Committee for Risk Assessment

RAC

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

18 March 2022

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **propyl 3,4,5-trihydroxybenzoate**

EC Number: **204-498-2**

CAS Number: **121-79-9**

The proposal was submitted by **Germany** and received by RAC on **19 May 2021.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **5 July 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **3 September 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Beata Pęczkowska**

Co-Rapporteur, appointed by RAC: **Riitta Leinonen**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **18 March 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-198-00-3	propyl 3,4,5-trihydroxybenzoate	204-498-2	121-79-9	Acute Tox. 4* Skin Sens. 1	H302 H317	GHS07 Wng	H302 H317			
Dossier submitters proposal	607-198-00-3	propyl 3,4,5-trihydroxybenzoate	204-498-2	121-79-9	**Modify** Acute Tox. 4 **Add** Aquatic Acute 1 Aquatic Chronic 2§	**Retain** H302 **Add** H400 H411	**Retain** GHS07 Wng **Add** GHS09	**Retain** H302 **Add** H410		**Add** oral: ATE = 1000 mg/kg bw M = 1	
RAC opinion	607-198-00-3	propyl 3,4,5-trihydroxybenzoate	204-498-2	121-79-9	**Modify** Acute Tox. 4 **Add** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H302 **Add** H400 H410	**Retain** GHS07 Wng **Add** GHS09	**Retain** H302 **Add** H410		**Add** oral: ATE = 1700 mg/kg bw M = 1 M = 1	
Resulting Annex VI entry if agreed by COM	607-198-00-3	propyl 3,4,5-trihydroxybenzoate	204-498-2	121-79-9	Acute Tox. 4 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H317 H400 H410	GHS07 GHS09 Wng	H302 H317 H410		oral: ATE = 1700 mg/kg bw M = 1 M = 1	

§ proposal changed to Aquatic Chronic 1, M factor = 1 after the commenting period

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute toxicity - oral route

The DS evaluated the acute toxicity of propyl 3,4,5-trihydroxybenzoate (propyl gallate) by the oral route based on results of two animal studies and additional animal data summarised in two reports with limited details (BIBRA, 1989; CIR, 2007).

Two NTP acute oral toxicity studies (NTP, 1982) similar to OECD TG 401, no GLP, carried out in mice and rats, were reported as reliable with restrictions. Groups of B6C3F1 mice and F344 rats (5/sex/group) received by gavage 125, 250, 500, 1000, or 2000 mg/kg bw propyl gallate (98% purity) in 20% ethanol in water.

In mice, one of five male and 3 of 5 female mice receiving 2000 mg/kg bw propyl gallate died within 2 hours of dosing. The surviving animals in this group were slightly inactive for 1 day after dosing. No death occurred among the 125, 250, 500, or 1000 mg/kg bw dose groups. Moreover, no other compound-related effects were observed. Based on the results, the LD_{50} value is considered to be greater than 1000, but lower than 2000 mg/kg bw in female mice.

In rats, the only death observed was a male that was administered 1000 mg/kg propyl gallate on day 5. No other compound-related effects were observed. The LD_{50} value was determined to be greater than 2000 mg/kg bw.

Several additional studies are available in rats or mice, as well as one each in rabbits, hamsters and pigs, but are less reliable because essential study details are missing. The following LD_{50} values have been reported based on BIBRA, 1989 (summarised in Table 10 of CLH report) for several species: mice 1700-3500 mg/kg bw, rats 2600-3800 mg/kg bw, hamsters 2480 mg/kg bw, rabbits 2750 mg/kg bw and pigs >6000 mg/kg bw. The acute oral LD_{50} values of propyl gallate in rats were reported in CIR, 2007 (summarised in Table 11 of CLH report) between 2100-7000 mg/kg. The intraperitoneal LD_{50} value in the rat was reported to be 380 mg/kg bw for rats.

Based on the data shown above, DS proposed to classify propyl gallate for Acute Tox. 4; H302 – Harmful if swallowed, with an ATE value of 1000 mg/kg bw.

Comments received during consultation

Two MSCAs supported the DS proposal for category 4. One MSCA supported the DS proposal for an ATE value of 1000 mg/kg bw and the other MSCA proposed an ATE value of 1570 mg/kg bw as 'the most sensitive LD50, from one of the most reliable studies, probably combined for both sexes'. However, considering that it is not known how the LD_{50} value of 1570 mg/kg bw was estimated, RAC supports the use of the LD_{50} of 1700 mg/kg bw as the ATE value in agreement with the DS proposal provided in response to this comment.

An industry organization supported the proposed adaption of classification as Acute Tox. 4 (H302) and questioned the ATE value of 1000 mg/kg bw, stating that it does not reflect the LD_{50} resulting from the available studies. RAC agrees with setting the ATE at the lowest reliable LD_{50} value, considering all available information in the CLH report.

Assessment and comparison with the classification criteria

In the most reliable study, similar to OECD TG 401, reported in NTP 1982, 1/5 male and 3/5 female mice died at 2000 mg/kg bw after 2 hours of dosing, thus the LD_{50} value for female mice (the most sensitive species) was between 1000 and 2000 mg/kg bw.

In the other available, but less reliable, studies summarised in CIR, 2007 the lowest LD_{50} of 1700 mg was reported for mouse species.

Based on the available data, RAC considers that propyl gallate meets the criteria (LD_{50} in a range of 300 - 2000 mg/kg bw) for **classification as Acute Tox. 4; H302**.

RAC does not agree with setting an ATE value of 1000 mg/kg bw as initially proposed by the DS, considering the results of NTP study (1982) - no deaths in mice and 1/10 death in rats were observed at dose of 1000 mg/kg bw. The LD_{50} in the most sensitive species and sex (female mice) in the most reliable study available is >1000 and below 2000 mg/kg bw. Based on simple linear interpolation of the dose response data (NTP 1982), the LD_{50} value was determined to be 1833 mg/kg bw for female mice. Furthermore, the lowest LD_{50} value of 1700 mg/kg bw was identified in the mouse study by Karplyuk (1959) as reported in Table 11 of the CLH report. This study is of low reliability due to weak description of experimental design, however, it indicates a good agreement with the NTP results in mice. Therefore, RAC proposes an **ATE of 1700 mg/kg bw** as the lowest experimentally derived acute oral LD_{50} value in all available data for propyl gallate.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Propyl-3,4,5-trihydroxybenzoate is not classified for environmental effects in Annex VI of the CLP Regulation. The Dossier Submitter proposes to classify the substance in Aquatic Acute 1 category based on the algae 72-h E_rC_{50} of 0.22 mg/L which warrants an M-factor of 1 ($0.1 < LC/EC_{50} \leq 1$) and in Aquatic Chronic 2 category based on the algae 72-h E_rC_{10} of 0.103 mg/L and the fact that the substance is not rapidly degradable.

Degradation

The Dossier submitter concluded that propyl-3,4,5-trihydroxybenzoate was not rapidly degradable.

There was a ready biodegradability test available for propyl-3,4,5-trihydroxybenzoate. In the OECD TG 301 F Manometric respirometry test biodegradation of 49.4% was observed after 28 days showing that the substance was not readily biodegradable.

In the one hydrolysis study available (OECD TG 111, GLP) it was concluded that the half-life at pH 4 was greater than 1 year in the preliminary study at 50°C. In the main study half-lives of 141 hours (25°C) and 319 hours (20°C) were determined at pH 7 and 80 (25°C) and 176 hours (20°C) at pH 9, respectively. Gallic acid and propanol were expected as transformation products, but no transformation products were analysed in the study. Therefore, it could not be demonstrated that the transformation products do not fulfil the criteria for classification as hazardous for the aquatic environment.

Bioaccumulation

Propyl-3,4,5-trihydroxybenzoate was considered to have a low potential for bioaccumulation based on an experimental log K_{ow} of 1.8. No measured fish bioconcentration factor was available.

Acute aquatic toxicity

***Table**: Summary of relevant information on acute aquatic toxicity of propyl-3,4,5-trihydroxybenzoate*

Method	Species	Results	Reliability (assessed by the DS)	Reference
OECD TG 202 Semi-static	*Daphnia magna*	48-h EC_{50} = 19.6 mg/L (geometric mean)	Reliability 1	Registration dossier: Hydrotox GmbH 2017b
OECD TG 201 Static	*Pseudokirchneriella subcapitata*	72-h ErC_{50} = 0.22 mg/L (geometric mean, recalculated by DS)	Reliability 2 (concentration decrease below LOQ)	Registration dossier: Hydrotox GmbH 2017c

There were no reliable data for fish available. The only study available was a limit test with only one fish per vessel and only one replicate.

Regarding invertebrates there were two *Daphnia* studies available. One of the studies was rated with a reliability score of 4 due to missing study details. The reliable study gave a 48-hour EC_{50} value of 19.6 mg/L for *Daphnia*.

There were two algae studies available. One of the studies was rated with a reliability score of 4 due to missing study details. The study conducted according to OECD TG 201 algae growth inhibition test using *Pseudokirchneriella subcapitata* (*Raphidocelis subcapitata*) was considered reliable. The study was conducted with test concentrations of 0, 0.50, 1.50, 4.50, 13.5, 40.5, 121.5 mg/L as nominal and 0, 0.117, 0.157, 0.235, 0.340, 1.183 and 39.26 mg/L as geometric mean measured concentrations under static conditions. The test concentrations were rapidly decreased in the test. Analytical verification showed that at 24-hour, 48-hour and 72-hour the test substance was not detected in tested levels up to nominal concentrations of 40.5 mg/L. The analytical measurement was performed with a limit of quantification (LOQ) of 0.2 mg/L. For measurements which were < LOQ, the value of LOQ/2 was used for calculation of the measured concentration. As the REACH registrant calculated the geometric mean concentrations with the value of LOQ in the cases the measurements were < LOQ, the mean measured concentrations, EC_{50} and EC_{10} values were recalculated by the DS using ToxRat program.

The test resulted in a 72-h E_rC_{50} of 0.22 mg/L (geometric mean measured). All validity criteria were fulfilled but as the concentrations decreased after 24 hours below the limit of quantification, the reliability score of the study is rated with 2. The short-term aquatic acute classification proposal was based on this result.

Chronic aquatic toxicity

***Table**. Summary of relevant information on chronic aquatic toxicity of propyl-3,4,5-trihydroxybenzoate*

Method	Species	Results	Reliability (assessed by the DS)	Reference
OECD TG 201 Static	*Pseudokirchneriella subcapitata*	72-h E_rC_{10} = 0.103 mg/L 72-h NOE_rC < 0.117 mg/L (geometric mean measured, recalculated by DS)	Reliability 2 (concentration decrease below LOQ)	Registration dossier: Hydrotox GmbH 2017c

There were no studies available for fish and invertebrates. A reliable study conducted according to OECD TG 201 with *Pseudokirchneriella subcapitata* resulted in a 72-h E_rC_{10} of 0.103 mg/L and a 72-h NOE_rC of < 0.117 mg/L based on geometric mean concentrations. The test details are described under the heading Acute aquatic toxicity. The long-term aquatic classification proposal was based on this E_rC_{10} value.

Since chronic toxicity data were not available for all three trophic levels the surrogate approach was used for comparison. There were no reliable data for fish. The surrogate approach based on the *Daphnia* 48-h LC_{50} of 19.6 mg/L for a not rapidly degradable substance warranted an Aquatic Chronic 3 classification according to Table 4.1.0(b)(iii) of CLP Regulation.

Based on the available data, the DS proposed an Aquatic Chronic 2 classification according to Table 4.1.0(b)(i) of CLP Regulation considering the E_rC_{10} of 0.103 mg/L from the algae study.

Comments received during consultation

Two Member States (MS) supported the proposed classification. It was considered unclear why the concentration of the test substance decreased rapidly below the LOQ in the reliable algae study. The DS answered that there were no obvious reasons mentioned in the study report. It was pointed out that the recalculated chronic 72-h E_rC_{10} of 0.103 mg/L for algae was very close to the cut-off value of 0.1 mg/L for Aquatic Chronic 1.

One MS disagreed with Aquatic Chronic 2 classification. Since the chronic algae effect concentration was bordering on the classification threshold of Aquatic Chronic 1, they performed an additional recalculation by non-linear regression using GraphPad based on the available information provided in the CLH Report (using LOQ/2 value of 0.1 mg/L for all non-detected (n.d.) and below-the-LOQ (BLQ) cases and using the inhibition growth rates). The 72-h E_rC_{50} value was estimated to be 0.22 mg/L and the 72-h E_rC_{10} was estimated to be 0.096 mg/L. The MS pointed out that, 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 Figure 1 of the CLH Report), the E_rC_{10} 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 cases, the E_rC_{10} would be 0.091 mg/L.

The MS considered that due to the unavailability of the raw cell density data in the report or the registration dossier, it was not possible to estimate a more substantiated chronic algal effect value. Nevertheless, the analysis highlighted that the choice of the method for determining mean measured concentrations influences the final EC_{10} determined.

They also pointed out that 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. Additionally, the CLP Guidance advises to use limit of detection LOD/2 instead of LOQ/2 in cases where concentrations are below the analytical detection limit. This could affect the outcome as the LOD is generally lower than the LOQ. Alternatively, they asked the DS to reflect on the use of a TWA concentration rather than geometric mean.

The DS agreed that LOD/2 should be used in cases where concentrations decline this much in the test. Unfortunately, the LOD was not available in the test report. They made another recalculation of the effect values. As there were up to 72 % effect at 72-hour in the TWA-calculated concentration of 0.100 mg/L and dose-dependent lower effects at the next lower concentrations the DS agreed that using the TWA for mean measured concentration calculation makes it obvious that propyl-3,4,5-trihydroxybenzoate should be classified in Aquatic Chronic 1 category.

A National authority (NA) noted that the acute fish study conducted to OECD TG 201 and GLP used only one animal for both the treatment and the control and questioned this to be in line with the OECD TG or GLP and asked the DS for confirmation. The DS confirmed that according to the registrant only one fish per treatment was used.

The NA had calculated a 96-h LC_{50} of 12.63 mg/L for *Fathead minnow* with US EPA TEST v4.2.1 software using the consensus method which applies the average of all the toxicity values predicted by the QSAR models included in the software. This predicted effect value suggested that the experimental fish LC_{50} of >0.8 mg/L was reasonable, and that fish were not the most acutely sensitive trophic group.

Assessment and comparison with the classification criteria

Comparison with the criteria

Degradation

RAC agrees with the Dossier Submitter to consider propyl-3,4,5-trihydroxybenzoate as not rapidly degradable based on:

- 49.4 % biodegradation in the OECD TG 301 F ready biodegradability test in 28 days did not reach the pass level of 60 % of the CLP criteria for ready biodegradability
- no information on ultimate degradation in a surface water simulation test was available
- the half-lives in the hydrolysis study were > 1 year at pH 4 but < 16 days (as required in the criteria) at pH 7 and 9. But degradation products were not analysed in the study it could not be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment and rapid degradability could not be shown.

Bioaccumulation

RAC agrees with the Dossier Submitter to conclude that propyl-3,4,5-trihydroxybenzoate has a low potential for bioaccumulation based on an experimental log K_{ow} of 1.8 which is below the cut-off value for 4 of the CLP criteria.

Aquatic toxicity

Algae test

In the only reliable algae study available the test concentrations rapidly decreased. The data show that in measurements at 24-h, 48-h, and 72-h the substance was not even detected (limit of quantification (LOQ) 0.2 mg/L, limit of detection (LOD) not known) below nominal concentrations of 40.5 mg/L. Based on the information available in the CLH Report and in the original test reports made available to RAC, no obvious reason for this measured concentrations decrease can be found. The mean concentrations were originally calculated as geometric mean values using LOQ in cases < LOQ. The Dossier Submitter recalculated the values using LOQ/2 in those cases.

RAC agrees to this approach regarding this algae study when the LOD is not known. The OECD TG 23 recommends using LOQ/2 when the test chemical is detected but not quantified. The CLP Guidance advises to use LOD/2 instead of LOQ/2 in cases where concentrations are below the analytical detection limit. REACH Guidance (IR&CSR, Chapter R.7b) advises that in order to calculate a mean exposure concentration, the final concentration may be taken as the limit of detection for the method if the substance is not detected. When the substance is detected but not quantified in a sample, one possible method is to use a value of half of the limit of quantification.

It was noted in the consultation comments that the algae chronic toxicity value 72-h E_rC_{10} of 0.103 mg/L was very close to the classification cut-off value of 0.1 mg/L for Category Chronic 1. The additional recalculation reported above, done by one of the commenting Member States with a different method (nonlinear regression using GraphPad), gave a 72-h E_rC_{10} value of 0.096 mg/L. The second recalculation by the DS showed that there were up to 72 % effect at 72-h in the TWA-calculated concentration of 0.100 mg/L (4th concentration) and dose-dependent lower effects at the next lower concentrations. Consequently, the DS agreed that propyl-3,4,5-trihydroxybenzoate should be classified in Aquatic Chronic 1 category.

The REACH Guidance (IR&CSR R7.b) advises that for static tests, where the concentrations do not remain within 80-120% of nominal, the effect concentrations should be expressed relative to the geometric mean of the measured concentrations at the start and end of the test. Nevertheless, RAC agrees with the Dossier Submitter conclusion to classify propyl-3,4,5-trihydroxybenzoate in Aquatic Chronic category 1 based on the chronic toxicity data derived from TWA-calculated concentrations for this particular algae test, where the test concentrations decreased very quickly and were not even detected in most measurements. 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 conclusion, RAC agrees to base the classification on the 72-h E_rC_{10} of 0.096 mg/L supported by the conclusion of the DS based on their TWA calculation.

Acute

RAC agrees with the Dossier Submitter in concluding that there were reliable acute data available on invertebrates and algae. Reliable data on fish were lacking.

RAC considers the OECD TG 203 fish study not reliable. The test is a limit test with one vessel per concentration and only one fish per vessel and 1 vessel per control. According to the OECD TG 203 a limit test should be performed using at least 7 fish, with the same number in the control(s).

A QSAR calculation result for a 96-hour LC_{50} was calculated by a National Authority in the consultation but due to lack of details of the calculation RAC cannot take this calculation into account. 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.

Regarding invertebrates, only one reliable *Daphnia* study was available giving a 48-hour EC_{50} value of 19.6 mg/L.

The lowest acute toxicity value was a 72-hour E_rC_{50} of 0.22 mg/L for algae based on geometric mean values.

The lowest overall EC_{50} value was in the range of $0.1 < EC_{50} \leq 1$ and, thus, an M-factor of 1 is warranted.

Chronic

The only chronic toxicity data available resulted in a 72-hour E_rC_{10} of 0.103 mg/L (geometric mean) for algae. Using a different method for geometric calculation, a 72-hour E_rC_{10} of 0.096 mg/L was determined. This value, considered adequate by RAC for chronic classification, was supported by TWA based calculations, which showed that the 72-hour E_rC_{10} value would be lower than 0.1 mg/L.

There were no chronic data available on fish and invertebrates. Due to lack of fish data the surrogate method could only be used for *Daphnia*. The acute toxicity value 48-hour LC_{50} of 19.6

mg/L warrants an Aquatic Chronic 3 classification according to Table 4.1.0(b)(iii) of CLP Regulation.

Considering the 72-hour E_rC_{10} of 0.096 mg/L, according to Table 4.1.0(b)(i) a classification as Aquatic Chronic 1 is warranted. E_rC_{10} is in the range of $0.01 < E_rC_{10} \leq 0.1$ and for a not rapidly degradable substance M-factor of 1 is warranted. The most stringent outcome for chronic classification is taken into account.

RAC considers, however, that the classification of propyl-3,4,5-trihydroxybenzoate might have to be revisited in case acute data on fish toxicity or chronic data on fish and invertebrate toxicity warranting an M-factor greater that 1 will become available. Also, in case the limit of detection and/or limit of quantification would be lowered a revision of classification might be needed.

RAC agrees with the Dossier Submitter proposal revised after the consultation to classify propyl-3,4,5-trihydroxybenzoate with **Aquatic Acute 1, H400, M = 1 and Aquatic Chronic 1, H410, M = 1.**

Additional references

BIBRA, 1989: Propyl gallate. Toxicity profile. The British Industrial Biological Research Association, 9 pp.

CIR, 2007: Final report on the amended safety assessment of Propyl Gallate. International Journal of Toxicology 26 (SUPPL. 3), 89-118. DOI: 10.1080/10915810701663176.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).