Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

p-mentha-1,3-diene; 1-isopropyl-4-methylcyclohexa-1,3-diene; alpha-terpinene

EC Number: 202-795-1
CAS Number: 99-86-5

CLH-O-0000001412-86-274/F

Adopted

15 March 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON P-MENTHA-1,3-DIENE; 1-ISOPROPYL-4-METHYLCYCLOHEXA-1,3-DIENE; ALPHA-TERPINENE

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.

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Substance name: p-mentha-1,3-diene; 1-isopropyl-4-methylcyclohexa-1,3-diene; alpha-terpinene
EC number: 202-795-1
CAS number: 99-86-5
Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Belgium	Procter & Gamble	Company-Downstream user	1
Comment received				
We do not support the proposal for a harmonized classification of p-mentha-1,3-diene / alpha-terpinene (CAS#: 99-86-5; EC#: 202-795-1), as a Repr. 2 H361 (CMR 2). See below for further details.				
Dossier Submitter's Response				
See our response to comment 8				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	2
Comment received				
General comments The lead registrant of alpha-terpinene 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 alpha-terpinene 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 1-10 t/anno was submitted for the third deadline under REACH (31. May 2018). Therefore, several				

data/studies available for different 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 not aware of the use of the substance relevant for REACH based on chapter 2 of the CLH report although a registration intention under REACH should have been known since the lead nomination of Symrise.

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/additional 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 specific 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 alpha-terpinene would like to mention, that the proposal to classify the substance as 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.

References
1. CLH report 1-isopropyl-4-methylbenzene; alpha-terpinene
2. REACH dossier alpha-terpinene (CAS 99-86-5), status April 2018
3. OECD 414, June 25, 2018
4. Araujo, I.B. et al. Study of the embryofoetotoxicity of α-terpinene in the rat. Food and Chemical Toxicology 34 (1996), 477-482.
5. DEREK Modelling (attached)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Derek report_99-86-5-alpha terpinene_20180620.pdf

Dossier Submitter's Response

Thank you for your comments and notification of the data in the REACH registration dossier. The endpoint-specific comments are addressed in response to comments 9, 16, 19, 23 and 24.
The dossier submitter has considered the information in the public REACH registration dossier. Only limited information is available that was not yet included in the CLH report and this information does not lead to a different classification proposal on some endpoints except for acute toxicity.
The information on acute toxicity is relevant for classification and will be taken into consideration (see response to comment 16).

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	United Kingdom	Givaudan UK Limited	Company-Downstream user	3

Comment received

Alpha-Terpinene (1-isopropyl-4-methylcyclohexa-1,3-diene; TER) is a naturally occuring monocyclic monoterpene. It is a component in essential oils of numerous aromatic plant extracts like cardamom, marjoram, coriander, peppermint, thyme, basil. Due to its anti-

oxidant properties, TER compound is used in food, cosmetics and plant protection products and also due to its pleasant odour TER is used as fragrances in soap, detergents, lotions and perfumes. TER has not previously been assessed for harmonized classification. Therefore, National Institute for Public Health and the Environment (RIVM) on behalf of Rapporteur Member State (RMS) has reviewed the available data and proposed a harmonized classification and labeling for TER based on EC CLP regulation (No 1272/2008, Annex VI, Part 2) [ref 1].

Givaudan, a Switzerland based Fragrance Company with significant business in Europe and a formulation site in the UK, would like to take this opportunity, during public commenting period, to review and provide comments to the proposed classification. We do not agree with the RMS proposal to classify this product as Category 2 for reproduction. A detailed justification for non-classification for reproductive toxicity is provided in the relevant "open hazard class" comments field.

Similarly, we do not agree with the Aquatic Acute 1 proposal. Based on a full acute data set, which has be-come available following the REACH 2018 deadline, the substance should not be classified for acute hazards. In the absence of chronic toxicity data for alpha terpinene, Givaudan supports the read-across from d-limonene and the Aquatic Chronic 3 classification. A detailed justification for our opinion is provided in the relevant "open hazard class" comments field.

References:
1.CLH report, Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2
2.Anonymous 1996, 'Study of the embryofoetotoxicity of alpha-terpinene in the rat', Food Chem Toxicol, 34 (5), 477-82.

Dossier Submitter's Response

Thank you for your comments, see our response to comments 10 and 25.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	United States	Bayer AG	Company-Manufacturer	4

Comment received

We disagree with the process of classifying terpenoid blend QRD 460 via its three terpenes rather than assessing it as it's registered in the EU - as a single substance. Particular to this is the repro classification.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Rclass_420substance (003).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 with 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. See also our response to comment 11.
RAC's response
We support the justification provided by DS.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	United States	Bayer AG	Company-Manufacturer	5
Comment received				
General comment on the review process of alpha-terpinene 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				
See our response to comment 4				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2018	Spain	<confidential>	Company-Manufacturer	6
Comment received				
The CLH report prepared by The Netherlands takes into account data on alpha-terpinene collected from the DAR of terpenoid blend QRD460 and the publically available information until 2017-05-12. Nevertheless, the substance has been recently registered under REACH Regulation (EC) No 1907/2006 and this information should be also taken into account.				
Dossier Submitter's Response				
Thank you for your comment. See our response to comment 2, and our response to the endpoint-specific comments 9, 16, 19, 23 and 24.				
RAC's response				
Thank you for information and opinion. We consider the response provided by DS as appropriate.				

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	7
Comment received				
In part B section 4.6.1.1 of the CLH-Report the dossier submitter states, that "alpha-terpinene is expected to autoxidise upon air exposure to form allergenic compounds […]" and that "compared to the pure compound, autoxidized alpha-terpinene has increased sensitization potency". Consequently the dossier submitter proposes a classification as Skin Sens. 1A; H317 based on the LLNA results of "alpha-terpinene containing autoxidation products". Pursuant to the agreed strategy in the CLH process in principle an Annex VI entry should deal with the substance as such and not with a specific marketed composition of a manufactured substance*. Especially as the ICI of an Annex VI entry does not reflect				

which (if any) impurities or additives have been considered§.

Therefore the influence of the autoxidation products on the classification of the substance needs to be reflected in the Annex VI entry.

However, as the autoxidation products form over time, they cannot be regarded as impurities of the substance in the meaning of the REACH and CLP regulations and guidance, as impurities are only regarded as part of a substance if they are "derived from the process used [to manufacture or obtain the substance]". This is also elaborated in the Guidance for identification and naming of substances under REACH and CLP, Section 4.2.

Moreover, substances which result from a chemical reaction that occurs incidental to exposure of another substance or article to environmental factors such as air, moisture, microbial organisms or sunlight should be exempted from registration#. That means that the oxidation products should be regarded as substances acc. to the substance definition under REACH and CLP.

Therefore the German CA is of the opinion that the autoxidation products are not part of the substance as described by the current SID and should in principle be disregarded for harmonised classification of the substance.

However, to utilize the available data to the greatest extent and to maintain a high level of protection of human health different ways forward to implement the substance entry into Annex VI could be considered.

1) Listing the substance in Annex VI as proposed by the DS but utilizing only the data on the non-oxidised substance (i.e classify as Skin Sens. 1B, see our specific comments on classification as a skin sensitiser below). In this proposal the oxidation products are not considered for the entry. And adding an additional entry for the autoxidation products (classified as Skin Sens. 1A) and derive the classification of the actual marketed substance(s) by way of the mixture rules.

This would actually be the systematically most desirable approach; however as SID information on the autoxidation products in the report is scarce, formulating an appropriate entry may be difficult. In addition suppliers may fail to realize that such an additional entry relates to their substance.

2) Listing the substance in Annex VI as proposed by the DS based on the data of the oxidised substance (i.e. classify as Skin Sens. 1A, see specific comments below) and amend the ICI with an appropriate minimum concentration of oxidation products pursuant to Annex VI Section 1.1.1.4 Paragraph 6 of the CLP Regulation, while optionally listing a second entry for the "ideal" (or potentially stabilised) substance.

This would actually be not entirely formally correct, as the oxidisation products are strictly speaking not regarded as impurities, however it would reflect the contribution of the peroxides to the classification.

3) Listing the substance in Annex VI as proposed by the DS based on the data of the non-oxidised substance (i.e. classify as Skin Sens. 1B, see specific comments below) and add nota D pursuant to Annex VI Section 1.1.3.1 of the CLP Regulation, while optionally listing a second entry for the "non-stabilised" substance (i.e. Skin Sens. 1A) or the oxidisation products (again relying on the summation method)

*)https://echa.europa.eu/documents/10162/13626/clh_impurities_purity_en.pdf/cc0406ba-2e6c-4ee0-3082-2b2b3f123ee4
§)Pursuant to Annex VI Section 1.1.1.4 Paragraph 2 of Regulation (EG) 1272/2008 (CLP Regulation), regarding the international chemical Identification in Annex VI, "[i]mpurities, additives and minor components are normally not mentioned unless they contribute significantly to the classification of the substance."
#)Regulation (EC) 1907/2006, Annex V Number 1.

Dossier Submitter's Response

Thank you for your comments. It is agreed CLP should deal with the substance itself rather than any impurities or substances that result from chemical reactions by incidental contact with e.g. air or water. However, in this case, alpha-terpinene will be exposed to air (many applications in consumer products etc.) and auto-oxidation occurs very rapidly. In this specific case, because of the rapid formation of the auto-oxidation products, it is not considered an "incidental" reaction. Therefore this process is inherent to the substance and should be considered for classification of the substance itself. In a similar way we also classify parent chemicals when the metabolites formed are responsible for the effects observed and not the parent. The combined information on sensitisation in animals, uvcb substances containing alpha-terpinene causing allergic reactions in humans and rapid auto-oxidation, warrants classification of alpha-terpinene as Skin Sens. 1A.
We believe option 1 proposed will likely not yield a proper classification of alpha-terpinene in practice because the auto-oxidation products will be formed generally after labelling and it is unlikely some kind of quality control will be performed during the lifetime of the product. In a similar way, option 2 is interesting, but in practice the mixtures will likely be classified as Skin Sens. 1B because of the initial concentration of alpha-terpinene regardless of the time that it has been exposed to air. Option 3 is also possible and could be supported by the DS when an additional entry for the non-stabilized product as Skin Sens. 1A is possible. However only if stabilization of the product can be demonstrated because this may be difficult in practice. Therefore we would prefer that the compound is labelled as Skin Sens. 1A instead of adding note D, where the supplier only has to mention that the product is not-stabilized (if applicable) in combination with Skin. Sens. 1B. In practice we think that stabilization of alpha-terpinene will be difficult unless used in high volumes (not possible for consumer products) and combined with stabilizing agents because of the rapid auto-oxidation. In summary, we would prefer to classify the substance itself as Skin. Sens. 1A.

RAC's response

Thank you for your comment.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Belgium	Procter & Gamble	Company-Downstream user	8

Comment received

We do not support the proposal for a harmonized classification of p-mentha-1,3-diene / alpha-terpinene (CAS#: 99-86-5; EC#: 202-795-1), as a Repr. 2 H361 (CMR 2).
The effect claimed by the CLH dossier submitter to be indicative of reproductive toxicity is instead an experimental artefact. The dossier submitter asserts that the discrepancy between sperm positive and pregnant females in the high dose is the result of whole-litter loss produced by the compound in the one published developmental toxicity study. However, administration of the compound did not begin until gestation day 6, when implantation occurs in the rat fetus. Therefore, had the animals that were sperm positive

actually been pregnant, they would have left evidence in the form of implantation scars on the uterine wall. These can sometimes be difficult to observe when resorption occurs very early; however, the authors of the report indicate that they used the Salewski method (ammonium sulfide detection) to enhance detection of implantation sites. This method has been shown to be sensitive for observing implantation loss even when it is induced on gestation day 6 in the rat (e.g., Narotsky et al., 1997, Teratology 56: 252-261). The fact that the authors of the alpha-terpinene study saw no evidence of implantation despite using the Salewski technique leads to a much more likely explanation of the results: the sperm-positive animals were not pregnant at any time, an effect that is attributable to animal husbandry, not the test compound.
The description of the mating procedure used in the study indicated that females were placed with males for two hours and then checked for sperm in the vaginal smear. There is no indication that the animals were checked to determine whether they were in estrus/proestrus at the time of mating. Therefore, it is entirely possible that the animals were incapable of pregnancy because they were cohabited during the wrong phase of the estrus cycle. While females are generally not receptive to copulation when they are not in estrus, this is not a rigid rule of animal behavior, and a female in close quarters (i.e., a small cage) with a male may not be impervious to copulation. Furthermore, it is also worth noting that the body weights of the high dose females were different from the other groups at the start of the experiment. While the difference is small, it could have affected fertility, again in a manner that is not related to treatment.
In summary, there is no evidence that alpha-terpinene caused whole litter loss, and therefore the proposal for any classification as a reproductive toxicant is inappropriate.

Dossier Submitter's Response

Thank you for your comments. The study authors state the following: "The ratio of pregnant (i.e. rats with implantation sites detected by the method of Salewski at term)/sperm-positive treated dam was reduced at 250 mg/kg bw/day". IND suggests that the observed reduction might be due to true non-pregnancy (no implantations to begin with) rather than total litter loss, since dosing started at day 6 and implantation scars should have been visible based on the staining method used. The dossier submitter believes this is unlikely because the chance this only applies to the high dose group is very small. It would be expected that non-pregnant females without implantation sites to begin with would be evenly distributed over the groups.
The lower maternal body weight of high-dose females is not expected to have any effect on this reproduction parameter since it was <10% and a feed restriction resulting in <10% body weight loss was shown not to have an impact on reproduction (Fleeman et al 2005). Therefore, the dossier submitter remains of the opinion that the lowered ratio of pregnant/sperm positive rats warrants classification as Repr. 2 H361 for alpha-terpinene.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	9

Comment received

Reproductive/Developmental toxicity

The RMS proposes to classify the substance as Repr. Tox 2 (H361: suspected to damaging fertility or the unborn child). The lead registrant does not agree with this conclusion for the following reasons:
1. The conclusion on developmental toxic effects is based on an OECD 414 study reported

in the literature, which even according to the RMS has massive limitations, lack in important information and raises doubts in the interpretation of the findings noted.
2. The effects considered critical by the RMS (significant reduction of the ratio of pregnant/sperm positive females) were noted in the high dose group, in which a massive reduction of weight gain during gestation (6-11 day: -17.8 versus +13.6 in controls) was noted (Table 14 of the CHL report). In addition, the massive reduced weight gain is according to the study authors due to systemic toxicity and obviously not due to reduced feed consumption as no information in the report is given, that the feed consumption was affected by the treatment. Thus, the argument of the RMS, that feed restriction (which is not equivalent to systemic toxic effects) causing body weight loss of 10% from day 6-9 and 5 % from day 9-12 does not result in a reduction of pregnant females, is of no relevance for this study. In addition, the effects noted in the high dose group were significant higher. Effects in the offspring noted as such massive systemic toxic doses in dams should not be taken into account for classification and labelling. The RMS also concluded, that it cannot be excluded that the observed maternal reproductive effects are secondary to general maternal toxicity.
The RMS also concluded with regard to the reduction of the ratio pregnant/sperm positive females "as it is unclear whether this effect is on the ability to get pregnant, on implantation or on development; it is unclear whether H361f or H361d would be appropriate. Therefore, H361 without further specification of the effect is proposed." This conclusion however ignores, that in the high dose group other significant signs of general toxicity in the offspring due to malnutrition by the dams (e.g. reduced foetal body weight and delayed ossification) and no effects on implantation sites (as also stated by the RMS) are noted. Taken together, this clearly indicates developmental toxic effects caused by the maternal toxicity of the test item at the high dose. See also point 5.
3. In addition, the absence of reduction in implantations per pregnant female indicate that the critical finding (see 2.) is caused by whole litter loss. Thus, it would be important to check the body weight development of these specific dams in detail to assess the health status, which is not possible.
4. According to the most recent OECD 414 guideline (June 25, 2018) the highest test dose should aim "to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight)". No classification and labelling relevant findings were noted at 125 mg/kg bw/day, at which clear signs of systemic toxicity evident in a clear reduction in body weight gain in dams during gestation is reported (Table 14 in the CLH report). The RMS also concludes that the NOAEL for systemic toxicity is 60 m/kg bw/day and for developmental toxicity 125 mg/kg bw/day.
5. A second developmental toxicity study according to OECD 414 with a mixture containing 38.5% alpha-terpinene does not reveal any indication for developmental toxicity up to 240 mg/kg bw/day (equal to 93.1 mg/kg bw/day alpha-terpinene).
6. QSAR modelling (DEREK) does not indicate any alerts with regard to reproductive toxicity.

In summary:
Based on a weight of evidence approach considering both OECD 414 studies together and in line with the CLP criteria, the conclusion should be drawn that alpha-terpinene does not qualify for a classification as reproductive/developmental toxic substance.
This conclusion is based on the fact, that the substance if tested a systemically toxic doses fulfilling the criteria of the respective OECD guideline for the highest test dose does not cause effects triggering classification. The effects noted at the highest test dose noted in one study should be ignored, as those are very likely of secondary nature caused by the massive systemic toxicity in the dams and are therefore not relevant according to the CLP criteria.
Thus, no classification with regard to reproductive/developmental toxicity should be

proposed.

In addition, it should be noted that the conclusion is anyhow drawn from a study with significant limitation and weaknesses. Thus, if one is still concerned about the effects noted at the massive systemic toxic doses, the more appropriate approach would be to request a third state of the art OECD 414 study before draw any conclusion with regard to reproductive/developmental toxicity on a more than questionable basis.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Derek report_99-86-5-alpha terpinene_20180620.pdf

Dossier Submitter's Response

Thank you for your comments.
In response to (1), the study may have limitations, but was considered sufficiently reliable (klimisch score of 2) and should thus not be ignored.
2. The dossier submitter does not agree that the feed restriction study (Fleeman et al. 2005), indicating that a 10% reduction of maternal weight loss does not affect the reproduction, is not relevant. The registrant refers to massive reduction in body weight gain being obvious a result of maternal toxicity. However, the dossier submitter considers that reduced body weight gain is of minor importance compared to total body weight loss at GD20, which was <10% and therefore unlikely to have impacted the developing foetuses. Overall, the dossier submitter does not believe there was overt general maternal toxicity that may have had a significant and observable effect on the developing offspring.
3. This information may indeed have been helpful, but the dossier submitter does not believe there is high maternal toxicity and therefore considers it unlikely a few dams will have had a high significant body weight loss (significant maternal toxicity) resulting in the variations in the foetuses. Further, the variations were considered of minor toxicological relevance and the proposed classification is not based on these effects.
4. As mentioned with (2), the reduction in body weight gain (absolute) is not as relevant as the overall reduction of the (absolute, relative and corrected) body weight, which was below 10%. The significance of the effect indicates a lower body weight gain and thus "maternal toxicity" but this has not likely impacted the reproduction.
5. The maximum dose of alpha-terpinene in the developmental toxicity study with the mixture (i.e. 93.1 mg/kg bw/d alpha-terpinene) was a factor of 2.4 below the effective dose level of 250 mg/kg bw/d in the study of Anonymous (1996), therefore these studies do not conflict as also mentioned in the CLH proposal.
6. QSAR modelling is informative as it can support read-across hypotheses/analogue approaches and/or indicate potential effects and prioritise efforts for further investigation. It should however not be used to exclude effects.
Overall, the lower ratio of pregnant females vs sperm positive females is considered to warrant classification as Repr. 2 H361

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	United Kingdom	Givaudan UK Limited	Company-Downstream user	10

Comment received

Givaudan has carefully evaluated the CLH Report (Ref 1) and respectfully disagrees with the interpretation and conclusion in this report regarding reproductive and developmental toxicity. The main reasons for disagreement are listed below.

A. There is no standard regulatory-required study available to reliably evaluate the reproductive and developmental toxicity of TER. The study cited (Anonymous 1996, ref 2) is not a GLP study and therefore the repeatability and reproducibility of the results cannot be fully assessed in a regulatory frame-work. This study lacks the quality to meet the standard generally required by the authority from a chemical registrant. From the peer reviewed publication it was also not clear if the authors followed the appropriate OECD guideline (OECD 414) to conduct a developmental study. Moreover the RMS in this CLH report has identified many weaknesses which points to the poor quality of data and information. A few of the statements from the CLH report indicating the lack of reliability of the study for regulatory purposes are cited below.

"The publication lacks key information which could be used to better understand the reasons for the apparent increase in occurrence of these altered areas of ossification."….." but unfortunately no litter based information is reported". " In addition, there is no information provided for the range of normal variation in frequency of occurrence in control foetuses (i.e. historical control data)". .." However, additional data is needed to confirm the (absence of) observed effects."…"However, again, the publication lacks information for better understanding the altered/delayed ossification."…." Although the study lacks some key information, clear maternal and developmental toxicity is observed."

In spite of a) so many weaknesses as identified by RIVM, b) the study being non-GLP and c) the study not following standard OECD guideline, a Klimisch (K) score of 2 was nonetheless assigned to this study.
B. The data presented in this peer reviewed publication lacks clarity from many aspects. No information was provided for the range of normal variation in frequency of occurrence in control foetus. In other words, the historical control data is not provided in this publication. No litter based information is available in this report to correlate with overall growth and development of the foetus. The possible cause for delayed ossification has not been provided in this publication. No possible explanation is provided for effect, reduction of the ratio of pregnant/sperm-positive females, for which the repro classification is recommended.
C. On ossification, we agree with the RMS conclusion that the effects are transient and not adverse. The RMS clearly states that the retarded ossification and foetal body weight reduction are associated with the observed maternal toxicity (a maternal weight gain during whole pregnancy and a significant reduction in total pregnancy weight gain minus gravid uterus weight was also found at 125 and 250 mg/kg bw). The CLH report also states that "changes in ossification are too minimal to be considered indicative of developmental toxicity per se, i.e., they are of no toxicological significance". The delayed-ossification effects are not specific to any developmental toxicity but to severe maternal toxicity. It is interesting to note that in one hand the RMS links ossification to maternal toxicity whereas, the reduction of the ratio of pregnant/ sperm-positive females (discussed later) is not associated with maternal toxicity without proper biological explanation.
D. The 'reduction of the ratio of pregnant/sperm-positive females' highest treatment group, 250 mg/kg bw is the only toxicity end point considered to be significant for classification. It is interesting to note that only 56% (15 out of 27) of the females were found to be pregnant. The absence of a reduction in implantations per pregnant female suggests that this is probably caused by whole litter loss (Anonymous 1996, ref 2). Those females that had litter did not display any sign of reproductive effect. There was no effect on Corpora lutea, # of implantation site/litter, resorption/implantation, live foetuses per litter and sex ratios. Lack of effects to the corpora lutea in dam and sex ratio in foetuses indicates that the hormonal mechanism responsible for reproduction was not impacted by

the exposure. At the highest concentration of 250 mg/kg bw the number of live foetuses per litter was not impacted, indicating TER did not impact the mean number of implantations sites/pregnant dam or the survival of the foetuses in pregnant dams. Therefore TER seems to have caused whole-litter and not intra-litter individual losses. The original authors (Anonymous 1996, ref 2) have concluded that the TER induced whole-litter peri-implantation losses are a maternally mediated effect. It is not clear why TER would cause peri-implantation losses in some and not in others at the highest concentration tested. Moreover no biological explanation is provided in the original publication or CLH report for this unusual observation. Also, there is no corroborative information that would point to potential developmental effects. The RMS's proposal for a category 2 classification without a proper Weight-of-Evidence analysis and not considering the overall quality of the available data is surprising. As cited in the peer reviewed paper, it is important to mention that Citral, an acyclic monoterpene has also been reported to cause similar early whole-litter losses in pregnant rats. However, even after going through a full CoRAP evaluation, Citral was not deemed to need a classification as a reproductive toxicant. Except for this unusual early effect on implantation only found in high concentration triggering maternal toxicity, no other indication of TER-induced embryo-lethality was observed in any concentrations tested.

E. The CLH report seems to have contradictory observations and statements. In section 4.11.5 it has been mentioned that "it cannot be excluded that the observed maternal reproductive effects are secondary to general maternal toxicity". This means there are possibilities that the observed maternal toxicity can contribute to the observed maternal reproductive effect. However in the concluding statement it is mentioned that "adverse effects on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects". It has been not clarified what are the 'other toxic effects' that is indicated here. "The other toxic effects" mentioned were not reported and a proper discussion on their relevance with regards to their impact on the reproduction effects observed can-not be elaborated. As presented, it is only a speculative statement, and no argument is provided to support the assumption made that the effects on reproduction were not secondary to maternal toxicity.

F. According to REACH regulation guidance for reproductive toxicity classification the reproductive toxicity effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects. However in this case, the rare occurrence of reduction of the ratio of pregnant/sperm-positive females' at only highest treatment group which caused overt maternal toxicity should be considered as a secondary effect to maternal toxicity.

Based on above weight-of-evidence analysis, it can be concluded that TER does not qualify classification for reproduction as the maternal reproductive effects are observed at only the highest test concentration which is secondary to the overt maternal toxicity.

Dossier Submitter's Response

Thank you for your comments. Please view our response to comment no 9 as it should address most of your comments.

We would like to note that we did indicate that the delayed ossification was transient and limited. We do think the maternal toxicity cannot be considered "overt" and is actually rather limited. The total weight reduction at GD20 does not likely have an influence on the developing foetuses as is indicated by feed restriction studies (Freeman et al 2005). Therefore, the limited ossification is more likely to be attributed to the treatment even though it may not be considered adverse or of toxicological concern. As mentioned, the proposed classification is based on the lower ratio of pregnant vs sperm positive females.

RAC's response
Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	United States	Bayer AG	Company-Manufacturer	11
Comment received				
We disagree with the classification of alpha-terpinene as it relates to the QRD 460 active substance and the data available. See attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Rclass_420substance (003).pdf				
Dossier Submitter's Response				
With regards to the toxic effect of the mixture, please see our response to comment 4. As suggested we have already included information on the mixture for reproductive toxicity in the CLH proposal, which is the only CMR endpoint proposed for classification. The studies with the mixture do not indicate any adverse effects on reproduction. However, the individual component alpha-terpinene, was present at a lower concentration compared to the positive results with the single substance alpha-terpinene. The maximum dose of alpha-terpinene in the developmental toxicity study with the mixture (i.e. 93.1 mg/kg bw/d a-terpinene) was a factor of 2.4 below the effective dose level of 250 mg/kg bw/d in the study of Anonymous (1996), therefore these studies do not conflict as also mentioned in the CLH proposal. Therefore the dossier submitter remains of the opinion that classification as Repr. 2 is warranted.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	United States	Bayer AG	Company-Manufacturer	12
Comment received				
We disagree with this classification of alpha-terpinene and provide an attachment outlining our position and supporting data. ECHA note – An attachment was submitted with the comment above. Refer to public attachment alpha_Rdoc_final (002).pdf				
Dossier Submitter's Response				
See our response to comment 4 and 11				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2018	Spain	<confidential>	Company-Manufacturer	13
Comment received				
The CLH report bases its proposal for the classification for Toxicity to Reproduction Category 2 (H361) on the reduction in the ratio of pregnant/sperm positive females observed in the embryo toxicity test of alpha-terpinene performed by Araujo et. al., 1996.				

Alpha-terpinene (30, 60, 125 and 250 mg/kg body weight) in corn oil was given by gavage to female Wistar rats from day 6 to 15 of pregnancy. Caesarean sections were performed on day 21 of pregnancy. A reduction in body weight minus uterine weight at term indicated that the two highest doses tested (125 and 250mg/kg body weight orally) were maternally toxic. The highest dose of 250 mg/kg body weight reduced the ratio of pregnant/treated female.
It should be taken into account that marked reductions in overall pregnancy weight gain minus uterine weight at term clearly indicate that the two highest doses of 125 and 250 mg/kg body weight are maternally toxic. The significant reduction of the ratio of pregnant/ sperm-positive females was only observed at the highest dose tested, i.e. it is unclear whether the decrease in pregnant females is secondary to the maternal toxicity. As there are no repeated dose toxicity studies which could indicate more specific effects, it cannot be excluded that alpha-terpinene also induces other maternal effects that were not determined in this developmental study. Therefore, it cannot be excluded that the observed maternal reproductive effects are secondary to general maternal toxicity.
The CLP Regulation (EC) no. 1272/2008 clearly states that the effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.
In the present case, there is no evidence that alpha-terpinene has teratogenic or embryotoxic effects in the absence of maternal toxicity and thus, the classification for Toxicity to Reproduction should not be warranted.
Similar effects have been observed with the analogue substance d-Limonene.
In rats, the oral administration of d-limonene (2,869 mg/kg body weight per day) on days 9-15 of gestation resulted in decreased body weight and deaths among the dams. Delayed ossification and decreased total body and organ weights (thymus, spleen, and ovary) were observed in the offspring (Tsuji et al., 1975). In mice, the oral administration of d-limonene (2,869 mg/kg body weight per day) on days 7-12 of gestation resulted in reduced growth in the mothers and a significantly increased incidence of skeletal anomalies and delayed ossification in the offspring (Kodama et al., 1977a). The oral administration of d-limonene (250, 500, or 1,000 mg/kg body weight per day) to rabbits on days 6–18 of gestation had no dose-related effects on the offspring. At the highest dose, there were some deaths and reduced weight gain among the dams; at the intermediate dose, growth was decreased (Kodama et al., 1977b).
The CICAD on Limonene (WHO, 1998) stated that there is no evidence that limonene has teratogenic or embryotoxic effects in the absence of maternal toxicity, concluding that the substance is essentially non-toxic for human health hazards.
Moreover, the European Food Safety Authority made a review of the toxicological properties of d-limonene in 2010, and concluded on the absence of safety concern due to d-limonene intake, with no specific concern related to the absence of any study for toxicity to reproduction for this substance (EFSA, 2010).

Araujo, IB., et al. Study of the embryofoetotoxicity of alpha-terpinene in the rat. Food Chem Toxicol. 1996 May;34(5):477-82.
Tsuji, M., Y. Fujisaki, Y. Arikawa et al. 1975. Studies on d-limonene as a gallstone solubilizer. (III). Chronic toxicity in rats. Oyo Yakuri. 9(3): 403-412.
Kodama, R., A. Okubo, E. Araki, K. Noda, H. Ide, and T. Ikeda. 1977a. Studies on d-limonene as a gallstone solubilizer. (VII). Effects on development of mouse fetuses and offsprings. Oyo Yakuri. 13(6): 863-873.
Kodama, R., A. Okubo, K. Sato et al. 1977b. Studies on d-limonene as a gallstone solubilizer. (IX). Effects on development of mouse fetuses and offsprings. Oyo Yakuri. 13(6): 885-898.

WHO, 1998. Concise International Chemical Assessment Document 5 (CICAD). Limonene. WHO, Geneva 1998.
EFSA, 2010. Scientific Opinion on Flavouring Group Evaluation 25Rev1: Aliphatic and aromatic hydrocarbons from chemical group 31. EFSA Journal 2010; 8(5): 1334

Dossier Submitter's Response

Thank you for your comments. We believe the comments regarding alpha-terpinene have been addressed in our responses to comments 8-11.
Regarding the studies with d-limonene. They do not indicate as clearly reproductive effects as compared to alpha-terpinene. Most importantly, effects are only observed at doses far above the limit dose.
The effects observed with alpha-terpinene may be attributable to development or fertility, therefore subcategory d or f was not proposed as mentioned in the report. It is acknowledged that the observed effect cannot be considered as an effect on the ability to get pregnant because exposure was not started before of the start of gestation. However, it is not clear whether this effect is on the implantation or on development, therefore H361 is still proposed.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	14

Comment received

The German CA supports the classification proposed for alpha-terpinene for reproductive toxicity as Repr. 2.
The classification based on the adverse effect: reduction of the ratio of pregnant/spermpositive females, observed in the developmental toxicity study in rat. This effect occurs in the presence of maternal toxicity, namely reduced body weight gain during treatment and during the whole pregnancy. In addition to statistical significant reduction in total pregnancy weight minus gravid uterus weight. Because the adverse effect on reproduction take place before the body weight gain reduction is established, we support the hypothesis, that the effect is considered not a secondary non-specific consequence of the decreased body weight gain. Furthermore the dam show no distinct maternal toxicity, with a maximal body weight loss of approximately 10% (day 6-9), and no other signs of toxicity or even mortality.

The teratogenicity study however is not appropriate for assessing the question of toxic effects on fertility because the substance is administered after fertilization, i.e. GD 6-15. For this, a one-gen, two-gen and/or extended one-gen study is required. As a consequence, nothing can be concluded regarding fertility, so H361 is not supported.

However, the appropriate hazard statement may be H361d (Suspected of damaging the unborn child) rather than H361

Dossier Submitter's Response

Thank you for your support. The effects observed with alpha-terpinene may be attributable to development or fertility, therefore subcategory d or f was not proposed as mentioned in the report. It is acknowledged that the observed effect cannot be considered as an effect on the ability to get pregnant, as exposure did not start before the start of gestation. However, it is not clear whether this effect is on the implantation or on development, therefore H361 is still proposed.

RAC's response
Thank you for your comment.

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 your support.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	16
Comment received				
The lead registrant supports the conclusion in the CLH report, that no classification and labelling is required for acute dermal and inhalation toxicity. However, based on the data presented in the dossier (LD50 = 1680 mg/kg bw/day) derived from the study report, acute tox. 4 (H302, harmful if swallowed) is warranted. The RMS was aware of this result, but did not conclude on classification and labelling, as no details and only secondary sources were available for his assessment. Considering the new information available, the substance should be classified and labelled as Acute Tox . 4 (H302, harmful is swallowed). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Derek report_99-86-5-alpha terpinene_20180620.pdf				
Dossier Submitter's Response				
Thank you for your comments. In the registration dossier a study summary of an oral acute toxicity study, also referred to in the classification proposal, has been provided. The dossier submitter did not have access to the study, when preparing the CLH-dossier (although a request was made), and was unable to verify the contents and reliability of the study. The study summary describes that the study was considered reliable with restriction (klimisch score of 2) and similar to OECD 401. Ten rats/dose group (strain and sex not specified) were exposed to a single dose of 1050, 1310, 1640, 2050 or 5000 mg/kg bw alpha-terpinene (purity 94.1%) by gavage. A 14 day observational period was included after the treatment. Mortality was observed on day 1, where 4, 1, 3 and 8 rats died at 1310, 1640, 2050 and 5000 mg/kg bw, respectively. On the second day, 2, 4 and remaining 2 rats died at 1640, 2050 and 5000 mg/kg bw, respectively. A single rat died at 1640 on day 4 and on day 10 at 2050 mg/kg bw. Therefore within the 14 day observation period, 4/10, 4/10, 6/10 and 10/10 rats died at 1310, 1640, 2050 and 5000 mg/kg bw, respectively. An LD_{50} of 1680 mg/kg bw (95% confidence interval 1460-1900 mg/kg bw) was calculated. No clinical findings and deaths occurred in the lowest tested dose group (1050 mg/kg bw). Lethargy was observed on the day of dosing in rats dosed at 1310, 1640, 2050 and 5000 mg/kg bw. The rats dosed at 2050 and 5000 mg/kg bw exhibited loss of righting reflex and piloerection.				

Though the original study report is still not available to the DS, the data presented in the registration dossier support a classification as Acute. Tox. 4 - H302.
RAC's response
Thank you for the comments. Taking into account the data presented in the registration dossier, the classification as Acute. Tox. 4; H302 is justified.

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2018	Spain	<confidential>	Company-Manufacturer	17
Comment received				
Acute oral toxicity: According to the REACH Registration dossier an Acute Oral Toxicity test is available on alpha-terpinene. Ten rats per dose were exposed to 1.05, 1.31, 1.64, 2.05 and 5 g/kg test item by gavage. The animals were observed for 14 days. No clinical findings and deaths occurred in the lowest tested dose (1.05 g/kg). Lethargy was observed on the day of dosing in rats dosed at 1.31, 1.64, 2.05 and 5 g/kg. The rats dosed at 2.05 and 5 g/kg exhibited loss of righting reflex and piloerection. The exposure to the middle doses (1.31 and 1.64 g/kg) caused 40% of death. 80% of death animals were found at 2.05 g/kg within 10 days after a single exposure. The highest dose caused 100% of death. Based on the results, the LD50 was calculated to be 1.68 g/kg (1.46 - 1.90). According to the CLP Regulation (EC) no. 1272/2008, alpha-terpinene should be classified for Acute Oral Toxicity Category 4 (H302) since the obtained LD50 is between 300 and 2000 mg/kg bw.				
Dossier Submitter's Response				
Thank you for your comment. See also our response to comment 16				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2018	Spain	<confidential>	Company-Manufacturer	18
Comment received				
According to the CLH report, three LLNA studies investigating the sensitizing potential of alpha-terpinene in mice reported EC3 values of 8.9, 0.9 and 1% w/v (alpha-terpinene, three weeks air-exposed oxidized alpha-terpinene, and seven weeks air-exposed oxidized alpha-terpinene, respectively). The CLH report takes into account the result obtained with the oxidized alpha-terpinene for classification purposes. The report states that given that the results of the LLNA showed an EC3-value of 0.9% for alpha-terpinene containing autoxidation products, classification as Skin Sensitizer Category 1A (H317) is warranted. Nevertheless, although chemical analysis showed that alpha-terpinene degrades rapidly forming oxidation products upon exposure to air, there is no information whether the test material as used in the skin sensitization study can be considered representative for the compound marketed in the EU. In fact, in 2015, the RAC concluded for Linalool, that exposure to its form was not relevant considering its current use and classification was therefore based on the compound linalool only. It was the opinion of RAC that skin sensitisation to humans to either stabilised or non-stabilised linalool was limited. RAC recognised that there were no				

animal studies available on stabilised linalool which appears to be the predominant form of the substance on the market in the EU. While, there was no reaction in the FCAT test with non-stabilized linalool, RAC considers on balance the results from the animal study with non-stabilised, purified linalool to be appropriate for the purposes of classification. In the present case, based on one valid animal study (LLNA) with an appropriate sample of alpha-terpinene for which the estimated concentration (EC) required to induce a stimulation index (SI) of 3 (EC3) was 8.9% w/v, it could be concluded that the substance should be classified as Skin Sensitizer Category 1B (H317) according to the CLP Regulation (EC) no. 1272/2008.
Dossier Submitter's Response
Thank you for your comment. RAC considered the auto-oxidized products of linalool were not very representative of the marketed products because they were shown to have fewer than 2% of oxidized products while the experiments were performed with up to 19% of oxidized linalool. Further they considered that neither stabilized linalool, nor unstabilized linalool would reach such high concentration. The dossier submitter has reviewed the case of linalool and considers it not applicable to alpha-terpinene for the following reasons: - Alpha-terpinene has a significant higher auto-oxidation rate. In the skin sensitisation experiments performed, alpha-terpinene is oxidized for about 50% within 10 **days.** In contrast, less than 25% of the linalool is oxidized after 10 **weeks** of air exposure (Sköld *et al*., 2004, CLH report & RAC opinion of linalool, 2015). The alpha-terpinene present in products on the market will therefore likely contain a significant level of auto-oxidated alpha-terpinene. - The commercial product with linalool was stated to may or may not contain a stabilizer, which is not known to be the case for alpha-terpinene. It was also demonstrated that the auto-oxidation of linalool was significantly reduced in the presence of a stabilizer, which is also not the case for alpha-terpinene. Anti-oxidants may be added to stabilize/slow down the auto-oxidation of alpha-terpinene in a similar way as with linalool. However, the auto-oxidation rate of alpha-terpinene is many fold faster and therefore added anti-oxidants will have a more limited impact as compared to stabilization of linalool. Stabilization with anti-oxidants is also (time) limited since these will oxidize over time and deplete. - The skin-sensitisation potential of alpha-terpinene does not increase much after 3 months of air exposure considering that the EC3 of these products do not differ (0.9 vs 1%). It is uncertain how much air-exposure is required to obtain sufficient reactions applicable for classification in category 1A (EC3 below 2%). 75% auto-oxidized alpha-terpinene (3-months air exposed) resulted in an EC3 of 1%. Although speculative, it is reasonable to assume that fewer than 50% auto-oxidized alpha terpinene will already cause EC3s below 2% that would be sufficient for classification as Skin Sens. 1A. Tea trea oil with a likely lower percentage of alpha-terpinene (oxidation products) was able to illicit reactions in humans. Overall, the auto-oxidation is fast and therefore should be considered an inherent property of alpha-terpinene. The auto-oxidation rate cannot be considered limited in terms of the CLP-regulation (see also our response to comment 7) and should therefore be considered for the classification of alpha-terpinene in this case. - In another classification proposal for d-limonene as Skin Sens. 1B, the DS follows the reasoning for the case of linalool because the rate of oxidation is not as clear and certainly slower as compared to alpha-terpinene. The EC3 seen with the animal experiments is higher (>22% for the non-oxidised substance, compared to 9% for alpha-terpinene, although in both cases it is likely some auto-oxidation has occurred before treatment). Overall it is less likely significant auto-oxidation

products will be formed compared to alpha-terpinene and stabilization may be easier.

Considering the above and the human data with tea-tree oil, it is reasonable to assume that commercial products will be able to reach sufficient auto-oxidized fractions of alpha-terpinene to illicit strong sensitising reactions in humans. Auto-oxidation occurs rapidly in air exposed alpha-terpinene and in UVCB substances containing alpha-terpinene. Products containing alpha-terpinene such as tea-tree oil have been shown to illicit strong reactions in humans, although it cannot be excluded that other components may have contributed to the effect. It is considered highly likely that the alpha-terpinene marketed in the EU is subject to sufficient autoxidation upon exposure to air that will be able to cause skin sensitisation reactions justifying Skin Sens. 1A.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	19

Comment received

Skin sensitisation

The lead registrant, does not agree to the proposal by the RMS to classify the substance as Skin Sens. 1A (H317, may cause an allergic skin reaction), but considers Skin Sens. 1B as more appropriate for the following reasons:
1. The substance revealed in a LLNA an EC3 of 8.9%, thus being well above the trigger value of 2 % for sub-category 1A.
2. The EC3 values (0.9 and 1) obtained with artificially and to a high degree oxidised and decomposed material with 53 % and 21% remaining alpha-terpinene, respectively are not considered relevant for the classification and labelling of the substance, for which a specification ≥ 90% is defined in the REACH dossier and to be guaranteed within the supply chain. The substance tested in this assay is not the substance registered under REACH and therefore those results are not representative for the substance. In addition, the results with this mixture also show, that a massive oxidiation is needed to obtain EC 3 values below the trigger value of 2.
The relevance of the sensitisation potential of products containing high concentrations of oxidation products was already assessed by the RAC for other substances. In 2015, the RAC concluded for Linalool, that exposure to its oxidised form was not relevant considering its current use and classification was therefore based on the compound linalool only.

Based on the above consideration a classification and labelling, as Skin Sens. 1B (H317, may cause an allergic skin reaction) is warranted.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Derek report_99-86-5-alpha terpinene_20180620.pdf

Dossier Submitter's Response

Thank you for your comments. Please also view our response to comment 18.
Indeed a high auto-oxidation level may be required to result in an EC3 value below 2%. However, because of the rapid auto-oxidation of alpha-terpinene it is reasonable to assume such auto-oxidation levels will be reached in practice. It can certainly not be excluded based on the available information. We would be quite interested in data demonstrating that alpha-terpinene does not auto-oxidize significantly in some products

(for example with stabilizers) if that would be achievable. It is considered likely that the overall auto-oxidation rate can be slowed down significantly when stabilized with additives and when present in very large volumes with a minimum exposure surface to air. However, we think that in practice such situations will not apply to general consumer products or UVCBs where alpha-terpinene can be present in quite large fractions. Because we consider exposure to significant amounts of auto-oxidized alpha-terpinene likely when using products with alpha-terpinene, while significant exposure cannot be excluded, classification as Skin Sens. 1A is warranted for alpha-terpinene.
RAC's response
Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	20
Comment received				
Three LLNA studies investigating the sensitizing potential of alpha-terpinene in mice reported EC3 values of 8.9% (pure, unoxidized alpha-terpinene) 0.9% (three weeks air-exposed oxidized alpha-terpinene) and 1% (seven weeks air-exposed alpha-terpinene). The EC3 values show that the pure (unoxidized) alpha-terpinene (EC3 value 8.9%) is a moderate sensitizer. The Two EC3 values (0.9%; 1%) of the oxidized alpha-terpinene show, that these degradation products are strong sensitizers and fulfil the criteria for classification as skin sensitizer 1A. Chemical analysis demonstrates that alpha-terpinene degrades forming oxidation products upon exposure to air. The experimental data point towards very fast autoxidation of pure alpha-terpinene. Besides no information is available on the extent of autoxidation upon exposure to air of the commercial product. Additionally it is not known whether autoxidation of alpha-terpinene marketed in the EU is limited by the presence of an additive (antioxidant). For these reasons the DE CA proposes several ways forward in phrasing the actual Annex VI entry (see general comments above).				
Dossier Submitter's Response				
Thank you for your comments. Please view our response to comment 7. In short we think the best way forward is to simply classify the substance alpha-terpinene including the auto-oxidation products (not separately) because it is considered likely that a significant fraction of auto-oxidised components will arise from alpha-terpinene in a product unless it is completely used within a very short period of time, or in high volumes with minimum of air exposure and stabilisation. Significant exposure to the auto-oxidised products cannot be excluded as also explained in response to comment 19.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	France		MemberState	21
Comment received				
FR agrees with the proposed classification				

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

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	22
Comment received				
The German CA supports the classification Aspiration Toxicity Hazard Category 1 (Asp. Tox. 1 H 304), because alpha-terpinene is a hydrocarbon and has a kinematic viscosity of < 7 mm2/s (at 20°C). Therefore, alpha-terpinene is provided in the classification criteria for hazard category aspiration toxicity category 1: kinematic viscosity of < 20.5 mm2/s at 40°C.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	23
Comment received				
Aspiration Hazard The current REACH dossier does not contain information on viscosity and no classification with regard to aspiration hazard was therefore deduced. However, Symrise support the proposal, Asp. Tox. 1 (H304: May be fatal if swallowed and enters airways), based on the data presented in the CLH Report. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Derek report_99-86-5-alpha terpinene_20180620.pdf				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	Germany	Symrise AG	Company-Importer	24
Comment received				
Biodegradation The RMS states, that there are no experimental data on biodegradation for alpha-terpinene and used QSAR to assess the biodegradation. This statement is however not correct. In the submitted dossier available from the ECHA homepage, an OECD 301 F study is reported. In this study it was shown that alpha-terpinene undergoes 40% biodegradation after 28 days under the chosen test conditions which is below the 60%				

required in the guidelines to classify this substance as "readily biodegradable". However, there was 62% degradation after 60 days and 66% degradation at 70 days. As such, alpha-terpinene is inherently and ultimately biodegradable. Thus the experimental findings fit quite well with QSAR data cited in the CLH report.

Aquatic toxicity

Acute aquatic toxicity: proposal H400 in the CLH dossier

The proposal for H400 is triggered by the fact that the RMS had only access to a limited data set for alpha-terpinene and therefore used a read across to D-Limonene as a worst case scenario (based on RMS's own assessment) to assess the acute effects in algae together with QSAR modelling. However, the REACH dossier contains very recent state of the art studies for daphnia and algae. Thus, the read across for the acute effects is not longer needed nor the appropriate approach.

1. For fish the conclusion was drawn, that a LC50 (96 h) value of 3.15 mg/L (EC50 (96 h) = 1.48 mg/L) obtained in study with alpha-terpinene is considered for the C&L proposal. In the QSAR modelling a lower figure (LC50 (96 h) = 1.07 mg/L) was obtained.
2. For invertebrates, a LC50 and EC50 (48 h) for daphnia of 1.85 mg/L was considered in the CLH report based on test data for alpha-terpinene. Another study was considered invalid. The respective QSAR data revealed LC50 values of 0.75 mg/L (48h daphnid) and 0.22 mg/L (96 h mysid)
3. Acute effects in algae and aquatic plants were assessed based on data for D-Limonene as the assessable data for alpha-terpinene were considered invalid by the RMS. In two studies with P. subcapitata ErC50 values of 0.32 and 0.25 mg/L, respectively were reported. The QSAR for alpha-terpinene in contrast resulted in a LC50 value > 1 mg/L (1.31 mg/L).

It should be mentioned, that in cases where experimental data and ECOSAR modelling was available, the QSAR modelling revealed always lower figures, thus slightly overestimating the toxic potential of alpha-terpinene.

Based on the results obtained in the algae studies with D-Limonene showing values of > 0.1 mg/L and < 1mg/L, an aquatic acute 1 (H400, M=1) was deduced in a read across approach for alpha-terpinene.
For all other trophic levels values > 1mg/L were deduced from studies with alpha-terpinene, which do not warrant classification for acute aquatic toxicity.

However, in the context of the REACH registration new state of the art algae and daphnia study were performed.
The results in the new daphnia study revealed an EC50 of 1.7 mg/L, which fits very well to the figure used in the CLH report based on literature data (1.85 mg/L).
In the new algae study a NOEC of 3.7 mg/L and NOEC >3.7 mg/L was obtained, which is in line with QSAR data, that also predicted a value of > 1mg/L. Thus, this trophic level can be properly assessed by experimental findings, which overrule the proposed worst case read across to D-Limonene.

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 mainly experimental data with the worst case read across substance D-Limonene to assess the long-term aquatic toxicity of alpha-terpinene. The new algae study further supports the conclusion that the read across to D-Limonene represents a "conservative" approach. The observed NOEC of 3.7 mg/L for alpha-terpinene is significantly higher than the respective values for D-Limonene (0.14 and 0.174 mg/L) used in the CLH report.

Based on the results for all three trophic levels revealing NOEC values in the range of >0.1 and < 1 mg/L (or even > 1 mg/L for algae based on the new study), alpha-terpinene 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 alpha-terpinene fully supports the approach taken be the RMS. In addition, the new data provided in the REACH dossier further support the assessment that the read across to D-Limonene represent a conservative worst case scenario.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Derek report_99-86-5-alpha terpinene_20180620.pdf

Dossier Submitter's Response

Thank you for your comments.

Biodegradation
A study on biodegradation that has not been considered in the CLH report is indeed available in the REACH dossier. Thank you for pointing this out. The study is reported as a GLP study performed according to OECD guideline 301F. The study tested the degradation of alpha-terpinene with a purity of 94.1% by an inoculum originating from a waste water treatment plant in Switzerland, treating predominantly domestic sewage. The test was performed at 20.8-21.9°C and the pH of the medium was 7.6-8.2. The test lasted 70 days and samples were taken at day 14, 21, 28, 42, 56, 60 and 70 when the theoretical oxygen demand was determined. A toxic control as recommended in the guideline is not performed. The percentage of degradation based on the CO_2 development is given in the table below.

Day	14	21	28	42	56	60	70
% degradation	30	34	40	48	60	62	66

The degradation results indicate that the substance is not rapidly degradable as 60% degradation was not reached within 28 days. The substance is concluded to be inherently and ultimately degradable.
The study is considered reliable and indicates that alpha-terpinene should be considered not rapidly degradable. This result overrules the read-across with d-limonene as performed in the CLH report and should be taken forward for the classification.

Aquatic toxicity
New studies on aquatic toxic to dapnids and algae are indeed available in the REACH dossier.
The daphnid study is a GLP study performed according to OECD guideline 202. The study tested the toxicity of alpha-terpinene with a purity of 92.7% to *Daphnia magna* <24

hours old in standard Elendt M4 medium. The test was performed at 18-22°C and the pH of the medium was 6-9. The test lasted 48 hours. The EC50 from the test is 1.7 mg/L and the endpoint is considered reliable. This endpoint confirms the endpoint for D. magna used in the CLH report.
The algae study is a GLP study performed according to OECD guideline 201. The study tested the toxicity of alpha-terpinene with a purity of 92.7% to *Pseudokirchneriella subcapitata* in the exponential phase. The test was performed at 21-24°C for 72 hours under continuous illumination of approximately 6000 lux. The nominal test concentrations were 0, 0.625, 1.25, 2.5, 5.0 and 10 mg/L, after 72 hours all test concentrations were below the LOQ and the mean measured concentrations were 0.16, 0.47, 1.1, 2.7 and 3.7 mg/L (arithmetic mean, where the concentration at t = 72h is taken a 0 mg/L). No effects were observed up to the highest test concentration and the NOEC is reported as the highest test concentrations. The EC50 for growth rate as well as yield can therefore be considered as higher than 3.7 mg/L. It should be noted that the arithmetic means are an under estimation of the actual exposure concentrations as these should be determined as the time weighted average. Since the test concentrations were only determined at two time points, a dissipation rate cannot be determined. This limits the reliability of the endpoints but they are considered to be sufficient for classification purposes.

Reconsideration of the proposed classification with the new endpoints.
Acute
For the aquatic acute classification new data is available that the EC50 for alpha-terpinene is higher than 1 mg/L. Because of the read-across with d-limonene for acute toxicity to algae becomes obsolete. Since the available endpoints for aquatic acute are all higher than 1 mg/L, a classification for Aquatic acute toxicity is not required.

Chronic
The available NOEC for algae makes the read-across with d-limonene for chronic toxicity to algae obsolete, this new endpoint is higher than 1 mg/L and replaces the key endpoint for the chronic classification in the CLH report. The read-across endpoints for daphnids and fish still remain. The new key endpoint is therefore that of 0.15 mg/L for *D. magna*. The new information on the biodegradability of alpha-terpinene indicated that the substances should be considered as not rapidly degradable. These facts lead to the conclusion that the classification should be Aquatic chronic 2.
It should however be noted that in the public consultation for d-limonene, the endpoints for fish originating from an OECD 212 study is considered insufficient as chronic endpoint. This is because d-limonene has a log Kow higher than 4 indicating that the chronic toxicity is potentially under estimated by this study. If for d-limonene would be concluded that this endpoint is indeed insufficient as chronic endpoint, this would also apply to the read-across. In that case, only the chronic endpoint for d-magna remains for read-across. The surrogate method applied for fish with a critical EC50 of 1.48 mg/L does however also lead to a classification as Aquatic chronic 2, confirming the classification based on the read-across from d-limonene for *D. magna*.

RAC's response

RAC agrees with the DS on the reliability of the data presented in the REACH Registration dossier. Based on this data RAC sees that the classification of alpha-terpinene should be based on the data on the substance itself leading to Aquatic Chronic 2 classification. No read-across from d-limonene is needed.

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2018	United Kingdom	Givaudan UK Limited	Company-Downstream user	25

Comment received

The CLH dossier proposes a harmonised classification of Aquatic Acute 1 (H400: Very toxic to aquatic life), M=1 and Aquatic Chronic 3 (H412: Harmful to aquatic life with long lasting effects).

Givaudan does not agree with the Aquatic Acute 1 proposal. Based on a full acute data set, which has become available following the REACH 2018 deadline, the substance should not be classified for acute hazards. In the absence of chronic toxicity data for alpha terpinene, Givaudan supports the read-across from d-limonene and the Aquatic Chronic 3 classification. A detailed justification for our opinion is provided in the following paragraphs.

Acute Aquatic Hazard:

The proposed Aquatic Acute 1 classification is based on read-across data from d-limonene (acute value for algae 0.15mg/L, page 10 of CLH report). Read-across was used for the algae endpoint because only acute toxicity data for fish and daphnia had been identified for alpha-terpinene in the CLH report (EC50s are 1.48 and 1.85 mg/L respectively, table 29). The CLH report is dated March 2018. A REACH registration dossier for alpha-terpinene was submitted for the 31 May 2018 deadline and become publicly available on the ECHA dissemination site on 04 May 2018. Acute aquatic toxicity data is available for algae and daphnia. The EC50s are respectively > 3.7 and 1.7 mg/L. Both studies are considered reliable (Klimisch 1) having being performed to OECD guidelines under GLP, using a sample of alpha-terpinene that was 92.7% pure and with results based on the geometric mean measured concentrations. The daphnia EC50 result of 1.7mg/L is in agreement with the result of 1.85 mg/L in the CLH report. In the algae study no significant effects were observed at any of the five test concentrations. Thus it can be concluded that the EC50 is greater than the highest test concentration, which is 3.7mg/L based on geometric mean measured concentrations.

Since acute toxicity data now exists for all three trophic levels, read-across to d-limonene is no longer war-ranted. The acute EC50 values for alpha-terpinene are 1.48 (fish, CLH report), 1.7 (daphnia, CLH report), 1.85 (daphnia, REACH dossier) and > 3.7 mg/L (algae, REACH dossier). Since all EC50 values are > 1mg/L, Givaudan considers that alpha-terpinene should not be classified for short-term (acute) aquatic hazards under CLP.

Chronic Aquatic Hazard:

In the absence of chronic toxicity data for alpha terpinene, Givaudan agrees with the proposal to read-across from d-Limonene for the assessment of the long-term (chronic) aquatic hazard. As stated in the CLH report (page 10), the relevant chronic endpoints for fish, daphnia and algae range from 0.14 to 0.32mg/L. This read-across is expected to be conservative and worst-case, based on a comparison of the acute aquatic toxicity data that is available for both substances (e.g. acute EC50s range from 0.15-0.70mg/L for d-limonene (Table 30, CLH report) but only 1.48 to > 3.7mg/L for alpha-terpinene (Table 29 of CLH report and REACH dossier)).

For a rapidly degradable substance, a NOEC or ECx of > 0.1 and ≤ 1mg/L results in a Chronic 3 classification. In the CLH report, alpha-terpinene is considered to be rapidly biodegradable based on read-across from d-limonene (71.4% in 28days, King 1992). As stated in section 5.1.4 of the CLH report, "based on the close structural similarity for both substances, common biodegradation properties and pathways are expected". The read-across in the CLH report was also supported by biodegradation estimates performed with the BIOWIN v4.10 QSAR, which gives comparable results for both d-limonene and alpha-terpinene. Givaudan biodegradation experts agree that alpha-terpinene is expected to be rapidly biodegradable when tested under suitable conditions. However, the biodegradation study available in the REACH dossier for alpha-terpinene was performed at a test concentration (15.2 mg/L) that is above the water solubility of the substance (9.1 mg/L, REACH dossier). This means that the biodegradation rate will be controlled by the dissolution rate. This is indicated by the biodegradation curve which shows a gradual increase in the percentage of biodegra-dation over time; for example 30% (14d), 34% (21d), 40% (28d), 48% (42d) 60% (56d), 62% (60d) and 66% (70d). Since, the 60% pass criteria was not met within the 28 days the substance was considered as not readily but inherently and ultimately biodegradable according to this test. In contrast, the biodegradation test performed on d-Limonene was conducted at a lower test concentration (10 mg/L). This could explain the more rapid degradation of d-Limonene in the sealed CO2 test performed by King (1992) versus the OECD 301F test performed on alpha-terpinene. It should be noted that Givaudan is the data owner of both these biodegradation studies and can provide additional information if required. The importance of the test concentration on the readily biodegradability assessment of this family of monoterpene hydrocarbons, is further supported by data for the structurally similar p-mentha-1,4(8)-diene (REACH dossier, EC 209-578-0) which achieved 81% after 28 days in a 301D test (test conc 2mg/L, water solubility 7.03 mg/L). Taken together as weight-of-evidence, the above information indicates that this family of monoterpenes are readily biodegradable. Thus Givaudan agrees with the RMS proposal of a Chronic 3 Classification for alpha-terpinene based on the substance being expected to be rapidly degradable and chronic aquatic toxicity data for the close structural analogue, d-Limonene.

Dossier Submitter's Response

Thank you for your comments.
New data on biodegradation and acute toxicity to daphnids and algae are indeed available on the public dissemination site of ECHA. These new data are discussed in a response to Comment number 24 and do lead to the conclusion that a classification for aquatic acute toxicity is indeed not required. The new data on biodegradation does however lead to the conclusion that for chronic toxicity, the substance should be classified as aquatic chronic 2.

RAC's response

RAC agrees with the DS on the reliability of the data presented in the REACH Registration dossier. Based on this data RAC sees that the classification of alpha-terpinene should be based on the data on the substance itself leading to Aquatic Chronic 2 classification. No read-across from d-limonene is needed. RAC sees no reason to doubt the validity of the biodegradation study presented in the REACH Registration dossier based on the test substance concentration used in the test.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2018	United Kingdom		MemberState	26
Comment received				

Aquatic Acute classification:
Valid acute endpoints for fish and invertebrates for alpha-terpinene are >1 mg/l. The referenced acute algal QSAR endpoint for alpha-terpinene is also >1 mg/l. We note that the alpha-terpinene acute QSAR endpoints for fish and invertebrates are slightly lower than measured endpoints indicating, if valid, that the QSAR is slightly more precautionary.

The acute classification proposal is based on read-across to the source d-limonene with acute endpoints in the range 0.1-1 mg/l. We note that experimental acute endpoints for d-limonene are <1 mg/l for all trophic levels with algae as the most sensitive. This indicates the read-across approach is more precautionary for fish and invertebrates and of unknown sensitivity for algae. Therefore, please can you provide further details to consider the algal QSAR for alpha-terpinene. This should include whether the model domain is met, presence of structural analogues in the training set, reliability of QSAR model and which fragments are included in the QSAR. This information if required to consider if RAX is relevant for acute classification or if the algal QSAR is adequate for hazard classification. It may be useful to consider available data in the context of ECHA's Read-Across Framework document (2017).

Aquatic chronic classification:
Alpha-terpinene is predicted to partition from the aquatic environment to air. The DS considers alpha-terpinene as rapidly degradable on the basis of read-across to d-limonene. A CLH proposal for d-limonene is also available for Public Consultation. We have provided comments on the reliability of the ready biodegradation study for d-limonene (King, 1992) which should be considered if the endpoint is read across to alpha-terpinene. In summary, at present we consider there are significant study limitations which impact the reliability of the study and it is unclear if d-limonene meets the criteria for rapidly degradable.

The detailed comments are as follows:
'The CLH proposal considers d-limonene rapidly degradable on the basis of a non-GLP OECD TG301 B study (King, 1992) with a Klimish score of 2. We think further information is required to assess the reliability of the study to determine if d-limonene can be considered rapidly degradable for hazard classification. Please can you present study information to support OECD TG 301 and CO2 evolution method validity criteria. In addition we note that while 60.6% degradation was observed on day 10, 58.8% degradation was observed on day 14. Please can you present degradation displayed graphically to determine if the 10-day window was met.

QSAR predictions do not fully support d-limonene as rapidly degradable. Although it is unclear if these QSAR are fully valid on the basis of the presented data. It would be useful to present details of model fragments, analogues in the training set and full BIOWIN outputs to consider the QSARs further.

If the above data cannot be validated, we feel the case for considering d-limonene as

rapidly degradable for hazard classification may be insufficient. Therefore the default position of non-rapidly degradable should apply unless further information is available.'

QSAR predictions for alpha-terpinene do not fully support the substance as rapidly degradable although it is unclear if these QSAR are fully valid on the basis of the presented data. It would be useful to present details of model fragments, analogues in the training set and full BIOWIN outputs to consider the QSARs further.

There is no further reliable evidence to support the substance as rapidly degradable for hazard classification. On this basis, we feel the case for considering alpha-pinene as rapidly degradable for hazard classification is insufficient. Therefore the default position of non-rapidly degradable should apply unless further information is available.

Due to the presented log Kow value, the DS considers that alpha-terpinene meets hazard classification bioaccumulation criteria in the absence of experimental BCF data.

The aquatic chronic classification is based on read-across from an algal 48-hour ErC10 of 0.14 mg/l (mm) [Betat, 2013] for d-limonene. As noted above a public consultation for d-limonene is available. We have provided comments on algal ecotoxicity endpoints for d-limonene and the Betat, 2013 study as follows:

'Please can you confirm that OECD TG 201 study validity criteria were met for the Betat, 2013 study? During the study, test item losses were observed and while endpoints are based on mean measured concentrations it is noted that some treatments were below the limit of detection.

A second algal study using d-limonene (Seiero, 2015) is available with Reliability score 3 and 72 hour endpoints are not considered reliable. This appears to be due to test item losses over the 48-72 hour period. Please can you explain why the 72 hour results are not reliable as endpoints based on half the limit of detection at 72 hours have previously been employed where losses are observed? [Refer to section I.4.1 of 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. July 2017]. It would also be useful to clarify if test guideline validation criteria are met. This is required to consider if the 72-h ErC10 of 0.09 mg/l (mm) is relevant for hazard classification resulting in a more stringent chronic classification.'

As valid acute endpoints are available for fish and invertebrates using alpha-terpinene, these should be considered with the surrogate approach for chronic classification. Noting the points about rapid degradability and bioaccumulation, this would indicate Aquatic Chronic 2.

However, noting the Public Consultation for d-limonene we have provided additional ecotoxicity endpoint comments relating to chronic toxicity to fish which indicate a more stringent classification, potentially Aquatic Chronic 1 (M=1) may be relevant. These are as follows:

'The CLH presents d-limonene chronic toxicity to fish endpoints based on an OECD Test Guideline 212 (Fish, Short-term Toxicity Test on Embryo and Sac-fry Stages). According to ECHA Guidance (section R.7.8.4)* this is not a chronic endpoint test and is considered an short-term toxicity endpoint. As an additional chronic toxicity endpoint to fish is not available, the DS should consider the surrogate approach for fish using available acute toxicity data. This would result in Aquatic Chronic 1 (M=1) as d-limonene is considered to

meet the bioaccumulation criteria for hazard classification.

The d-limonene CLH briefly mentions that QSARs are available for the chronic toxicity to fish endpoint and that a QMRF is available for one of the model endpoints. As these data support Aquatic Chronic 1 (M=1) for a not rapidly degradable substance, it would useful to clarify it the QSARs are reliable.'

*ECHA (2017) Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7b: Endpoint specific guidance Version 4.0 June 2017

Dossier Submitter's Response

Thank you for your comments.
You request information on the QSAR model for algae. Please note that a new study on the toxicity to algae has become available in the REACH dossier. This new study is discussed in a response to Comment number 24. This study is considered reliable and makes the read-across and use of QSAR for the toxicity to algae obsolete and therefore we consider that it is not required anymore to provide more data on the QSAR. The new data does lead to the conclusion that a classification for aquatic acute toxicity is not required.

For the chronic classification, a new study on biodegradation is also available in the REACH dossier. This new study is also discussed in a response to Comment number 24. The study is considered reliable and makes the read-across to the study of King obsolete. On the basis of the new information, alpha-terpinene should be considered as not rapidly degradable. The new algae study also makes the read-across and use of QSARs for chronic toxicity to algae obsolete. The new studies on algae and biodegradation taken into account the substance should be classified as aquatic chronic 2. Applying the surrogate method for fish and daphnids leads to the same classification as the acute E/LC50s for these tropic levels are between 1 and 10 mg/L.

RAC's response

RAC acknowledges the issues presented in this comment. However, with the new data presented in the REACH Registration dossier QSAR estimations and read-across from d-limonene are no longer needed for classifying alpha-terpinene.

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2018	Spain	<confidential>	Company-Manufacturer	27

Comment received

On the basis of read-across data from d-limonene, the CLH report considers alpha-terpinene as rapidly degradable. In the contrary, according to the REACH Registration dossier, the substance is determined to be non-readily biodegradable reaching 40% of bidegradation over 28 days (OECD 301F, GLP).
CLP-Acute aquatic hazards:
The CLH report does not consider the available experimental data on alpha-terpinene included in the REACH Registration dossier:
- Short-term Daphnia immobilization test (OECD 202, GLP): 48h EC50 = 1.7 mg/L
- Algae growth inhibition test (OECD 201, GLP): 72h NOEC = 3.7 mg/L
Other experimental endpoints on acute aquatic toxicity of alpha-terpinene range from 1.5 to 3.2 mg/L for algae and fish (refer to CLH report).
According to the CLP Regulation (EC) no. 1272/2008, since the L(E)C50 values are higher than 1 mg/L, the substance should not be classified for Aquatic Acute Toxicity.

CLP-Chronic aquatic hazards: No experimental chronic toxicity endpoints are available for alpha-terpinene. According to the Annex I, Table 4.1.0 (iii) of CLP CLP Regulation (EC) no. 1272/2008, alpha-terpinene would be classified for Aquatic Chronic Category 2 (H411) since no adequate chronic toxicity data are available. In fact, this is the classification suggested in the REACH Registration dossier. Nevertheless, the CLH report suggests a read-across approach from d-limonene. The relevant chronic endpoints for fish, daphnia and algae range from 0.14 to 0.32 mg/L. On the basis of these endpoints, classifications as Aquatic Chronic 3 (H412) would be warranted.
Dossier Submitter's Response
Thank you for your comments. The new data available in the REACH dossier are discussed in reply to Comment number 24. These data lead to the conclusion that a classification for aquatic acute toxicity is not required. For chronic toxicity, the classification should be aquatic chronic 2 because of the new data on biodegradation.
RAC's response
Thank you for your comments. Please see the responses to previous comments.

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	28
Comment received				
The German CA agrees 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. Please note that the proposed classification should be adapted because of new data in the REACH dossier as discussed in Comment number 24.				
RAC's response				
The new data in the REACH Registration dossier has changed the proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	France		MemberState	29
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. Please note that the proposed classification should be adapted because of new data in the REACH dossier as discussed in Comment number 24.				
RAC's response				
The new data in the REACH Registration dossier has changed the proposal.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	Germany		MemberState	30

Comment received

As stated in the CLH report "section 4.6.1.1 Non-human information" alpha-terpinene forms unstable peroxides when exposed to air.

In the opinion of the German CA the labelling of alpha-terpinene with EUH019 "May form explosive peroxide" is justified.

1,5-p-Menthadiene (isomer of alpha-terpinene) is described as a peroxidisable compound in Bretherick's Handbook of Reactive Chemical Hazards just like Tetrahydronaphthalene (CAS-No. 119-64-2) which is labelled with EUH019 in Annex VI of the CLP Regulation.

P. G. Urben (Ed.): Bretherick's Handbook of Reactive Chemical Hazards, 6th ed., Elsevier 1999, No 3338.

Dossier Submitter's Response

Thank you for your comments. A fraction of oxidation products of alpha-terpinene are peroxides. Since these are generally regarded as explosive and the oxidation rate is fast, additional labelling with EUH019 may be supported.
According to the registration dossier, tetrahydrophtalene (tetralin) does not have oxidizing properties. However, according to general information sources and suppliers (e.g. Sigma Aldrich), the substance does indeed oxidise and form peroxides with recommended maximum shelf lives of 3 months or 12 months (stabilized). The speed of peroxide formation of tetralin is unknown to the dossier submitter. Some information about the rate can be found in various papers but most applied high temperatures and/or catalysts. For example in Woodward et al. (1953), a conversion of about 7-10% tetralin to its peroxide was achieved at 70 degrees (celcius) within 48 hours air exposure (blown through the liquid). It is unclear how this would reflect the oxidation state at normal temperatures or without catalysts, which would have been helpful to compare to the information available with alpha-terpinene. According to Martan et al., 1970, tetralin primarily oxidizes to a peroxide, which is not known to be the case for alpha-terpinene. Peroxide formation is not as relevant at lower temperatures for tetralin.
In conclusion, the DS has doubts whether there is sufficient information that alpha-terpinene will produce significant amounts of peroxide upon auto-oxidation under common circumstances that justifies labelling with EUH019.

Woodward et al., (1953), Low temperature Auto-oxidation of Hydrocarbons. The Kinetics of Tetralin Oxidation, *J. Am. Chem. Soc.* 75 (24), pp 6189-6195
Martan (1970), Oxidation of Tetralin, alpha tetralol and alpha-tetralone. Dependence of alcohol to ketone ratio on conversion. *Tetrahedron,* 26 (5), pp 3815-3827

RAC's response

Thank you for comments. Taking into account the lack of sufficient data on the formation of explosive peroxide during storage of alpha-terpinene, RAC is of the opinion that labelling with EUH019 (May form explosive peroxides) is not justified.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON P-MENTHA-1,3-DIENE; 1-ISOPROPYL-4-METHYLCYCLOHEXA-1,3-DIENE; ALPHA-TERPINENE

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2018	France		MemberState	31
Comment received				
FR agrees with the proposed classification				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for opinion.				

PUBLIC ATTACHMENTS
1. Rclass_420substance (003).pdf [Please refer to comment No. 4, 11]
2. alpha_Rdoc_final (002).pdf [Please refer to comment No. 12]
3. Comment letter on QRD 460 ECHA.pdf [Please refer to comment No. 5]
4. Derek report_99-86-5-alpha terpinene_20180620.pdf [Please refer to comment No. 2, 9, 16, 19, 23, 24]