Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1-ISOPROPYL-4-METHYLBENZENE; P-CYMENE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: 1-isopropyl-4-methylbenzene; *p*-cymene
EC number: 202-796-7
CAS number: 99-87-6
Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	United States	Bayer AG	Company-Manufacturer	1
Comment received				
General comment on the review process of p-cymene as a separate substance rather than as part of Terpenoid Blend QRD 460. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment letter on QRD 460 ECHA.pdf				
Dossier Submitter's Response				
Thank you for your comments. A harmonised classification is, according to Title V of CLP, only possible for substances. It is not possible to propose a harmonised classification for a mixture of chemicals other than UVCBs. Notably, for non-CMR endpoints, it is possible to classify a mixture based on mixture-specific data (if available) rather than based on information of the individual components. Mixtures do have to be classified for CMR endpoints based on the individual components rather than information with the mixture itself. This information can be derived from the CLP guidance paragraph 1.1.6.2. and to some extend from the CLP regulation (EC 1272/2008) Title II, article 6, paragraph 2 and 3.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	2
Comment received				
The proposed classification with regard to the environmental hazards is Aquatic Acute 1, H400 (Very toxic to aquatic life) Aquatic Chronic 3, H412 (Harmful to aquatic life with long lasting effects)				

The dossier submitter then assigns the hazard phrase H410 (Very toxic to Aquatic organisms with long-term effects).

According to Article 27, required hazard statements appear on the label if there is no duplication or they are not clearly redundant.

In this case, there are no duplications for H400 and H412. Instead of these two H-phrases The dossier submitter assigns H410, which is not required due to the classification of the substance.

A summation of two H phrases to a new H phrase (without submission of a Duplication) is not forseen in the CLP Regulation.
Instead of H410, the two H-phrases H400 and H412 should be included in the labeling.

Dossier Submitter's Response
Thank you for your comment. In the guidance on Guidance on the Application of the CLP Criteria (Version 5.0 – July 2017) page 551-552 is stated that where a substance or a mixture is classified both in acute and long-term hazard categories, it is possible to use only hazard statement H410 on the label. In table 4.1 is indicated that this also applies to a combination of H400 and H412.
RAC's response
RAC agrees with the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	3

Comment received

1. General comments

The lead registrant of p-cymene under REACH (Symrise AG, Holzminden, Germany) was astonished about the timing of the CLH proposal for this substance. The assessment was obviously initiated to generate a harmonised classification and labelling of an active ingredient for plant protection products. This active ingredient represents a mixture for which almost no data are available and with p-cymene being one prominent constituent. Thus, it was concluded to assess the constituents separately to then conclude on a C&L for active ingredient.
The assessment and the derived proposal for classification and labelling (report date March 2018) was done before the respective REACH dossier covering 10-100 t/anno was submitted for the third deadline under REACH (31. May 2018). Therefore, data available for some endpoints were not considered in the CLH proposal and conclusions. Consequently, conclusions are premature for endpoints for which new data are available now. The RMS (RIVM) was obviously aware of the use of the substance relevant for REACH but not of the respective registration activities based on chapter 2 of the CLH report.

By awaiting and reviewing the REACH dossier for this specific compound, some uncertainties and read across approaches could have been avoided, as there are other data including recently performed studies reported in this dossier. These new data have a significant impact on the assessment and the final conclusion on classification and labelling. Respective comments will be given in the different sections for which a different

classification and labelling might be more appropriate. We therefore would like to ask the RMS (RIVM) to evaluate those new data before drawing any conclusions on classification and labelling. The lead registrant of p-cymene would like to mention, that the proposal to classify the substance with Asp. Tox 1 (H304) and Flam. Liquid. 3 (H226) is in line with the proposal in the respective REACH dossier and is therefore not specifically addressed under the respective endpoints All other proposals are addressed in the specific sections. 1. Manufacture and uses It should be mentioned, that a REACH dossier covering 10-100t/anno was submitted for the deadline May 31. 2018, although some studies (e.g. an OECD 422 study) are not available yet. Thus the substance is not only registered as an intermediate as stated in the CLH report. References 1. CLH report 1-isopropyl-4-methylbenzene; p-cymene 2. REACH dossier para-cumene (CAS 99-87-6), status April 2018 3 OECD 403 (7. September 2009)
Dossier Submitter's Response
Thank you for your comments and notification of the data in the REACH registration dossier. The only information in the public registration dossier is the acute oral toxicity study which is already mentioned in the CLH report.
RAC's response
There is only one registration dossier available in ECHA website. The registration is for intermediate use and last modified on 4.11.2018. Regarding environmental classification all relevant data are already included in the CLH Report.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	4
Comment received				
The lead registrant agrees with the conclusion that based on the data available no classification with regard to mutagenicity or carcinogenicity is triggered. The additional studies reported in the REACH dossier are fully in line with this conclusion.				
Dossier Submitter's Response				
Thank your for your support. The dossier submitter was not able to detect any new studies in the public or confidential registration dossier that were not presented in the CLH proposal.				
RAC's response				
Thank you for comment. No classification is warranted due to insufficient data.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	5
Comment received				
Classification Acute Tox. 3 (inhalation/vapours): 1. Because assignment to category 3 relies on a single dose study and known LC100, the argumentation for excluding categories 1, 2 should be further discussed. Considering that mouse is the most sensitive species, results from the reported rat studies cannot be regarded as adequate justification for excluding categories 1 and 2. 2. The dossier is to be completed with ATE for Annex VI CLP: A point estimate cannot be determined from the relevant experiment. Therefore, Table 3.1.2 in section 3.1.3.6.2.3 of the CLP regulation for Category 3/vapours applies: Inhalation: ATE (*)= 3 mg/L (vapours)				
Dossier Submitter's Response				
Thank you for your comments. 1. It is agreed that the results from the rat 4-week inhalation study are not able to exclude acute tox. category 1 or 2 with a 100% certainty. It is rather a hint that it is not very likely that p-cymene may meet the criteria for acute tox. 2 or even 1 in a study with mice. However, this cannot be excluded as pointed out by the German MSCA. 2. The use of the general ATE is supported by the DS because indeed no point estimate of an LC_{50} can be determined based on the available data. According to table 3.1.2 of Annex I of CLP, the proposed ATE would be 3 mg/L.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	6
Comment received				
The lead registrant supports the conclusion, that no classification and labelling is required for acute oral and dermal toxicity. However, from his point of view, the conclusion Acute Tox. 3 (toxic if inhaled) based on the effects seen exclusively in the mouse is at least questionable. The rat is considered the standard animal model for this type of investigation and results obtained in this species should be used for C&L. This is supported by OECD 403 (updated in 2009). According to this guideline, the preferred species is the rat and the use of other species has to be specifically justified. The values obtained in the rat in the same study in which the mouse was investigated do not trigger any classification. In addition, the data obtained with guinea pig also does not trigger a classification. Furthermore, there is no indication, that the mouse represent a better model to assess p-cymene with regard to its potential hazard in humans. It should also be noted that data for similar chemical substances also give no indication for a classification regarding inhalation toxicity. Considering a WOE approach, no classification with regard to inhalation toxicity seems to be more appropriate.				
Dossier Submitter's Response				
Thank you for your comments. 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. This is in line with the Guidance on the CLP criteria version 5.0 (July 2017) chapter 3.1.2.3.2. Evaluation of non-human data.
RAC's response
Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	7
Comment received				
The conclusion by the RMS, that neither for skin/eye irritation nor for skin sensitisation a classification and labelling is triggered is in line with the findings and conclusions in the REACH dossier.				
Dossier Submitter's Response				
Thank you for your support. The dossier submitter was not able to detect any new studies in the public or confidential registration dossier that were not presented in the CLH proposal.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	8
Comment received				
The conclusion by the RMS, that neither for skin/eye irritation nor for skin sensitisation a classification and labelling is triggered is in line with the findings and conclusions in the REACH dossier.				
Dossier Submitter's Response				
Thank you for your support. The dossier submitter was not able to detect any new studies in the public or confidential registration dossier that were not presented in the CLH proposal.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	9
Comment received				
The lead registrant agrees with the conclusion that based on the data available no classification with regard to STOT SE or STOT RE is triggered. However, the running OECD 422 study with this substance might require a reassessment depending on the results obtained.				
Dossier Submitter's Response				
Thank you for your support and notifying us that a 422 study is currently being conducted, although it will be more relevant for STOT RE and reproductive toxicity.				

RAC's response
Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	10
Comment received				
The lead registrant agrees with the conclusion that based on the data available no classification with regard to STOT SE or STOT RE is triggered. However, the running OECD 422 study with this substance might require a reassessment depending on the results obtained.				
Dossier Submitter's Response				
Thank you for your support and notifying us that a 422 study is currently being conducted.				
RAC's response				
Thank you for comment.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	France		MemberState	11
Comment received				
FR agrees with the classification for environmental hazard and acute M-factor proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2018	United Kingdom		MemberState	12
Comment received				
Acute classification: QSAR predictions are presented for acute toxicity to Daphnia and Mysids with QMRF and QPRF documents included for the Daphnia endpoint. Some CLH text states that the acute classification is based on the Daphnia QSAR (page 67 'Therefore, QSAR endpoints for short-term daphnia will be used as key data for classification purposes') and some text states that the acute classification is based on the Mysid QSAR (section 5.6 'The classification proposal is based on the most critical endpoint, i.e. the mysid endpoint.'). Please can you clarify which endpoint is the valid acute key endpoint as QMRF and QPRF documents are only included for the Daphnia QSAR. If the Mysid endpoint is considered the key endpoint, QMRF and QPRF documents should be presented to consider the reliability of the prediction for hazard classification. In addition, it would be useful to include information to describe the range of training set				

substances and if they include relevant structural analogues for p-cymene.

Chronic toxicity to invertebrates:
In the chronic toxicity to Daphna magna study (NITE, 2015) test item concentrations declined over the study period based on available analytical information. Is it possible to present chronic endpoints as mean measured endpoint accounting for this decline by using half the detection limit in the calculation (refer to section I.4.1 of ECHA (2017) Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0 July 2017).

Regarding the chronic toxicity to Daphnia QSAR, we are unclear if a 16 day endpoint is considered suitable to fulfil the chronic toxicity to invertebrates endpoint where a standard measured endpoint is based on a 21 day endpoint. In addition, it would be useful to include information to describe the range of training set substances and if they include relevant structural analogues for p-cymene.

Toxicity to algae
We note the Ward, 2003 study report did not include a NOEC based on growth rate. Are raw study data available to calculate a chronic endpoint (e.g. ErC10 or ErC50) based on growth rate as this is preferable for hazard classification?

At present a valid chronic growth rate endpoint is not available for algae. If it is not possible to determine such a value from the Ward, 2003 study, the surrogate approach using the acute algal key endpoint should be considered.

In addition, it would be useful to present a QMRF and QPRF for the algal QSAR to consider the predicted chronic endpoint validity.

Dossier Submitter's Response

Thank you for your comments.
Acute classifications
Our appologies for the inconsistency in clarifying which QSAR end point is used as key for the classification proposal, daphnia or mysid. The QSAR endpoint for the mysid was used as key and the QMRF and QPRF for the mysid QSAR that should have been included in the CLH report are given at the end of this response.
To give you more detail on the training sets, the training set of the QSAR for acute toxicity to Daphnia magna contains more than 100 compounds including benzene and several substituted benzenes like ethylbenzene, xylene and toluene. The training set of the Mysid acute QSAR contains 14 substances including benzene, toluene and ethylbenzene.

Chronic classification
Considering the endpoints of the chronic D. magna study (NITE, 2015), we do not have sufficient details to calculate the mean measured concentration, this is one of the reasons that we consider the endpoints unreliable. We have considered that the 16 day QSAR endpoint might underestimate the chronic toxicity but considered it the most realistic option for the classification proposal. Furthermore, we consider the use of this QSAR generated endpoint for chronic toxicity preferable over the use of a QSAR generated acute toxicity endpoint in the surrogate method. The training set of the chronic Daphnia QSAR contains 23 substances including benzene, toluene, xylene, ethylbenzene and an alkylbenzene.

Where it considers the Ward, 2003 study, unfortunately, the data available does not include an EC10 for growth rate or any raw data enabling to determine an EC10. You ask to consider the surrogate method when determining an EC10 would not be possible. It should however be noted that the study of Ward, 2003 is not the key study for the proposed classification and only used as supporting information. If this study is not taken into account, the surrogate method is still not necessary. The QSAR endpoints for algae were not used for the classification proposal because experimental endpoints are available. Thefore, QMRF and QPRF for the algae QSAR are not presented.

QSAR model reporting format Acute mysid

QMRF Title: **ECOlogical Structure Activity Relationship (ECOSAR), Acute Mysid Shrimp 96-hour LC_{50}- Neutral Organics**

Printing Date: **Oct 1, 2015**

1. QSAR identifier

1.1. QSAR identifier (title):

ECOlogical Structure Activity Relationship (ECOSAR), Acute Mysid Shrimp 96-hour LC_{50}- Neutral Organics

Please note: The (Q)SAR under evaluation is one on many available in the ECOSAR Program (see section 1.3). The evaluation, statistics and data presented are only applicable to the acute mysid 96-hour LC_{50} (Q)SAR and no other (Q)SARs available within the program.

1.2. Other related models:

1.3. Software coding the model:

ECOSAR™ Version 1.11 (Sept 2012): The Ecological Structure Activity Relationships (ECOSAR) Class Program estimates the aquatic toxicity of industrial chemicals. The program estimates acute (short-term) toxicity and chronic (long-term or delayed) toxicity to aquatic organisms to fish, aquatic invertebrates, and green algae, and has limited SARs for other salt water and terrestrial species, where data were available.

ECOSAR is included in the EPI (Estimation Programs Interface) Suite which is a window based suite of physical/chemical property, environmental fate and ecotoxicity models.

2. General information

2.1. Date of QMRF:

1 October 2015

2.2. QMRF author(s) and contact details:

Bureau REACH
The National Institute of Public Health and the Environment (RIVM)
The Netherlands
Email: bureau- reach@rivm.nl

2.3. Date of QMRF update(s):

Not known

2.4. QMRF update(s):

Not known

2.5. Model developer(s) and contact details:

Kelly E. Mayo-Bean Risk Assessment Division (7403M), 1200 Pennsylvania Ave, N.W., Washington, DC 20460-0001 202-564-7662 mayo.kelly@epa.gov

Gordon G. Cash Risk Assessment Division (7403), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460-0001 Phone: 202-564-8923 cash.gordon@epa.gov

2.6. Date of model development and/or publication: September 2012

2.7. Reference(s) to main scientific papers and/or software package:

ECOSAR v 1.11 Methodology Document for the ECOlogical Structure Activity Relationship Model (ECOSAR) Class program. Estimating toxicity of industrials chemicals to aquatic organisms using ECOSAR (Ecological structure activity relationship) class program. MS-Windows Version 1.11.Mayo-Bean K, Moran K, Meylan B, Ranslow P. May 2012. PFD document available in the ECOSAR help menu.

ECOSAR v 1.11 Operation Manual for the ECOlogical Structure Activity Relationship Model (ECOSAR) Class program. Estimating toxicity of industrials chemicals to aquatic organisms using ECOSAR (Ecological structure activity relationship) class program. MS-Windows Version 1.11.Mayo-Bean K, Moran K, Nabholz JV, Meylan E, Howard PH. March 2012. PFD document available in the ECOSAR help menu.

EPISuite (Version 4.1.1) program is publically available at: http://www2.epa.gov/tsca-screening-tools/download-epi-suitetm-estimation-program-interface-v411

2.8. Availability of information about the model:

The model is non-proprietary but some of the information within the predictive system is confidential business information (CBI) collected by EPA under the New Chemicals Programs and is therefore restricted from being revealed.

2.9. Availability of another QMRF for exactly the same model:

Not known.

3. Defining the endpoint - OECD Principle 1

3.1. Species:

The mysid shrimp, *Mysidopsis bahia*

3.2. Endpoint:

Ecotoxic effects, Short-term toxicity to invertebrates (saltwater)

3.3. Comment on endpoint:

3.4. Endpoint units:

LC50 values are presented in mg/L

3.5. Dependent variable:

Log 96-hour LC50

"LC_{50}" means that experimentally derived concentration of test substance that is calculated to kill 50 percent of a test population during continuous exposure over a specified period of time.

3.6. Experimental protocol(s):

40 CFR 797.1930 - Mysid shrimp acute toxicity test

USA-EPA OPPTS 850.1035 (Mysid acute toxicity)

3.7. Endpoint data quality and variability:

The data used for ECOSAR development undergo an extensive data validation step to ensure appropriateness for inclusion in the model. ECOSAR study criteria articulate that the toxicity should be measured at pH levels between 6 and 8 (replicating environmental conditions), the total organic carbon content should not exceed 2 mg/L, the water hardness should be less than 150 mg/L CaCO3, results should be adjusted to, or measured at, 100% active ingredient, and measured test concentrations maintained at greater than 80% of nominal concentrations.

4. Defining the algorithm - OECD Principle 2

4.1. Type of model:

Regression based QSAR

4.2. Explicit algorithm:

Log Toxicity (mmol/L) = - 1.1897 (log Kow) + 2.2651

4.3. Descriptors in the model:

To estimate the toxicity of aquatic organisms, the low Kow and MW are required.

Log Kow: Log of octanol/water partition coefficient (no units)

MW: Molecular weight. The LC50 predictions from the equation are presented in millimoles per liter (mmol/L). ECOSAR then converts the LC50 from mmol/L to mg/L, by multiplying value by molecular weight of the compound.

4.4. Descriptor selection:

The use of log Kow and MW to predict acute toxicity was determined experimentally through experience in US EPA, OPPT New Chemical Program and a need to derive the simplest approach for calculating acute toxicity to Daphnia.

4.5. Algorithm and descriptor generation:

To estimate LogKow, ECOSAR uses the KOWWIN v1.68 program from the EPISuite model. The underlying predictive methodology is described in the reference listed below: Meylan, WM; Howard, P. (1995) Atom/Fragment Contribution Method for Estimating Octanol-Water Partition Coefficients. J Pharm Sci 84: 83-92.

ECOSAR will accept user entered Log Kow.

4.6. Software name and version for descriptor generation:

KOWWIN v1.67

4.7. Chemicals/Descriptors ratio:

7.5 (15 chemicals/ 2 descriptors)

5. Defining the applicability domain - OECD Principle 3

5.1. Description of the applicability domain of the model:

ECOSAR cannot be used for all chemical substances. The intended domain is organic chemicals.

Class definition

ECOSAR derives toxicity values for three general types of chemicals: neutral organics, organics with excess toxicity and surfactant (Surface-Active) organic chemicals. The (Q)SAR under evaluation, acute mysid 96-hour LC_{50} falls under the neutral organics class.

LogKow

In general, when the logKow is less than or equal to 5.0 for daphnid, ECOSAR provides reliable quantitative (numeric) toxicity estimates for acute effects. However, the method may be used to estimate toxic effects equal to "no-toxic-effect-at-saturation or "*" for chemicals exceeding logKow values of 5. Therefore, the domain of the model is much larger than the values covered in the regression equation and covers all logKow ranges.

Molecular weight:

The molecular weight may also be considered to determine the absorption cutoff limit for aquatic organisms. Compounds with a molecular weight of greater than 1000 g/mol are considered too large to present any significant toxicity.

Water solubility

If the predicted toxicity exceeds the water solubility, no acute toxicity is expected to be observed in the absence of an organic carrier solvent.

5.2. Method used to assess the applicability domain:

Assess if substances properties fall within the limits of applicability of the model mentioned in sections 5.1 and 5.4.

5.3. Software name and version for applicability domain assessment:

Not applicable

5.4. Limits of applicability:

Maximum logKow: 5.0

Maximum MW: 1000

Limitations:

If the log Kow value is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

6. Internal validation - OECD Principle 4

6.1. Availability of the training set:

Yes, however some information of the information contained in the training set is confidential business information (CBI) collected by EPA under the New Chemicals Program and is therefore restricted from being revealed. For these substances the name and CAS numbers are not revealed but data on the descriptors and dependent variables are available in the QSAR equation document.

6.2. Available information for the training set:

CAS RN: Yes Chemical Name: Yes

Smiles: No

Formula: No INChI: No MOL

file: No

Data table for the neutral organics - training set is available in the ECOSAR User Guide accessible via the Help tab.

6.3. Data for each descriptor variable for the training set:

MW, log Kow (CLogP) log Kow (EPI), log Kow (M)

6.4. Data for the dependent variable for the training set:

Mysid 96-h LC50 (mg/L) and Log Mysid 96-h LC50 (mmol/L)

6.5. Other information about the training set:

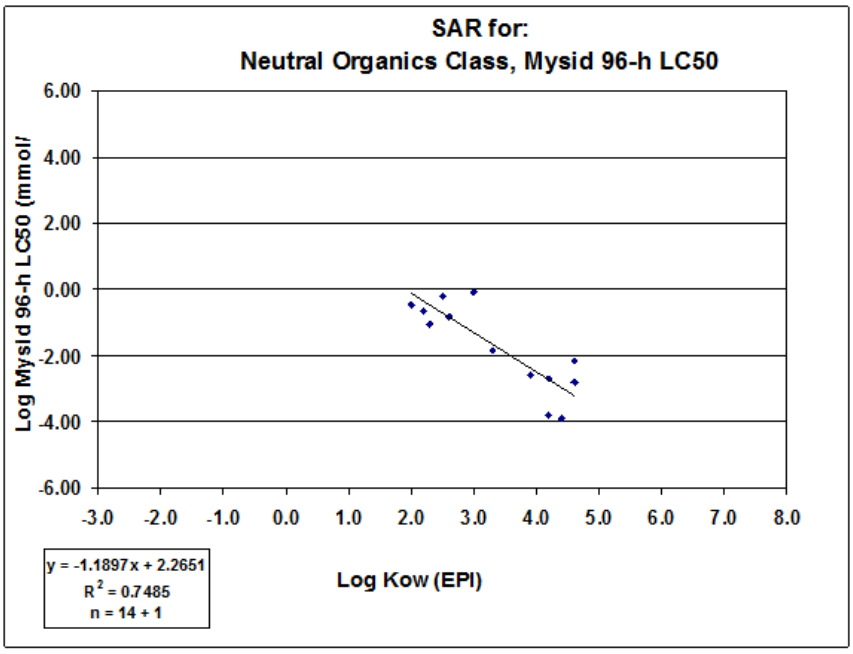
References for (measured Kow) and References (Mysid 96-h LC50) are provided.

6.6. Pre-processing of data before modelling:

Not applicable

6.7. Statistics for goodness-of-fit:

The correlation (r^2) for neutral organics Mysid 96-hour (Q)SAR equals 0.7485 obtained from standard statistical regression software.



The number of chemicals in the training set is represented by N = x + y where 'x' equals the number of studies used in the actual equation development and 'y' equals 1) logKow cut-off and/or 2) SAR data not included in regression equation.

6.8. Robustness - Statistics obtained by leave-one-out cross-validation:

Not applicable

6.9. Robustness - Statistics obtained by leave-many-out cross-validation

Not applicable

6.10. Robustness - Statistics obtained by Y-scrambling:

Not applicable

6.11. Robustness - Statistics obtained by bootstrap:

Not applicable

6.12. Robustness - Statistics obtained by other methods:

Not applicable

7. External validation - OECD Principle 4

7.1. Availability of the external validation set:

See section 7.9

7.2. Available information for the external validation set:

See section 7.9

7.3. Data for each descriptor variable for the external validation set:

See section 7.9

7.4. Data for the dependent variable for the external validation set:

See section 7.9

7.5. Other information about the external validation set:

See section 7.9

7.6. Experimental design of test set:

See section 7.9

7.7. Predictivity - Statistics obtained by external validation:

See section 7.9

7.8. Predictivity - Assessment of the external validation set:

See section 7.9

7.9. Comments on the external validation of the model:

All available valid data were used by U.S. EPA/OPPT in development of the (Q)SARs within ECOSAR. Subsequent validation studies have been completed by multiple stakeholders. A list of supporting validation exercise performed in conjunction with EPA and other stakeholders on the ECOSOR model are listed below.

• External Peer Reviews

An independent peer review of ECOSAR was conducted as part of the development of the Organization for Economic Cooperation and Development's (OECD) guidance, The Principles for Establishing the Status of Development and Validation of (Quantitative)
Structure-Activity Relationships [(Q)SARs] (OECD, 2004a).

• Participation in US-European Union Validation Exercise

EPA participated with the European Union in a large-scale verification study of ECOSAR to compare SAR predictions with the results of data from testing. That study (OECD 1994; U.S.EPA 1994) found our methods to be accurate 60-90% of the time depending on the endpoint assessed.

• International Collaboration in Development of Effective Predictive Tools

ECOSAR was included in OECD's Report on the Regulatory Uses and Applications in OECD Member Countries of (Q)SAR Models in the Assessment of New and Existing Chemicals (OECD, 2006). Subsequently, the OECD solicited EPA to include ECOSAR into the OECD QSAR Application Toolbox, which was developed starting in 2006. Inclusion in the OECD toolbox
requires specific documentation, validation and acceptability criteria and subjects ECOSAR to international use, review, providing a means for receiving additional and on-going input for improvements. In an evaluation of a number of predictive tools used to profile chemicals and group them together based on similar toxicity, ECOSAR was the top performer.
[http://www.oecd.org/document/23/0,3343,en_2649_34379_33957015_1_1_1_1,00.html#Additional_information_on_the_QSARs_Application_Toolbox]

8.Providing a mechanistic interpretation - OECD Principle 5

8.1. Mechanistic basis of the model:

Neutral organic chemicals are nonionizable and nonreactive and act via simple nonpolar narcosis generally thought of as a reversible, drug induced loss of conscience (general anesthesia**).** The octanol/water partition coefficient (Kow) is the major physical-chemical attribute correlating a chemical structure to toxic effect for

nonreactive neutral organic chemicals. The most frequently used relationship is the logarithm of the Kow value versus the median toxicity (LC50 and EC50) value. This general narcosis is often referred to baseline toxicity.

The types of chemicals that are known to present general narcosis include, but are not limited to, alcohols, ketones, ethers, alkyl halides, aryl halides, aromatic hydrocarbons, aliphatic hydrocarbons, cyanates, sulfides, and disulfides.

8.2. A priori or a posteriori mechanistic interpretation:

8.3. Other information about the mechanistic interpretation:

9.Miscellaneous information

9.1.Comments:

9.2.Bibliography:

References Neutral Organics (Q)SAR

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9.3.Supporting information:

Training set(s)Test set(s)Supporting information

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

10.2.Publication date:

10.3.Keywords:

10.4.Comments:

QSAR Prediction reporting format acute mysid

QSAR Prediction Reporting Format (QPRF): *p*-cymene, Acute toxicity to Mysid

1. Substance

1.1 CAS number:

99-87-6

1.2 EC number:

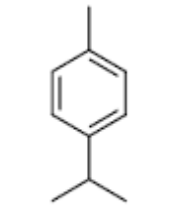
202-796-7

1.3 Chemical name:

Substance name: 1-isopropyl-4-methylbenzene

Synonym: *p*-cymene

1.4 Structural formula:



1.5 Structure codes:

SMILES: c(ccc(c1)C)(c1)C(C)C

2. General information

2.1 Date of QPRF: 23 November 2015

2.2 QPRF author and contact details:

Bureau REACH
The National Institute of Public Health and the Environment (RIVM)
The Netherlands
Email: bureau- reach@rivm.nl

3. Prediction

3.1 Endpoint (OECD Principle 1)

a. **Endpoint**: Short-term toxicity to Mysid 96-hour
b. **Dependent variable:** Log 96-hour LC50

3.2 Algorithm (OECD Principle 2)

a. **Model or submodel name:** ECOSAR

b. **Model version:** Version 1.11 (Sept 2012)

c. **Reference to QMRF:**

Title: ECOlogical Structure Activity Relationship (ECOSAR), Acute Mysid Shrimp 96-hour LC_{50} –Neutral Organics.

Date: 1 October 2015

Author: Bureau REACH, The Netherlands

d. Predicted value (model result):

Mysid Shrimp 96-hour LC_{50} = 0.327 mg/L

e. Predicted value (comments):

Acute aquatic toxicity for crustacea

The predicted value will be compared to the criteria for classifying and categorizing a substance as "hazardous to the aquatic environment" as summarized in Table 4.1.0 (a) of the CLP Annex I:

Acute (short-term) aquatic hazard **Acute Category 1**	Note 1
96 hr LC50 (for fish)	≤ 1 mg/l and/or
48 hr EC (for crustacea)	≤ 1 mg/l and/or
72 or 96 hr (for algae or other aquatic plants)	≤ 1 mg/l. Note 2

Note 1: When classifying substances as Acute Category 1 and/or Chronic Category 1 it is necessary at the same time to indicate an appropriate M-factor (see table 4.1.3).
Note 2: Classification shall be based on the ErC50 [= EC50 (growth rate)]. In circumstances where the basis of the EC50 is not specified or no ErC50 is recorded, classification shall be based on the lowest EC50 available.

f. Input for prediction:

See section 1.5

g. Descriptor values:

Log Kow (user entered): 4.1 (measured value)

Water solubility (user entered): 23.35 mg/L (measured value)

Applicability domain (OECD principle 3)

h. Domains:

The applicability domain criteria are fulfilled.

Descriptor domain

p-cymene: log Kow = 4.1 and molecular weight = 134.22

LogKow is less than maximum Log Kow 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50) and the molecular weight is less than the maximum of 1000.

Structural fragment domain and mechanism domain

Class definition: Neutral organic class

Neutral organic chemicals are nonionizable and nonreactive and act via simple nonpolar narcosis generally thought of as a reversible, drug-induced loss of conscience (general anesthesia). This general narcosis is often referred to as baseline toxicity (Franks and Lieb 1990, Veith and Broderius 1990). The types of chemicals that are known to present general narcosis include, but are not limited to, alcohols, ketones, ethers, alkyl halides, aryl halides, aromatic hydrocarbons, aliphatic hydrocarbons, cyanates, sulfides, and disulfides.

The structural formula of p-cymene (section 1.4) shows that it is an aromatic hydrocarbon and therefore falls within the neutral organic class as defined in ECOSAR.

i. Structural analogues: -

j. Considerations on structural analogues:

Data tables on the neutral organics - training set is available (see related - QMRF).

3.3 The uncertainty of the prediction (OECD principle 4)

Model performance:

$y = 1.1987x + 2.2651$ ($R^2 = 0.7485$)

$n = 14 + 1$

3.4 The chemical and biological mechanisms according to the model underpinning the predicted result (OECD principle 5).

Neutral organic chemicals are nonionizable and nonreactive and act via simple nonpolar narcosis generally thought of as a reversible, drug induced loss of conscience (general anesthesia).
The octanol/water partition coefficient (Kow) is the major physical-chemical attribute correlating a chemical structure to toxic effect for nonreactive neutral organic chemicals. The most frequently used relationship is the logarithm of the Kow value versus the median toxicity (LC50 and EC50) value. This general narcosis is often referred to baseline toxicity.

The types of chemicals that are known to present general narcosis include, but are not limited to, alcohols, ketones, ethers, alkyl halides, aryl halides, aromatic hydrocarbons, aliphatic hydrocarbons, cyanates, sulfides, and disulfides.

4. Adequacy (Optional)

4.1 Regulatory purpose:

The present prediction will be used for classification and labelling purposes as required by Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

4.2 Approach for regulatory interpretation of the model result:

The predicted result (numeric value) is presented in the format directly useable for the intended regulatory purpose.

4.3 Outcome:

The estimated mysid shrimp 96-hr LC 50 of 0.327 mg/L is below the threshold value of 1 mg/L. Based on this information p-cymene would meet the criteria for classification for Aquatic Acute Category 1.

4.4 Conclusion:

Considering the above, the predicted result can be considered adequate for the regulatory conclusion described in 4.1.

RAC's response

RAC thanks the MSCA and DS for clarifications. More details can be found in the RAC opinion document.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1-ISOPROPYL-4-METHYLBENZENE; P-CYMENE

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	13
Comment received				
We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 3 (H412) and the acute M-factor of 1				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	14
Comment received				

Biodegradation

The registrant supports the conclusion, that p-cymene is readily biodegradable based on the data available to the RMS.

Aquatic toxicity

Acute aquatic toxicity: proposal H400 in the CLH dossier

The proposal for H400 is triggered by the fact that the studies available to the RMS for daphnia were not considered valid (due to the lack of analytical determination of the test concentrations) and therefore QSAR values were used for the assessment and the conclusion on classification and labelling especially for aquatic invertebrates.

1. For fish several studies were evaluated and the conclusion drawn, that a LC50 value of 2 mg/L is considered for the C&L proposal. In the QSAR modelling a lower figure (1.434 mg/L) was obtained.
2. For invertebrates, all four studies available to and assessed by RMS were evaluated as invalid (Klimisch Score 3) mainly due to the lack of analytical measurement of the substance. Therefore, QSAR data were generated, resulting in LC50 values of 0.327 mg/L (96 h mysid) and 0.988 mg/L (48 h, daphnid). Thus, for this trophic level an LC 50 value < 1 mg/L was deduced.
It should however be mentioned, that the lowest result (EC50 = 3.52 mg/L) reported in those invalid studies fits quite well to the results obtained in the new state of the art study (see below). Thus, the potential loss of substance due to the high volatility of the substance seems to have a rather limited effect on the resulting EC50 values.
3. Acute effects in algae and aquatic plants were assessed based on two studies. A third one was considered invalid. Based on this an ErC50 of 4.03 mg/L was considered for the C&L proposal. Again, the also performed QSAR revealed a lower figure (1.641 mg/L).

Based on the result obtained in the QSAR modelling for the daphnia, resulting in a values of > 0.1 mg/L and < 1mg/L, an aquatic acute 1 (H400, M=1) was deduced. For all other trophic levels values > 1 mg/L were deduced, which does not warrant classification for acute aquatic toxicity.

However, in the context of the REACH registration a new state of the art daphnia study

including analytics was performed, resulting in an EC50 value of 3.7 mg/L. Thus, this trophic level can be properly assessed by experimental findings, which overrule the QSAR estimates.
In addition, as can be seen for the other species the QSAR modelling obviously overestimates the aquatic toxicity potential of the compound.

Based on this new data, no classification for acute aquatic toxicity is triggered and therefore the proposal of H400 is obsolete.

Long-term aquatic toxicity (proposal H412)

The RMS used experimental data for fish and algae. These data were supported by QSAR modelling, resulting in similar but again lower figures compared to the experimental findings.
It should however be mentioned, that both approaches resulted in figures > 0.1 mg/L.
For daphnia QSAR (ECOSAR) estimates were used as the available study was not considered valid due to lack of analytical data. This modelling resulted in a NOEC of > 0.1 mg/L (0.116 mg/L).
Taken into account, that the QSAR modelling tend to overestimate the toxicity of this compound, the use of QSAR data as a worst case assumption for daphnia is scientifically justified.

Based on the results for all three trophic levels revealing NOEC values in the range of > 0.1 and < 1 mg/L and the fact that the substance is ready biodegradable, p-cymene is proposed to be classified as aquatic chronic 3, H412.

As not all of the above data are currently considered in the REACH dossier, a different approach and conclusion was drawn.
However, the lead registrant of p-cymene fully supports the approach taken be the RMS.
In addition, the new data provided in the REACH dossier further support the assessment in the CLH report that the QSAR modelling tend to overestimate the toxicity of the compound and can be considered as a worst case assumption. In addition, based on the new data it also becomes obvious that daphnia based on acute aquatic toxicity data are not more sensitive than fish or algae as suggested by the QSAR data.

Dossier Submitter's Response
Thank you for your comments and your support for the chronic classification. You mention a new acute aquatic study on D. magna available in the REACH dossier. However, we cannot find such a study for p-cymene in the REACH dosser on the disemination site of ECHA. Therefore, we cannot consider this study for the proposed classification.
RAC's response
Thank you for the new Daphnia data. Although not yet published at the ECHA website the rapporteur has validated the study and RAC will use it for classification.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	France		MemberState	15
Comment received				
FR agrees with the proposed classification				

Dossier Submitter's Response
Thank you for the support
RAC's response
Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	16
Comment received				
Editorial note to CLH report Table 9 on page 22: Self-ignition temperature: 817 °C (NOAA 1999) According to the reference https://cameochemicals.noaa.gov/chris/CMP.pdf the auto-ignition temperature is 817 °F and not "°C"				
Dossier Submitter's Response				
Thank you for pointing us towards this error. The auto-ignition temperature should be 436 °C (817 °F)				
RAC's response				
Thank you for your remark.				

PUBLIC ATTACHMENTS
1. Comment letter on QRD 460 ECHA.pdf [Please refer to comment No. 1]