Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1-isopropyl-4-methylbenzene; p-cymene

EC Number: 202-796-7
CAS Number: 99-87-6

CLH-O-0000001412-86-273/F

Adopted

15 March 2019

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CLH-O-0000001412-86-273/F

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: **1-isopropyl-4-methylbenzene; p-cymene**

EC Number: **202-796-7**

CAS Number: **99-87-6**

The proposal was submitted by **Netherlands** and received by RAC on **17 April 2018.**

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

PROCESS FOR ADOPTION OF THE OPINION

Netherlands 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 **21 May 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **20 July 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

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 **15 March 2019** by **consensus**.

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

	Index No	International Chemical Identification	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	No current Annex VI entry										
Dossier submitters proposal	TBD	1-isopropyl-4-methylbenzene; p-cymene	202-796-7	99-87-6	Flam. Liq. 3 Acute Tox. 3 Asp. Tox. 1 Aquatic Acute 1 Aquatic Chronic 3	H226 H331 H304 H400 H412	GHS02 GHS06 GHS08 GHS09 Dgr	H226 H331 H304 H410		M=1	
RAC opinion	TBD	1-isopropyl-4-methylbenzene; p-cymene	202-796-7	99-87-6	Flam. Liq. 3 Acute Tox. 3 Asp. Tox. 1 Aquatic Chronic 2	H226 H331 H304 H411	GHS02 GHS06 GHS08 GHS09 Dgr	H226 H331 H304 H411		inhalation: ATE = 3 mg/L (vapour)	
Resulting Annex VI entry if agreed by COM	TBD	1-isopropyl-4-methylbenzene; p-cymene	202-796-7	99-87-6	Flam. Liq. 3 Acute Tox. 3 Asp. Tox. 1 Aquatic Chronic 2	H226 H331 H304 H411	GHS02 GHS06 GHS08 GHS09 Dgr	H226 H331 H304 H411		inhalation: ATE = 3 mg/L (vapour)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

p-Cymene is one of the ingredients of the active substance Terpenoid Blend QRD 460. The terpenoid blend, consisting of p-cymene, d-limonene and alpha-terpinene, was approved as an active substance (insecticide) for plant protection products under Regulation (EC) 1109/2009. Besides its use as a pesticide, it is widely used and can be found in foods, consumer products (e.g. use in cleaning agents and as a solvent), personal care products (as a fragrance) and cosmetics. It is registered under REACH.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

p-Cymene is a colourless transparent liquid at 20 °C and 101.3 kPa.

A summary of relevant physico-chemical studies/statements submitted by Dossier Submitter is provided in the table below:

Method	Results	Remarks	Reference
Explosive properties	Examination of the structure indicates that there are no chemical groups associated with explosive properties. Not explosive	Purity: 90.4 % Statement: Based on the structure of the substance, explosive behaviour is not expected	LyondellBasell, 2010b TOXNET 2014
Self-ignition temperature	436 °C (817 °F)	Measured: method not known Purity not provided	NOAA, 1999
Oxidising properties	p-cymene does not contain any functional group associated with oxidizing properties listed in the Guidance for the implementation of REACH R.7a table R.7.1-29.	-	-
Flash point	47.2 °C	Measured: equilibrium method closed up Purity not provided	EPA, 2014
	52 °C	Measured: Tag closed cup Purity: 99.20 % Comment DAR: Acceptable; Data from SDS. Description of used method is not sufficient. However, since this a commonly used terpene, the information provided is considered acceptable; Not GLP.	LyondellBasell, 2010b
	47 °C	Measured: method not known Purity not provided	Polarome MSDS 2009b according to DAR for substance terpenoid blend QRD460 (Volume 3, annex B.1-5), May 2014

p-Cymene has a flash point of 47.2 °C which is higher than 23 °C but lower than 60 °C (Annex I, Table 2.6.1, CLP), therefore classification as Flam. Liq. 3; H226 according to regulation (EC) 1272/2008 (CLP regulation) is proposed by the Dossier Submitter (DS).

p-Cymene does not possess oxidising or explosive properties.

Comments received during public consultation

One Member State Competent Authority (MSCA) agreed with the proposed classification of p-cymene.

Assessment and comparison with the classification criteria

Based on the data provided, RAC agrees with the DS that p-cymene fulfils the criteria for classification in **Cat. 3 for flammability (Flam. Liq. 3; H226 – Flammable liquid and vapour)**.

No chemical groups associated with explosive properties present in the molecule, therefore p-cymene **does not warrant classification as explosive substance**.

p-Cymene does not contain either oxygen, fluorine or chlorine and therefore **does not warrant classification as an oxidising liquid**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral route

Summary of relevant acute oral toxicity studies provided in CLH report for p-cymene (modified from Table 11a of the CLH report):

Method	Results	Remarks	Reference
Rat (Osborne-Mendel) Oral Dose: unspecified doses Purity: not provided N= 10/sex/dose	LD_{50}: 4 750 mg/kg bw (95 % confidence limits: 3 720-6 060)	2 (reliable with restrictions) Key study	EPA, 2005, 2012
Rat Oral gavage Dose: 620, 940, 1 400, 2 100, 3 200, 4 700, 7 100 or 10 700 mg/kg bw. Purity: not provided N= 1-3/dose	LD_{50}: 3 200 mg/kg bw	2 (reliable with restrictions) Key study	EPA, 2005, 2012
Mouse oral: unspecified exposure regimen Dose: no data Purity: not provided N= not provided	LD_{50}: 1 695 mg/kg bw	4 (not assignable) supporting study experimental result	Various SDSs

For the oral LD_{50}, two key studies were reported. In the second study, male and female rats (1-3/dose) were dosed by oral gavage with 620, 940, 1 400, 2 100, 3 200, 4 700, 7 100 or 10 700 mg/kg bw. Following a 14-day observation period, all rats in the 620, 940, 1 400 and 2 100 mg/kg bw groups survived and 1/2, 2/2, 3/3 and 1/1 had died in the 3 200, 4 700, 7 100 and 10 700 mg/kg bw groups, respectively. An LD_{50} of 3 200 mg/kg bw was determined in this study (EPA, 2005, 2012). In the first study, Osborne-Mendel rats (10/sex/dose) were administered various unspecified doses of the test substance. Rats were monitored for up to 2 weeks. An LD_{50} of 4 750 mg/kg bw was determined in this study (EPA, 2005, 2012). Various Safety Data Sheets (SDSs) have also reported an LD_{50} in mice of 1 695 mg/kg bw but the study where this LD_{50} was based on could not be found in the literature (Table above). Without the specific details of the study, an evaluation of the quality of the study cannot be made. Therefore the oral LD_{50} for rats is between 3 200 and 4 750 mg/kg bw.

No classification of p-cymene was proposed by the DS for acute oral toxicity.

Inhalation route

For the inhalation LC_{50}, one key study was reported for p-cymene (purity: not provided). Guinea pigs, rats and mice (2-3 animals per species, sex not indicated) were exposed by inhalation to a concentration of 9.7 mg/L (vapour) for 5 hours. Animals were observed for 1 week following exposure. No deaths were reported in guinea pigs or rats. All exposed mice died during or within 24 hours of exposure. The reported LC_{50} values were as follows: LC_{50} (guinea pig) > 9.7 mg/L; LC_{50} (rat) > 9.7 mg/L; and LC_{50} (mouse) < 9.7 mg/L (EPA, 2005, 2012). As the quality of the tests in these three species is comparable and it is unknown which species is the most relevant for humans, the most sensitive species was used for determination of the classification in line with the Guidance on the CLP criteria version 5 chapter 3.1.2.3.2.

Therefore, classification of p-cymene for acute inhalation toxicity as Acute Tox. 3; H331 – Toxic if inhaled) was proposed by the DS.

Dermal route

Summary of relevant acute dermal toxicity studies provided in CLH report for p-cymene (modified from Table 11c of the CLH report):

Method	Results	Remarks	Reference
Rabbit Dermal Dose: 5 000 mg/kg bw Purity: not provided N=10 (number per sex not reported)	LD_{50} > 5 000 mg/kg bw	2 (reliable with restrictions) Key study	EPA, 2005, 2012
Rabbit Dermal Dose: 5 140 mg/kg bw Purity: not provided N=1	no mortality in single test animal	3 (not reliable) Supporting study	EPA, 2005, 2012

For the dermal LD_{50}, the key study indicated in the table above was used. Ten rabbits were exposed to p-cymene at a dermal dose of 5 000 mg/kg bw. Animals were observed for 14 days. No animals died during the observation period. The reported LD_{50} was greater than 5 000 mg/kg bw (EPA, 2012). Therefore, no classification of p-cymene was proposed by the DS for acute dermal toxicity.

Comments received during public consultation

Concerning acute inhalation toxicity of p-cymene, one MSCA noted that "*considering that the mouse is the most sensitive species, results from the reported rat studies cannot be regarded as adequate justification for excluding categories 1 and 2*".

One company (the lead registrant) agreed with the conclusion that no classification and labelling is required for acute oral and dermal toxicity, but not with the proposal to classify as Acute Tox. 3 (toxic if inhaled). Their argument was based on the effects having been seen exclusively in the mouse, and not in the rat (or guinea pig).

The DS responded as follows: "*as the quality of the acute inhalation toxicity studies with the three species is comparable and it is unknown which species is the most relevant for humans, the most sensitive species is used for determination of the classification (in line with the Guidance on the CLP criteria version 5.0 (July 2017) chapter 3.1.2.3.2)*".

Assessment and comparison with the classification criteria

For the oral LD_{50}, classification is not warranted because the LD_{50}s from the key studies were between 3 200-4 750 mg/kg bw; both outside the border for Acute oral Category 4 of 300 to 2 000 mg/kg bw.

Classification for acute inhalation toxicity in Category 3 is considered warranted because the mouse LC_{50} is less than 9.7 mg/L (vapour) which is > 2 but ≤ 10 mg/L, but lower concentrations were not tested. Considering that the only results from the reported mouse study were that the mouse LC_{50} is less than 9.7 mg/L, classification in categories 1 and 2 for acute inhalation toxicity cannot be excluded but with the available data it is very speculative. In addition, exposure time for all tested animals was 5 hours, which is longer than the 4-hour experimental exposure period required in the classification criteria for acute inhalation toxicity (CLP Regulation, 3.1.1.1), overestimating the toxicity. RAC also notes that and no deaths in guinea pigs or rats were seen after exposure to p-cymene at 9.7 mg/L, so the LC_{50} value in rats and guinea pigs can be estimated to be higher than 9.7 mg/L. Based on the data available, classification in category 3 could be supported. Since the exact values of LC_{50} in mice has not been determined, all exposed mice died within 24 hours after 5 hour inhalation exposure at 9.7 mg/L (vapour), RAC agrees to use the standard acute toxicity point estimate (ATE) value for category 3, i.e. 3 mg/L, for cymene (see table 3.1.2 of Regulation 1272/2008).

For the dermal LD_{50}, classification is not warranted because the LD_{50} value from the key study is greater than 5 000 mg/kg bw, which is outside the range for acute dermal toxicity, Category 4 (1 000 to 2 000 mg/kg bw).

RAC supports of DS proposal for classification of p-cymene for acute inhalation toxicity as **Acute Tox. 3; H331 – Toxic if inhaled,** with an **ATE value of 3 mg/L,** and no classification for acute oral or dermal toxicity.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

In the acute toxicity studies (described above) no specific effects on target organs were observed, therefore no classification of p-cymene was proposed by the DS for STOT SE.

Comments received during public consultation

One company (the lead registrant) agreed with the proposal for no classification of p-cymene for STOT SE.

Assessment and comparison with the classification criteria

Substances should be classified for STOT-SE when specific target organ toxicity (Category 1 or 2) or narcotic effects or respiratory tract irritation (Category 3) are observed.

As no specific organ effects fulfilling the classification criteria for STOT SE were observed after single acute exposure via the oral, inhalation or dermal route, **classification of p-cymene for STOT SE is not required**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Animal data

In the first of the two acute dermal toxicity studies relevant for skin irritation (cf. CLH report, section 4.4, Table 12) 10 rabbits were dermally treated with 5 000 mg/kg bw of p-cymene and observed for 14 days. No rabbits died. The skin irritation results were described as follows: slight redness (3/10), moderate redness (7/10), slight oedema (3/10), and moderate oedema (7/10). No information was available on the quantitative skin irritation scores and whether the effects were observed immediately after exposure or continued until the end of the 14-day observation period (EPA, 2005, 2012).

In the second acute dermal toxicity study, undiluted p-cymene was applied to the shaven abdominal skin (10×15 cm area) of a single albino rabbit in 1 mL doses every hour for a total of 6 mL over a 6-hour exposure period. The rabbit was observed for one month following treatment. Slight hyperaemia of the skin was observed after 1 hour, persisting for approximately 4 hours, after which a slight subcutaneous oedema developed. After the exposure period, the skin was still slightly oedematous and over the next 5 days, it was slightly thickened, hyperaemic and showed fine cracks. After the first week, the skin began to return to normal and within the month it was normal with hair growth (EPA, 2005, 2012). No quantitative information on the scores of skin irritation are available.

Human information

p-Cymene was reported to be a primary skin irritant; contact with the undiluted liquid can produce erythema, dryness and defatting, the intensity depending on the dose and duration of contact (EPA, 2005, 2012). However, no study data were available to support this statement.

No classification of p-cymene was proposed by DS for skin corrosion/irritation.

Comments received during public consultation

One company (the lead registrant) agreed with no classification for skin irritation.

Assessment and comparison with the classification criteria

Based on the available data for p-cymene, none of the criteria are met and classification is therefore not warranted. Although the acute dermal toxicity data (rabbit) provide some evidence for skin irritation, no quantitative information is available to make a comparison with the criteria. Furthermore, the statement in the CLH report (referred to above) on skin irritation in humans is not supported by data.

RAC agrees with the DS's proposal for **no classification of p-cymene for skin corrosion/irritation due to inconclusive data.**

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Animal data

No relevant information available.

Human data

A maximization test carried out on 25 volunteers showed that a 4 % concentration of p-cymene (purity not provided) in petrolatum produced no sensitisation reactions (EPA, 2005). There were no data on skin sensitisation properties of the substance at concentrations higher than 4 %.

Comments received during public consultation

One company (the lead registrant) agreed with no classification for skin sensitisation.

Assessment and comparison with the classification criteria

Taking into account the information described above, RAC concludes that the data/information provided are not sufficient for assessing skin sensitisation of p-cymene, therefore **no classification is warranted due to inconclusive data**.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

According to the DS no relevant information on oral, inhalation or dermal repeated dose toxicity are available. However, this hazard can be assessed based on the subacute inhalation neurotoxicity study in male Long-Evans rats (described in detail in the CLH report, section 4.12.1.1; Neurotoxicity). In this study (non-GLP, not performed according to recognised international guidelines) rats were housed 2 per cage and subjected to a 12-hour light cycle, and exposed to p-cymene (purity 99 %) vapour at doses of 0, 50, or 250 ppm (approximately 0.25 and 1.23 mg/L) for 6 h/day, 5 days/week for 4 weeks during the dark cycle.

There was no overt toxicity in the treated rats and no effect on body weight or terminal weight of the brain, cerebellum or whole brain. There was also no effect on regional enzyme activities, regional protein synthesis or regional neurotransmitter concentrations.

At up to 250 ppm, p-cymene exposure did not produce signs of overt toxicity in male rats exposed for 4 weeks with an 8-week recovery period (EPA, 2005).

According to the DS, the results of the only available repeated dose toxicity study with p-cymene do not warrant classification for STOT RE.

Comments received during public consultation

The lead registrant agreed with the conclusion that based on the data available no classification with regard to STOT RE is triggered. However, following completion of the on-going OECD TG 422 study, the classification might require a reassessment depending on the results obtained.

Assessment and comparison with the classification criteria

In the neurotoxicity study, rats were exposed to p-cymene at concentrations (0.25 and 1.23 mg/L) below the guidance value of ≤ 0.6 mg/L for STOT RE 1 and below the guidance value of ≤ 3 mg/L for STOT RE 2. The treatment did not affect the body weight or terminal weight of the cerebellum or whole brain. However, no data on effect of p-cymene on behaviour of animals, performance in functional, behavioural tests or on effects in other internal organs of exposed rates were provided in the scanty description of this study. Taking into account the deficiency of the reported study in the assessment of repeated dose toxicity, RAC concludes **that no classification for STOT RE is warranted for p-cymene due to inconclusive data.**

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The DS presented in the CLH report two studies on mutagenicity of p-cymene reported in greater detail elsewhere (one in EPA, 2005 and the other in EFSA 2015; Anonymous, 1979) but none of them were reported to be performed in compliance with GLP or according to internationally recognised guidelines.

Based on results of these studies, the DS concluded that no classification for mutagenicity is warranted due to the lack of observed mutagenicity *in vitro* or *in vivo*.

Comments received during public consultation

The lead registrant agreed with the conclusion that based on the data available no classification with regard to mutagenicity or carcinogenicity is triggered.

Assessment and comparison with the classification criteria

In the first, non-GLP and performed not according to recognized guideline study (EPA, 2005) p-cymene produced no increase in the frequency of reversion from streptomycin dependence to independence in *Escherichia coli* strain Sd-4-73 cultured *in vitro*.

In the second, non-GLP, and performed not according to recognized guideline study (EFSA 2015; Anonymous, 1979) the Sprague-Dawley rats were given 0.5 mL of p-cymene (approximately 1 706 mg/kg bw) by gavage and urine was collected for 24 h. Three types of urine samples were tested in the Ames assay with *S. typhimurium* strains TA98 and TA100 with metabolic activation: a direct urine sample, a urine-ether extract, and the aqueous fraction of the urine–ether extract. The urine samples of rats treated with p-cymene did not show any evidence of mutagenicity, in either the presence or absence of beta-glucuronidase.

None of the tests reported in the CLH report meets criteria of well conducted, sufficiently validated test, performed according to methods described in Regulation (EC) No 440/2008. They are also not listed among the tests recommended in section 3.5.2.3. of the CLP Regulation for assessment of mutagenicity to be used for classification for heritable effects in human germ cells. Therefore, RAC is of the opinion that **no classification for germ cell mutagenicity for p-cymene is warranted due to lack of data.**

RAC evaluation of aspiration toxicity

Summary of the Dossier Submitter's proposal

p-Cymene has a kinematic viscosity of 7.1 mm^2/s at 40 °C (method not known, purity not provided; SDS, 2013), which might indicate the potential for aspiration toxicity.

The DS proposed that p-cymene be classified as Asp. Tox. 1; H304 – May be fatal if swallowed and enters airways.

Comments received during public consultation

There were no comments provided.

Assessment and comparison with the classification criteria

According to the CLP Regulation, a substance is classified in category 1 for aspiration toxicity:

- based on reliable and good quality human evidence or

- if it is a hydrocarbon and has a kinematic viscosity of 20.5 mm^2/s or less, measured at 40 °C.

Given that the only data available indicates that p-cymene is a hydrocarbon and has a kinematic viscosity of 7.1 mm^2/s at 40 °C, p-cymene, despite the limitations of this data, it should be **classified for Aspiration toxicity in Cat. 1 (Asp. Tox 1; H304 – May be fatal if swallowed and enters airways)**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The DS proposed to classify the substance as Aquatic Acute 1; H400 (M=1) and Aquatic Chronic 3; H412. The acute classification was based on a QSAR estimated mysid 96-hour LC_{50} of 0.327 mg/L.

The value was in the range of > 0.1 to ≤ 1 mg/L leading to an M-factor of 1. The chronic classification was based on a QSAR estimated daphnid NOEC of 0.117 mg/L. The lowest fish and algae QSAR data were of the same order of magnitude. The substance was considered rapidly degradable and to have a high potential for bioaccumulation.

Degradation

There were no experimental data available for the hydrolysis of p-cymene. The substance contains no functional groups that could hydrolyse such as esters, amides or epoxides. The vapour pressure of p-cymene was high (1.95-2.67 × 10^2 Pa) and its solubility in water was relatively low (23 mg/L) giving a high Henry's Law Constant (1.38 × 10^3 Pa m^3/mol), which predicted a high rate of volatility from water. In a level III fugacity model simulating application on crops, persistence in the total system or DT_{100} was predicted to be 46.4 hours because most of the p-cymene will partition to air and be degraded via interaction with hydroxyl radicals rapidly. Direct photolysis was not expected to be an important environmental fate process. The overall conclusion from BIOWIN v4.10 QSAR contained within EPI Suite™ version 4.11, was that p-cymene was not readily biodegradable. The biodegradation potential of p-cymene was evaluated using the MITI test method OECD TG 301C. The purity of p-cymene was 95.3 %. The test was conducted for 14 days. Test vessels were adapted for volatile substances. There was no oxygen consumption in the abiotic control and very limited oxygen consumption in the inoculum blank amounting to 3.8 mg O_2/L after 14 days. The percent degradation (based on BOD) in the positive control amounted to 53 and 87 % after 7 and 14 days, respectively. For the test substance average degradation after 14 days amounted to 88.0 ± 6.2 % based on BOD, 88.7 ± 1.2 based on TOC, and 100 ± 0.0 % based on GC. The 10-day window was met for all three replicates based on BOD. Thus, all validity criteria were met and p-cymene was shown to be readily biodegradable. In an aquatic simulation study without sediment, p-cymene volatilised from the natural water test systems rapidly with a DT_{50} of 11.2 and DT_{90}s of 37.4 hours. The trapping solution showed the presence of the test substance but no degradation products. Degradants were also not detected in the water. Thus, rapid escape (fugacity via volatility) appears to be the predominant pathway for p-cymene in natural water. The DS concluded that p-cymene is rapidly degradable for classification purposes.

Bioaccumulation

There were no experimental BCF data available on the bioaccumulation potential of p-cymene.

There was a reliable experimentally determined log K_{ow} of 4.1 available. In support of this value, there were also QSAR estimated log K_{ow} values of 4.00, 3.81, 4.02 and 4.10 from KOWWIN, LogP, ACD/LogP and ClogP models, respectively. Although surface tension values of 28.1 and 28.5 mN/m had been reported for p-cymene, the DS considered it unlikely that p-cymene would display surface active properties, as the molecule has only non-polar groups. A surfactant would have both polar and non-polar parts. Therefore, the log K_{ow} was considered a valid descriptor for assessing the bioaccumulation potential of p-cymene. The DS concluded, based on the log K_{ow} of 4.1, that p-cymene has a high potential for bioaccumulation.

Aquatic toxicity

Table*. Reliable aquatic toxicity data on p-cymene*.

Test	**Test species**	**Result mg/L**	**QSARs for *p-cymene* (mg/L)**
Fish			
p-cymene Short-term fish toxicity OECD TG 203	*Oryzias latipes*	96 h LC_{50}: 2.0[†] based on mean measured concentrations	96 h LC_{50}: 1.434 (freshwater fish); 96-h LC_{50}: 1.828 (saltwater fish) (ECOSAR v.1.11)[*]

Test	Test species	Result mg/L	QSARs for *p-cymene* (mg/L)
flow-through NITE 2015			
p-cymene Long-term fish toxicity Similar to OECD TG 210 flow-through NITE 2015	*Oryzias latipes*	40 day NOEC: 0.690 based on measured concentrations	Chronic NOEC: 0.124 (freshwater fish); 0.506 (saltwater fish) (ECOSAR v.1.11)*
Invertebrates			
			48 h LC_{50}: 0.988 (freshwater daphnids);96-h LC_{50}: 0.327 (saltwater mysids) (ECOSAR v.1.11)*
p-cymene	*Daphnia magna*		Chronic NOEC: 0.117, daphnids (ECOSAR v.1.11)*
Algae/Aquatic plants			
99.6 % p-cymene OECD TG 201 (Alga, Growth Inhibition Test), GLP, static Ward 2003	*Selenastrum capricornutum*	72 h E_rC_{50} = **4.03** 72 h E_bC_{50} = 2.04 72 h NOE_bC = 1.40 based on initial mean measured concentrations	96 h EC_{50}*: 1.641; NOEC*: 0.468 (ECOSAR v.1.11)
p-cymene OECD TG 201 (Alga, Growth Inhibition Test), GLP, static NITE 2015	*Selenastrum capricornutum*	24-48 h E_rC_{50} = 5.1 24-48 h NOE_rC = 1.3 24-72 h E_rC_{50} = 6.7 24-72 h NOE_rC = 2.7 72 h E_bC_{50} = 3.7 72 h NOE_bC = **0.51**† mean measured concentrations	

* neutral organics, based on log K_{ow} 4.1
† solvent used, not specified

Acute Aquatic Toxicity

In an OECD TG 203 study, *Oryzias latipes* were used in a 96-hour flow-through test to evaluate the toxicity of p-cymene. The nominal test concentrations were 1.0, 1.8, 3.2, 5.6 and 10 mg/L. Control and solvent controls (not specified which solvent) were included. Since the measured concentration differed more than ±20 % of the nominal test concentration, the results were based on the measured test concentrations. The 96 h LC_{50} was reported to be 2.0 mg/L. This value was used as a key data for classification.

QSAR based (neutral organics) LC_{50} values for fish were generated with ECOSAR v1.11 available in EPI suite. Based on the log K_{ow} value of 4.1 and a water solubility of 23.35 mg/L, 96-hour LC_{50} values of 1.434 and 1.828 mg/L were estimated for fresh and saltwater fish, respectively. The log K_{ow} was within the model applicability domain. The QSAR endpoints for short-term fish toxicity were considered reliable and were used as supporting information for classification purposes.

QSAR based (neutral organics) LC_{50} values for aquatic invertebrates were generated with ECOSAR v1.11 available in EPI suite. Based on the log K_{ow} value of 4.1 and a water solubility of 23.35 mg/L, 48-hour and 96-hour LC_{50} values of 0.988 and 0.327 were estimated for daphnids (fresh water) and for mysids (saltwater), respectively. The log K_{ow} is within the applicability domain. Thus, considering that there were no substance invertebrate data available, QSAR endpoints for short-term invertebrate toxicity were used as key data for classification purposes. A QSAR model reporting format (QMRF) and QSAR prediction reporting format (QPRF) were provided in Annex III of the CLH Report.

There were two reliable studies on algae toxicity. In a study performed according to the OECD TG 201 following GLP, p-cymene (purity 99.6 %) was tested with the green algae *Selenastrum capricornutum.* In the definitive test, algae were treated with nominal concentrations of 0, 0.65, 1.3, 2.5, 5.0 and 10.0 mg/L for 72 hours. Initial mean measured concentrations 0.623, 1.40, 1.91, 3.52, and 5.32 mg/L. Final measured concentrations were 53-108 % of nominal concentrations. Results were expressed as initial mean measured concentrations. Control algal populations grew at an acceptable rate (10 000 cells/mL) after 72 hours. The pH was unchanged by the test substance. At the end of the test, samples of test media from each test vessel with maximal growth inhibition were combined with fresh media. After 48 hours incubation, the number of cells increased from 1 500 cells/mL to 1 1328 000 cells/mL at 3.52 mg/L suggesting that the toxic effects were algistatic. The 72-h E_rC_{50} was 4.03 mg/L based on average specific growth rate. The 72-h E_rC_{50} value of 4.03 mg/L was used as key data for classification.

In the other algal growth inhibition test performed according to OECD TG 201 with *Selenastrum capricornutum*, the nominal test concentrations were: 1.0, 2.2, 4.6, 10, 22, 46 and 100 mg/L. Control and solvent control were included. Type of solvent was not specified. All treatments were conducted in triplicate with about 1×10^4 cells/mL at the start. As the measured test concentration deviated more than 20 % from the nominal test concentrations, the effect concentrations were based on the mean measured test concentrations. Section-by-section rates during the test were reported. The EC_{50} and NOEC values based on algal growth rate for the 72 h period were not provided and only results based on biomass are available.

QSAR based (neutral organics) EC_{50} and NOEC values for algae were generated with ECOSAR v1.11 available in EPI Suite. Based on the log K_{ow} value of 4.1 and a water solubility of 23.35 mg/L, an EC_{50} of 1.641 mg/L was estimated. The log K_{ow} value used was within the applicability domain. The QSAR endpoint for acute algal toxicity were considered reliable and were used as supporting information for classification purposes.

Based on the Mysid QSAR derived 96 h LC_{50} of 0.327 mg/L, the DS proposed classification as Aquatic Acute 1 (M=1).

Chronic Aquatic Toxicity

An early life stage toxicity test following OECD TG 210 was conducted with medaka (*Oryzias latipes*) to assess the toxicity of p-cymene. 60 fertilized eggs were used per test group. Five nominal test concentrations were tested, i.e. 0.125, 0.25, 0.5, 1.0 and 2.0 mg/L. The study design was flow-through. Exposure duration was 40 days (hatching after 31 days). Monitored endpoints were: hatching rate, time to hatch, developmental abnormalities, survival, toxic symptoms, body weight, and body length of surviving fry. Since the measured test concentrations ranged 58.4 to 80.0 % of nominal concentrations, the effect concentrations were based on measured concentrations. No significant effects were observed for the embryonic indicators; hatching rate, time to hatching and the developmental abnormalities rate. A significant effect was observed on the survival and growth after hatching of larval and juvenile fish at 1.44 mg/L. The LOEC was reported as 1.44 mg/L, and the NOEC as 0.690 mg/L. The 40-d NOEC value from this study was used as key data for classification.

QSAR based (neutral organics) NOEC values for fish were generated with ECOSAR v1.11 available in EPI Suite (US-EPA 2012). Based on the log K_{ow} value of 4.1 and a water solubility of 23.35 mg/L, NOECs of 0.124 and 0.506 mg/L were estimated for fresh and saltwater fish respectively. The log K_{ow} value used was within the applicability domain. The QSAR endpoints for long-term fish toxicity were considered reliable and were used as supporting information for classification purposes.

There are no experimental data on chronic invertebrate toxicity available. QSAR based (neutral organics) NOEC values for aquatic invertebrates were generated with ECOSAR v1.11 available in EPI Suite. Based on the log K_{ow} value of 4.1 and a water solubility of 23.35 mg/L, a NOEC of 0.117 mg/L was estimated for daphnids (fresh water). The log K_{ow} value used was within the applicability domain. Considering that there were no reliable experimental data on chronic invertebrate toxicity available, QSAR endpoints for chronic invertebrate toxicity were used as key data for classification. A QSAR model reporting format (QMRF) and QSAR prediction reporting format (QPRF) was provided in Annex III of the CLH Report.

The two reliable algae toxicity studies are described in detail under acute toxicity chronic algae toxicity on algae toxicity. Both studies were performed according to the OECD TG 201 with *Selenastrum caprocornutum*. In the first study, the 72-h NOE_bC = 1.40 mg/ L is based on number of cells/mL. A 72-h NOE_rC value is not reported so the 72-h NOE_bC of 1.4 mg/L was used as supporting data for classification. In the other study, the EC_{50} and NOEC values based on algal growth rate for the 72h period were not provided, with only biomass results available. As there were no 72-h NOE_rC values available, the NOE_bC of 0.51 mg/L from this study was used as a key data for classification.

QSAR values for chronic algae toxicity (neutral organics) were estimated with ECOSAR v1.11 available in EPI Suite. Based on the log K_{ow} value of 4.1 and a water solubility of 23.35 mg/L a NOEC of 0.468 mg/L were estimated. The log K_{ow} value used was within the applicability domain. The QSAR endpoint for chronic algal toxicity was considered reliable and was used as supporting information for classification purposes.

The DS proposed to classify as Aquatic Chronic 3 based on the daphniid QSAR NOEC of 0.117 mg/L and the substance being rapidly degradable.

Comments received during public consultation

Two Member States (MS) agreed with the Dossier Submitter (DS) proposal. One MS asked for QMRF and QPRF documents for QSAR predictions for Mysids in case the Mysid endpoint was to be used as key data for classification. They also wanted information of the training set substances. The DS confirmed that the mysid data is used as key data and added the QMRF and QPRF documents to the Response to Public Consultation Document. They informed that the training set of the Mysid acute QSAR contains 14 substances including benzene, toluene and ethylbenzene.

Regarding the chronic Daphnia magna study, the DS informed that they did not have sufficient details to calculate the mean measured concentrations which adds to the unreliability of the endpoint. The DS considered that the 16-day QSAR endpoint is the most realistic option for classification fully aware that the standard test duration is 21 days. They also preferred the 16-day value to the surrogate method with the QSAR generated endpoint. The training set of the chronic Daphnia QSAR contains 23 substances including benzene, toluene, xylene, ethylbenzene and an alkylbenzene.

One MS brought up that at present there was no valid chronic endpoint available for algae because the NOEC values available were not based on growth rate. They proposed to use the surrogate method for this endpoint. The DS did not agree because there were enough chronic data on algae even if the growth rate endpoint is not addressed.

An industry organisation was of the opinion that the QSAR modelling overestimates the aquatic toxicity potential of the compound and did not think the use of QSAR reliable for invertebrates. They also informed that they had submitted, in the context of a REACH registration, a new daphnia study including analytics, resulting in an EC_{50} value of 3.7 mg/L. As this data was not yet disseminated on the ECHA website, the DS was not able to review it. However, the information was available for review by RAC.

Assessment and comparison with the classification criteria

p-Cymene was not susceptible to hydrolysis because it contains no functional groups that could hydrolyse such as esters, amides or epoxides. Direct photolysis was not expected to be an important environmental fate process. The biodegradation potential of p-cymene was evaluated using the MITI test method OECD TG 301C where average degradation after 14 days amounted to 88.0 ± 6.2 % based on BOD, 88.7 ± 1.2 based on TOC, and 100 ± 0.0 % based on GC. The 10-day window was met. All validity criteria were met, and p-cymene was shown to be readily biodegradable. RAC agrees with the DS that p-cymene should be considered as rapidly degradable.

There were no experimental data available on the bioaccumulation potential of p-cymene. There was a reliable experimentally determined log K_{ow} of 4.1 available supported by several estimations from different models. Based on this, RAC agrees with the DS's conclusion that p-cymene has a high potential for bioaccumulation.

As a consequence of the OECD TG 202 study on Daphnia using p-cymene, there are now reliable experimental data for acute toxicity in fish, *Daphnia* and algae, and these are preferentially used instead of the QSAR derived toxicity values. The lowest value is a 96-hour LC_{50} for fish of 2.0 mg/L. Consequently, RAC disagrees with the DS and **concludes that no classification for acute aquatic hazards is warranted**.

There are reliable experimental data on chronic toxicity for fish and algae. The lowest value is a 72-h NOE_bC = 0.51 mg/L resulting to Aquatic Chronic 3 classification for a rapidly degradable substance, based on CLP table 4.1.0(b)(ii). No values based on growth rate are available. As there is no chronic data available for invertebrates, the classification criteria for the surrogate method outlined in table 4.1.0(b)(iii) of CLP are used for this trophic level. This approach using substance data is preferred to use of QSAR derived values. The 48-h EC_{50} for Daphnia is 3.7 mg/L and as p-cymene is rapidly degradable but has a high potential for bioaccumulation, this leads to Aquatic Chronic 2 classification. As this is the most stringent outcome after comparison with the CLP criteria, classification as Aquatic Chronic 2 is warranted.

In conclusion, RAC considers that classification of p-cymene as **Aquatic Chronic 2; H411** is warranted.

Additional references

Rudbäck, J., et al. (2012), 'alpha-Terpinene, an antioxidant in tea tree oil, autoxidizes rapidly to skin allergens on air exposure', Chem Res Toxicol., 25 (3), 713-21.

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 DS; the evaluation performed by RAC is contained in 'RAC boxes'.

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

Annex 3 Records of the targeted public consultation following the submission of an unpublished acute toxicity study in *Daphnia magna* that would potentially change the classification proposal for hazards to the aquatic environment.