000 mg/kg bw dose level already represents the LD60 (3/5 females died), the LD50 level is expected to be in the upper part of the 1000-2000 mg/kg bw range identified from the NTP study, which is supported by the very low mortality in males (1/5) at the top dose level. Simple linear interpolation of dose response data for female mice would yield an LD50 of 1833 mg/kg bw, which further supports this expectation. This value is in good accordance with the LD50 value of 1700 mg/kg bw identified in the study by Karpliuk (1959), which was mentioned in the CLH proposal, but has eventually not been taken into account for setting the ATE.

Therefore, it seems justified to reconsider an adjusted ATE level for the derivation of an appropriate specific concentration limit. Taking into account all relevant information in a weight-of-evidence approach, we would suggest setting the ATE at the 1700 mg/kg bw level, as it is an experimentally derived value and can be regarded as a conservative estimate of the LD50 in the context of the available information from the NTP study (1982).

Karpliuk IA (1959): Toxicological characteristics of phenols used as antioxidizing agents in edible fats; acute and subacute experiments, *Vopr Pitan*;18(4):24-29.

NTP (1982): Carcinogenesis bioassay of propyl gallate (CAS No. 121-79-9) in F344/N rats and B6C3F1 mice (feed study). *Natl Toxicol Program Tech Rep Ser No. 240*, 1-152

Dossier Submitter's Response

Thank you for your comment and support for classification as Acute Tox. 4, H302. In the light of the comments received from industry and BE CA, a reassessment of the data was performed.

As the cATpE (500 mg/kg bw) is not representative of the data available, the ATE value proposed (1000 mg/kg bw) represents the lowest value from the LD50 range of > 1000 to ≤ 2000 mg/kg bw in mice (NTP, 1982). However, the dose of 1000 mg/kg bw does not reflect the approximate LD50, as there was no mortality observed at this dose level. Besides, the 2000 mg/kg bw dose level represents the LD60 in female mice (3/5 females died) in the NTP study (1982). The lowest reliable LD50 value of 1700 mg/kg bw was determined in the study on mice by Karpyluk (1959), which indicates a good accordance with the NTP results. Therefore, we approve and endorse an ATE of 1700 mg/kg bw.

RAC's response

Thank you for your comment. RAC agrees with DS response (above).

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OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	United Kingdom	Health and Safety Executive	National Authority	7
Comment received				
<p>propyl 3,4,5-trihydroxybenzoate (EC: 204-498-2; CAS: 121-79-9)</p> <p>The threshold acute toxicity to fish study conducted to OECD TG 201 and GLP indicates that only one animal was used for both the treatment and the control. Given that this would be unusual in a guideline study that is also GLP-compliant, please could the DS confirm whether this is a typographical error e.g. were more animals actually used and the 'one' refers to a single treatment?</p> <p>Using the US EPA TEST v4.2.1 software, we calculated a 96-h LC50 of 12.63 mg/L for Fathead Minnow using the consensus method which applies the average of all of the toxicity values predicted by the QSAR models included in the software. This predicted endpoint suggests that the experimental fish LC50 of >0.8 mg/L is reasonable and that fish are not the most acutely sensitive trophic group</p>				
Dossier Submitter's Response				
Thank you for your comment. According to the registrant, the acute fish toxicity test was conducted as limit test with only one fish per treatment.				
RAC's response				
Noted. RAC does not consider the acute fish test reliable and concludes lack of data on acute fish toxicity. Without more background information from the QSAR calculation RAC cannot consider the calculated LC50 value in classification. RAC calculated the toxicity QSARs with EPIWIN v.4.11 but none of the ECOSAR classes (esters, polyphenols, baseline toxicity) gave a similar toxicity profile than the test results seen reliable in the CLH Report.				