Committee for Risk Assessment

RAC

Annex 1
Background document
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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

18 March 2022

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification: propyl 3,4,5-trihydroxybenzoate

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

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

Index Number: **607-198-00-3**

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ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON PROPYL 3,4,5-TRIHYDROXYBENZOATE

CONTENTS

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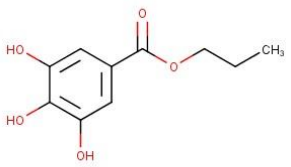
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	propyl-3,4,5-trihydroxybenzoate
Other names (usual name, trade name, abbreviation)	**Benzoic acid, 3,4,5-trihydroxy-, propyl ester** **3,4,5-Trihydroxybenzoic acid n-propyl ester** **propyl gallate**
ISO common name (if available and appropriate)	*n.a.*
EC number (if available and appropriate)	204-498-2
EC name (if available and appropriate)	propyl-3,4,5-trihydroxybenzoate
CAS number (if available)	121-79-9
Other identity code (if available)	
Molecular formula	$C_{10}H_{12}O_5$
Structural formula	
SMILES notation (if available)	CCCOC(=O)c1cc(O)c(O)c(O)c1
Molecular weight or molecular weight range	212.2 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	*mono-constituent substance; purity not relevant*

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
propyl-3,4,5-trihydroxybenzoate (CAS No. 121-79-9, EC No 204-498-2)	100	Acute Tox. 4* Skin Sens. 1	Acute Tox. 4* Skin Sens. 1 Eye Dam. 1 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
-				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
-					

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
-				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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			
Dossier submitters proposal					**Modify** Acute Tox. 4 **Add** Aquatic Acute 1 Aquatic Chronic 2	 H302 **Add** H400 H411	 GHS07 Wng **Add** GHS09	 H302 **Add** H410		oral: ATE= 1000 mg/kg bw M=1	
Resulting Annex VI entry if agreed by RAC and COM					Acute Tox. 4 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 2	H302 H317 H400 H411	GHS07 GHS09 Wng	H302 H410		oral: ATE= 1000 mg/kg bw M=1	

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route	***harmonised classification proposed***	**Yes**
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation		
Skin sensitisation		
Germ cell mutagenicity		
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment	***harmonised classification proposed***	**Yes**
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Propyl 3,4,5-trihydroxybenzoate is currently classified as Acute Tox. 4* (oral) and Skin. Sens. 1.

The current acute toxicity classification is based on Directive 67/548/EEC and translates into a minimum classification. Minimum classification for category is indicated by an asterisk.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

- *Change in existing entry due to changes in the criteria*

The current acute toxicity classification of propyl 3,4,5-trihydroxybenzoate is a minimum classification according to Directive 67/548/EEC. For certain hazard classes, including acute toxicity, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under the CLP Regulation.

Reason for a need for action at Community level:

Change in existing entry due to changes in the criteria
Disagreement by DS with current self-classification for hazardous to aquatic environment
Differences in self-classification for hazardous to aquatic environment

Notified classification and labelling for hazardous to aquatic environment are inconsistent and contradictory as seen below (as of 28.12.2020):

Aquatic Chronic 1 = 90 of 1786

Aquatic Acute 1 = 90 of 1786

No classification for aquatic environment = 1696 of 1786

5 IDENTIFIED USES

Widespread uses for professional workers are registered. Furthermore propyl 3,4,5-trihydroxybenzoate or propyl gallate (E310) is used as an antioxidant authorised as food additive. Additional exposure for consumers is expected from food contact materials and propyl 3,4,5-trihydroxybenzoate is also permitted in cosmetics without any concentration limits.

The substance is also used in pH regulators and water treatment products.

6 DATA SOURCES

In addition to the information that is available on the website of ECHA and in the IUCLID registration dossier, an extensive literature search was conducted in several relevant online resources (e.g. PubMed, SCOPUS, Web of Science, Wiley, Toxnet, Science Direct). Furthermore, the information from the EFSA report “Scientific Opinion on the re-evaluation of propyl gallate (E 310) as a food additive” was reviewed (EFSA Panel on Food additives and Nutrient Sources added to Food, 2014).

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101,3 kPa	Solid, crystalline	REACH registration data	experimental result (visual inspection)
Melting/freezing point	130 °C	REACH registration data	CRC Handbook of Chemistry and Physics (2011-2012)
Boiling point	Decomposition at 260 °C at 1013.25 hPa	REACH registration data	experimental result
Relative density	1.354 at 20 °C	REACH registration data	experimental result
Vapour pressure	0.00003 Pa at 20 °C	REACH registration data	experimental result
Surface tension	Based on chemical structure, no surface activity is predicted.	REACH registration data	estimated based on chemical structure
Water solubility	2.7 g/L	REACH registration data	experimental result
Partition coefficient n-octanol/water	log Kow: 1.8 (conditions not reported)	REACH registration data	Handbook data
Granulometry	MMAD: 232 µm D10: 31.6 µm D50: 232 µm D90: 507µm	REACH registration data	experimental result
Stability in organic solvents and identity of relevant degradation products	The substance's stability in organic solvents is not considered to be critical		
Dissociation constant	8.11 at 20 °C	REACH registration data	CRC Handbook of Chemistry and Physics (2011-2012)

The information in this table marked with "REACH registration data" is based on information taken from the REACH registration dossier and ECHA's public registration information as accessed on 19-06-2020.

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not assessed in this dossier.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Test substance, species, strain, sex, no/group	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute Oral Toxicity similar to OECD TG 401 Gavage	Propyl gallate (CAS 121-79-9) Purity >98 % Mouse, B6C3F1 5/sex/group	125, 250, 500, 1000, 2000 mg/kg bw (no control animals) Vehicle: 20 % ethanol in distilled water Observation period: 14 days 2000 mg/kg bw: 1/5 male and 3/5 female mice died within 2 hours of dosing; survivors slightly inactive for 1 day after dosing No death were observed in other dose groups	>1000 - ≤2000 mg/kg bw (female)	(NTP, 1982)
Acute Oral Toxicity similar to OECD TG 401 Gavage	Propyl gallate (CAS 121-79-9) Purity >98 % Rat, Fischer 344 5/sex/group	125, 250, 500, 1000, 2000 mg/kg bw (no control animals) Vehicle: 20 % ethanol in distilled water Observation period: 16 days 1000 mg/kg bw: 1/5 male died No other deaths	>2000 mg/kg bw	(NTP, 1982)

Additional studies are summarised in two reports on propyl gallate with limited details (BIBRA, 1989; CIR, 2007).

Table 10: Toxicity profile for propyl gallate (BIBRA, 1989 as reported by EFSA Panel on Food additives and Nutrient Sources added to Food, 2014)

Species	LD_{50} in mg/kg bw
Rats	2600-3800 mg/kg bw
Mice	1700-3500 mg/kg bw
Hamsters	2480 mg/kg
Rabbits	2750 mg/kg bw
Pigs	6000 mg/kg bw
Rats i.p.	380 mg/kg bw

Table 11: Acute toxicity of propyl gallate as given in CIR (2007)

Species	Number/group	Dose level in mg/kg bw	LD_{50} in mg/kg bw	Reference
Mouse	6-10	1000-4000	2000	(Boehm and Williams, 1943)
Mouse	Not given	Not given	3500	(Lehman, 1950)
Mouse	Not given	500-2500	1700	(Karpyluk, 1959)
Mouse	Not given	Not given	2850	((LSRO), 1973)
Rat	2-18	2000-5000	3800	(Orten et al., 1948)
Rat	Not given	Not given	5000-7000	(van Esch, 1955)
Rat	Not given	500-2500	2600	(Karpyluk, 1959)
Rat	Not given	Not given	3600	(Dacre, 1960)
Rat	Not given	Not given	2500	(Daniialov, 1966)
Rat	Not given	Not given	3000	((LSRO), 1973)
Rat	5	100-4000	2100	(Bionetics, 1974)
Rat	10	5000	>5000	(Bionetics, 1974)
Rat	Not given	Not given	4000	(Tanaka et al., 1979)
Hamster	Not given	Not given	2480	((LSRO), 1973)
Rabbit	Not given	Not given	2750	((LSRO), 1973)
Pig	Not given	2000-6000	>6000	(van Esch, 1955)

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Various studies are available in rats or mice, as well as one each in rabbits, hamsters and pigs, although most of these studies have limited reporting. The NTP performed studies similar to OECD TG 401 in rats and mice (NTP, 1982). The NTP reported a LD_{50} value for female mice in the range of >1000 - ≤2000 mg/kg bw, as at 2000 mg/kg bw 3/5 female mice died within 2 hours of dosing. Supporting this LD_{50} value for mice observed in the NTP study, Karpyluk (1959) reported an LD_{50} value of 1700 mg/kg bw for mice.

Further studies are less reliable as essential study details are missing. However, the following LD_{50} values have been determined for several species: mice 1700-3500 mg/kg bw, rats 2100-7000 mg/kg bw as well as data for hamsters (2480 mg/kg bw), rabbits (2750 mg/kg bw) and pigs (>6000 mg/kg bw). According to CIR (2007): "*Groups of animals received the test material at one or more doses, orally or by gastric intubation. Animals were observed for up to 10 days. In a number of studies, the tissues from animals that died were examined microscopically.*"

10.1.2 Comparison with the CLP criteria

The current acute toxicity classification of propyl 3,4,5-trihydroxybenzoate is a minimum classification according to Directive 67/548/EEC. For certain hazard classes, including acute toxicity, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under the CLP Regulation. Currently 3,4,5-trihydroxybenzoate is classified as Acute Tox. 4* (oral). As described above, the lowest available LD_{50} value, taken from the studies performed similar to OECD TG 401 (NTP, 1982), is in the range of > 1000 to ≤ 2000 mg/kg bw.

According to the criteria shown in the Table 3.1.1 of Annex I, Part 3 of CLP, substances can be allocated to one of four toxicity categories based on acute toxicity by the oral route. In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. Acute toxicity values are expressed as approximate LD_{50} values (oral) or as acute toxicity estimates (ATE):

Acute oral toxicity - Category 4: 300 < ATE ≤ 2000 mg/kg bw

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results shown above, it is proposed to classify propyl 3,4,5-trihydroxybenzoate as:

Acute Tox. 4 after oral exposure (H302 – Harmful if swallowed).

An ATE value based on the lowest identified LD_{50} value of > 1000 to ≤ 2000 would (according to the ATE values recommended in Table 3.1.2 of the CLP Regulation) justify an ATE value of 500 mg/kg bw. Taken into account that at 1000 mg/kg propyl 3,4,5-trihydroxybenzoate no mortality was observed in mice and 1/5 deaths occurred in the rat (NTP, 1982), an ATE value of 1000 mg/kg (the lowest value of the range of > 1000 to ≤ 2000 mg/kg) it is proposed in a WoE approach. No lower ATE was supported by additional, less valid studies available (Table 11).

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.

10.2 Acute toxicity - dermal route

Not assessed in this dossier.

10.3 Acute toxicity - inhalation route

Not assessed in this dossier.

10.4 Skin corrosion/irritation

Not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Not assessed in this dossier.

10.6 Respiratory sensitisation

Not assessed in this dossier.

10.7 Skin sensitisation

Not assessed in this dossier.

10.8 Germ cell mutagenicity

Not assessed in this dossier.

10.9 Carcinogenicity

10.10 Reproductive toxicity

Not assessed in this dossier.

10.11 Specific target organ toxicity-single exposure

Not assessed in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10.13 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 12: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
OECD 301 F	49.4 % O_2 consumption after 28 days (average of three replicates)	Reliability: 1, GLP	Registration dossier (Hydrotox GmbH, 2017a)
OECD 111	pH4 25 °C, DT50 > 1 year pH 7 20 °C, DT50 = 319 hours 40 °C, DT50 = 13.6 hours 50 °C, DT50 = 5.6 hours 25 °C, DT50 = 141 hours (calculated) pH 9 20 °C, DT50 = 176 hours 40 °C, DT50 = 8.4 hours 50 °C, DT50 = 2.8 hours 25 °C, DT50 = 80 hours (calculated) no transformation products analysed	Reliability: 1, GLP	Registration dossier (Ibacon GmbH, 2018)

11.1.1 Ready biodegradability

The ready biodegradability of propyl 3,4,5-trihydroxybenzoate was evaluated in a manometric respirometry test according to OECD TG 301 F). The initial concentration of propyl 3,4,5-trihydroxybenzoate used in this study was 101.2-104 mg/L (ThoD). Non-adapted activated sludge from a municipal wastewater treatment was used as inoculum (30 mg/L). After 28 days, a biodegradation of 49.4 % (average of three replicates) was determined. The degradation in the toxicity control reached 50.3 % within 4 days. Hence, the test substance had no inhibitory effects on the inoculum. In the abiotic control, degradation values between 8.1 % (day 4) and 2.7 % (day 28) were determined. The reference compound sodium acetate reached the pass level for ready biodegradability within 8 days. Propyl 3,4,5-trihydroxybenzoate is predicted to be not readily biodegradable.

11.1.2 BOD_5/COD

No data available.

11.1.3 Hydrolysis

A hydrolysis study according to OECD Guideline 111 (GLP compliant) is available and documented in the registration dossier. At the preliminary study (at 50 °C) ≥ 10 % hydrolysis was observed at pH 7 and pH 9 after 5 days. For pH 4 < 10 % hydrolysis was observed. Hence, the half-life time at 25 °C and pH 4 is greater than 1 year. In the main study half-lives of 141 hours (25 °C) and 319 hours (20 °C) were observed for pH 7 and 80 hours (25 °C) and 176 hours (20 °C) for pH 9. It was remarked that gallic acid and propanol are expected transformation products. But transformation products were not analysed in this study. Therefore, it could not be demonstrated that the transformation products do not fulfil the criteria for classification as hazardous for the aquatic environment. Consequently, propyl 3,4,5-trihydroxybenzoate should not be

considered as rapidly degradable according to CLP regulation (section 4.1.2.9.4) and ECHA Guidance on the application of the CLP criteria (Annex II 4).

11.1.4 Other convincing scientific evidence

No data available.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

No data available.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No data available.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

No data available.

11.1.4.4 Photochemical degradation

No data available.

11.2 Environmental fate and other relevant information

No experimental data on adsorption is available. Based on the log Kow of 1.8 a log Koc of 1.93 is estimated.

11.3 Bioaccumulation

Table 13: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
Handbook data	Log Kow = 1.8	Reliability 2	Registration dossier (Hansch, 1995)

11.3.1 Estimated bioaccumulation

According to the registration dossier a log Kow of 1.8 is predicted. This value is cited in the handbook of Hansch (1995) and is also used as data source for EPIsuite.

11.3.2 Measured partition coefficient and bioaccumulation test data

No data available.

11.4 Acute aquatic hazard

Table 14: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
OECD 203	*Danio rerio*	Propyl gallate (CAS 121-79-9) Purity 100.2 %	96h-$LC_{50} \geq 0.80$ mg/L (mean measured)	Reliability: 3 (only 1 fish per vessel + only 1 replicate used) (Registrant reliability: 1)	(Anonymous 1, 2017)
OECD 202	*Daphnia magna*	Propyl gallate (CAS 121-79-9)	**48h-EC_{50} = 19.6 mg/L (measured)**	Reliability: 1	Registration dossier: (Hydrotox GmbH, 2017b
Similar to OECD 202	*Daphnia magna*	Propyl gallate	48h-EC_{50} = 37.8 mg/L (nominal)	Reliability: 4 (study details missing)	(Zurita et al., 2007)
OECD 201	*Pseudokirchneriella subcapitata*	Propyl gallate (CAS 121-79-9)	**72h- E_rC_{50}= 0.22 mg/L** (mean measured – recalculated by DS)	Reliability: 2 (concentration decrease below LOQ) (Registrant reliability: 1)	Registration dossier: (Hydrotox GmbH, 2017c)
?	*Chlorella vulgaris*	Propyl gallate	EC_{50} = 690 µM (146.42 mg/L, nominal)	Reliability: 4 (study details missing)	(Zurita et al., 2007)

11.4.1 Acute (short-term) toxicity to fish

One study for short-term toxicity to fish is available.

The 96-hour acute toxicity test with zebrafish, *Danio rerio*, according to OECD TG 203 was conducted with the limit-test concentration of nominal 5 mg/L (0.80 mg/L, measured) in a semi-static test design. The test results in a LC_{50} of > 0.8 mg/L (measured). As only one organism per test vessel and only one vessel per concentration (replicate) was used, the test is not valid.

11.4.2 Acute (short-term) toxicity to aquatic invertebrates

Two studies for short-term toxicity to aquatic invertebrates are available.

The first study is an 48-hour acute toxicity test with *Daphnia magna Straus* according to OECD TG 202 was conducted in a semi-static test design with test concentrations of 4.0; 8.0; 16.0; 32.0; and 64.0 mg/L (nominal) or 1.44; 2.37; 3.75; 15.86; and 45.21 mg/L (measured). Five organisms per replicate and four replicates were used per test concentration. No mortality in the control was observed. The test results in a 48h-EC_{50} of 19.6 mg/L (measured).

The second study is a publication providing information about an acute immobilisation test up to 72 hours in standard reference water according to OECD TG 202 (2004). Four replicate groups of 10 neonates per 25 mL per concentration were used in 70 mL polystyrene flasks. The stock solutions were prepared in dimethyl sulfoxide (≤ 0.2 % v/v). The tests result in EC_{50} values for immobilisation of 203 µM (24h) and 178 µM (48h), as well as 158 µM (after 72 h). This correlates to EC_{50} values of 43.1 mg/L (24h) and 37.8 mg/L (48h). As there were study details missing to evaluate the validity of the test, it is rated with the reliability score of 4.

11.4.3 Acute (short-term) toxicity to algae or other aquatic plants

Two studies for short-term toxicity to algae or other aquatic plants are available.

The first study is a 72h-algae growth inhibition test using *Pseudokirchneriella subcapitata* (*Raphidocelis subcapitata*). It is conducted according to OECD TG 201 with test concentrations of 0, 0.117, 0.157, 0.235, 0.340, 1.183 and 39.26 mg/L (geometric mean) under static conditions in Holm-Hansen medium. An adjustment of pH was performed and the light intensitiy was 70.7 µE/m²s +/- 5.3 %. The determination of the cell concentrations was perfomed with a Coulter Counter Z2 (Beckman Coulter, Krefeld). The chlorophyll measurement was conducted in 96-well micro-plates (No.655 101, Greiner bio-one, Frickenhausen; Fluorescence Microplate Reader, Tecan infinite F200, Tecan Group Ltd. Männedorf, Switzerland). The analytical measurement was performed with HPLC/DAD (UV-detection) with a 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 registrant calculated the geometric mean concentrations with the value of LOQ in the cases the measurements were < LOQ, the mean measured concentrations were recalculated by the DS. Therefore also the EC_{50} and EC_{10}-values were recalculated by the DS using ToxRat programm. The initial measured test item concentrations were 38.0 to 120.3 % of the nominal concentrations. At the end of the exposure period, the measured test concentrations decreased to < LOQ to 14.6 % (72h) of the nominal concentrations. The decrease of the measured test concentrations results in some uncertainty in the effect concentrations. This is taken in to account according to Guidance on application of CLP criteria using LOQ/2 the calculation of the geometric mean of the measured concentrations

Figure 1: overview of analytical results from algae study

Table 6.2: 1 Overview of sample results (07.03.2017 – 10.03.2017).
Raw data see Tables 8: 1 to Tables 8: 3

	target PG Conc. [mg/L]	PG Concentration [mg/L]							
		0h	0h mean (%CV)	24h	24h mean (%CV)	48h	48h mean (%CV)	72h	72h mean (%CV)
1165-NC	**0.00**	n.d. n.d.	n.d.	BLQ n.d.	n.d.	BLQ n.d.	n.d.	n.d. n.d.	n.d.
1165-A	**0.50**	0.19 0.20	0.19 (0.93 %CV)	n.d. n.d.	n.d.	n.d. n.d.	n.d.	n.d. n.d.	n.d.
1165-B	**1.50**	0.60 0.62	0.61 (1.79 %CV)	n.d. n.d.	n.d.	n.d. n.d.	n.d.	n.d. n.d.	n.d.
1165-C	**4.50**	3.03 3.06	3.05 (0.58%CV)	n.d. n.d.	n.d.	n.d. n.d.	n.d.	n.d. n.d.	n.d.
1165-D	**13.5**	13.3 13.3	13.3 (0.22%CV)	n.d. n.d.	n.d.	n.d. n.d.	n.d.	n.d. n.d.	n.d.
1165-E	**40.5**	48.7 48.8	48.7 (0.09%CV)	4.00 4.04	4.02 (0.58%CV)	n.d. n.d.	n.d.	BLQ BLQ	BLQ*
1165-F	**121.5**	132 132	132 (0.10%CV)	55.8 56.0	55.9 (0.29%CV)	18.1 18.2	18.2 (0.33%CV)	17.7 17.8	17.7 (0.22%CV)

n.d.: not detected
BLQ: below limit of quantification 0.2 mg/L
*0.09 mg/L

The pH values were 7.3 to 7.7 in the control and 6.8 to 7.8 in the treatments, which is in the range of the OECD TG (increase ≤ 1.5). The temperature was also in the required range of 21 to 24 °C (22.3 to 22.6 °C). The biomass in the control cultures increased by a factor more than 16 (96.2). This corresponds to a specific growth rate of 1.521 day^{-1}. The means coefficient of variation for section-by-section specific growth rates in the control cultures was 32.5 % (<35 %). The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was 3.8 % (< 7 %). Therefore, all validity criteria were fulfilled.

Figure 2: inhibition fo growth rate of algae study

Table 2: Inhibition of growth rate after 24 h, 48 h and 72 h exposure

Geometric mean test item concentration [mg/L]	Inhibition of growth rate [%]		
	24 h	48 h	72 h
NC	--	--	--
0.20	-24.3	-4.0	8.7
0.26	-21.5	13.8	25.8
0.40	-0.2	49.8	62.1
0.57	1.3	54.6	71.0
1.67	25.6	58.5	76.3
39.27	42.9	55.9	73.7

The test results in a 72h-E_rC_{50} of 0.22 mg/L and an E_rC_{10} of 0.103 mg/L (geometric mean measured concentration). The NOE_rC is < 0.117 mg/L. All validity criteria were fulfilled but as the concentrations decreased after 24h below the limit of quantification, the reliability score of the study is rated with 2.

The second study is a non-guideline one with *Chlorella vulgaris var. viridis*. The test duration is 72 hours and it was conducted in a 96-well culture plate seeded with 200 µL/well of a 1,000,000 cells /mL algae culture in Bold's Basal Medium. No analytical confirmation of the test concentration was performed and DMSO was used as vehicle (< 0.2 % v/v). The test resulted in a 72h-EC_{50} of 146.42 mg/L (originally: 690 µM). As some test details are missing in the publication, the study is rated with reliability score 4.

11.4.4 Acute (short-term) toxicity to other aquatic organisms

No data available.

11.5 Long-term aquatic hazard

Table 15: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results [mg/L]	Remarks	Reference
OECD 201	*Pseudokirchneriella subcapitata*	Propyl gallate (CAS 121-79-9)	**72h- E_rC_{10}= 0.103** **72h- NOE_rC < 0.117** (both measured – recalculated by DS)	Reliability: 2 (concentration decrease below LOQ) (Registrant reliability: 1	Registration dossier: (Hydrotox GmbH, 2017c)

11.5.1 Chronic toxicity to fish

No data available.

11.5.2 Chronic toxicity to aquatic invertebrates

No data available.

11.5.3 Chronic toxicity to algae or other aquatic plants

For study details please consult Chapter 11.4.3.

The valid study conducted according to OECD TG 201 with *Pseudokirchneriella subcapitata* results in a 72h- E_rC_{10} of 0.11 mg/L and a 72h- NOE_rC of < 0.117 mg/L (measured).

11.5.4 Chronic toxicity to other aquatic organisms

No data available.

11.6 Comparison with the CLP criteria

11.6.1 Acute aquatic hazard

Table 16: Comparison with criteria for acute aquatic hazards

	Criteria for acute environmental hazards	propyl 3,4,5-trihydroxybenzoate	Conclusion
Acute Aquatic Toxicity	Cat. 1: $LC_{50}/EC_{50}/ErC_{50}$ ≤ 1 mg/L	Fish: no reliable test available Invertebrates: *Daphnia magna* 48h-LC_{50}= 19.6 mg/L (measured) Algae: *Pseudokirchneriella subcapitata* 72h-E_rC_{50}= 0.22 mg/L (measured)	**Acute Aquatic 1 (M = 1)** (based on Algae- E_rC_{50})

11.6.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 17: Comparison with criteria for long-term aquatic hazards

	Criteria for environmental hazards	propyl 3,4,5-trihydroxybenzoate	Conclusion
Rapid Degradation	Half-life hydrolysis < 16 days Readily biodegradable in a 28-day test for ready biodegradability (> 70 % DOC removal or > 60 % theoretical oxygen demand, theoretical carbon dioxide)	Rapid hydrolysis at pH 7 and 9 (25 °C) but degradation products not identified 49.4 % biodegradation after 28 days → not readily biodegradable	**Not rapidly degradable**
Bioaccumulation	Log Kow ≥ 4 BCF ≥ 500	Log Kow = 1.8 BCF: no data available	**Not bioaccumulative** (low potential for bioconcentration in the aquatic environment)
Aquatic Toxicity	Non-rapidly degradable substances: Cat. 1: NOEC ≤ 0.1 mg/L Cat. 2: NOEC ≤ 1 mg/L (based on Table 4.1.0 (b) (i) of the CLP Regulation) <u>Surrogate approach in absence of appropriate chronic toxicity reference data</u> (based on Table 4.1.0 (b) (iii) of the CLP Regulation)<u>:</u> Not rapidly degradable substances and/or bioaccumulative substances:	Algae: *Pseudokirchneriella subcapitata* 72h- E_rC_{10} = 0.103 mg/L (measured) No long-term toxicity data for aquatic invertebrates or fish available. Fish: no reliable data available Invertebrates: *Daphnia magna* 48h-LC_{50}= 19.6 mg/L (measured)	**Aquatic Chronic 2** (based on Algae- E_rC_{10})

	Cat. 1: E/LC_{50} ≤ 1 mg/L Cat. 2: E/LC_{50} > 1 to ≤ 10 mg/L Cat. 3: E/LC_{50} > 10 to ≤ 100 mg/L		

11.7 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Acute aquatic hazard:

Propyl 3,4,5-trihydroxybenzoate fulfils the classification criteria for Aquatic Acute 1 (M = 1) and a labelling with H400 based on the acute toxicity to the algae *Pseudokirchneriella subcapitata* (72h-E_rC_{50}= 0.22 mg/L).

Chronic aquatic hazard:

Propyl 3,4,5-trihydroxybenzoate is not rapidly degradable and has a low potential for bioconcentration in the aquatic environment.

Chronic toxicity data are not available for all three trophic levels. Therefore, according to Figure 4.1.1 of the CLP Regulation the aquatic chronic classification is based on the most stringent outcome of the two assessments according to Table 4.1.0 (b) (i) and (iii). For algae chronic toxicity data (72h- E_rC_{10} = 0.103 mg/L) results in the chronic classification Aquatic Chronic 2 according to Table 4.1.0 (b) (i). For aquatic invertebrates and fish chronic toxicity data is not available. Therefore, the surrogate approach according to Table 4.1.0 (b) (iii) is used for aquatic invertebrates and fish. For fish no valid acute toxicity data is available. The acute toxicity data for aquatic invertebrates (48h-LC_{50}= 19.6 mg/L; not rapidly degradable) leads to a chronic classification Aquatic Chronic 3.

The most stringent outcome of the two assessments according to Table 4.1.0 (b) (i) and (iii) results in a classification of Propyl 3,4,5-trihydroxybenzoate as Aquatic Chronic 2, H411 (based on Table 4.1.0 (b) (i)) of the CLP Regulation.

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} ≤ 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 (4^{th} 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.**

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