EUROPEAN CHEMICALS AGENCY

Helsinki, 15 October 2020

Addressees
Registrants of JS_Terpinyl Acetate multi listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
17/05/2013

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction mass of 1-methyl-4-(1-methylethylidene)cyclohexyl acetate and p-menth-1-en-8-yl acetate
List number: 904-693-9
CAS number: NS

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***20 January 2023***.

A. Requirements applicable to all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the Substance;

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method EU C.2./OECD TG 202) with the Substance;

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance;

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance

2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2.] is obtained, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method OECD TG 203) with the Substance;

C. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method

OECD TG 408) in rats with the Substance;

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the Substance;

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method EU C.20./OECD TG 211) with the Substance;

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance;

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;

Registrants are only required to share the costs of information that they are must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses common arguments that are applicable throughout the present decision while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

EUROPEAN CHEMICALS AGENCY

Appendix on general considerations

(i) Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.) if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained.
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

A. Predictions for (eco)toxicological properties

You have not provided a read-across justification document in IUCLID Section 13, but have provided a justification within the CSR.

You read across to your Substance from the structurally similar substances:

[1] Alpha -terpinyl acetate (1-methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl acetate), (CAS No 80-26-2; EC No. 201-265-7) *for short-term toxicity to aquatic invertebrates, Growth inhibition study aquatic plants, short-term toxicity testing on fish, Ames test, sub-chronic oral toxicity,*

[2] Terpineol multi (CAS No. 8000-41-7) *for combined repeated dose toxicity and screening for reproductive/developmental toxicity study and for in vitro chromosome aberration study,*

[3] Alpha-Terpineol (CAS No. 98-55-5) *for in vitro mammalin cell gene mutation test.*

You have provided the following read-across justification for reproductive and developmental toxicity:

*"Terpinyl Acetate multi has **similar** reproductive and developmental toxicity compared to alphaTerpinyl Acetate and Terpineol multi resulting in similar NOAELs for fertility and developmental toxicity. This is because 1) alpha-Terpinyl Acetate is the **main constituent** of Terpinyl Acetate multi and; 2) Terpineol multi has **a similar backbone** compared to Terpinyl Acetate multi and the latter acetic ester will metabolise into Terpineol multi when passing the gut and the liver, resulting in a similar reproductive and developmental toxic potential."*

The read-across justification for repeated dose toxicity and for genotoxicity include the same elements, i.e. that the source substance Alpha -terpinyl acetate (CAS No 80-26-2) is the main constituent of the target substance and that the source substances Terpineol multi (CAS No. 8000-41-7), Alpha-Terpineol (CAS No. 98-55-5), and Terpineol Acetate (CAS No. 8007-35-0) and the target substance have the same "backbone" and are metabolised similarly.

Furthermore, you have provided the following read-across justification for aquatic toxicity endpoints in section 7.1 of the CSR: *"The information from alpha-Terpinyl Acetate can be used for Terpinyl Acetate multi because the alpha is the main constituent of the multi. The other constituents are structural isomers having the same functional ester group, as shown in the toxico-kinetic section (IUCLID section 7.1) and are expected to have the same aquatic toxicity."*

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH.

In your comments on the draft decision, you have provided QSAR modelling results, information on the constituents of the Substance and the source substances and indicated your intention to provide information on the hydrolysis of the Substance.

ECHA notes the following shortcomings with regards to predictions of (eco)toxicological properties.

Missing well-founded hypothesis for human health and environment read-across

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and

your Substance[2]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the structural similarity between the source substance(s) and your Substance is a sufficient basis for predicting the properties of your Substance.
Your read-across hypothesis is based on two elements: first that the source substance is the **main constituent** of the Substance, and secondly, that the source and target substances have the same structural **backbone** and partly similar chemical **functionalities**.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar human health or environmental properties.

Your justification is considered incomplete, because the source substance of read-across is Terpineol multi, which according to your comments on the draft decision, constitutes of four terpineols. The Substance, terpinyl acetate multi constitutes of four acetates. Therefore, there is a structural difference with the Substance and the source substance Terpineol multi. Furthermore, you have not provided experimental data on the metabolites of the target and source substances.

Therefore, you have not provided a well-founded hypothesis to establish a reliable prediction for aquatic toxicity and human health effects, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

Missing supporting information/bridging studies to compare human health and environment properties

Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". Within this documentation "*it is important to provide supporting information to strengthen the rationale for the read-across*"[3]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

"*Adequate and reliable documentation*" must include bridging studies to compare properties of the target and source substances. As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substance is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the target and the source substances.

In the registration dossier you have provided aquatic toxicity studies only with the source substance. Similarly, all the provided human health toxicity studies have been performed with source substances. Hence, the data set reported in the technical dossier does not include relevant, reliable and adequate information for the target substance to support your read-across hypothesis.

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[2] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.
[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

In your comments on the draft decision, you provided several results of QSAR Toolbox modelling, on protein binding, bioaccumulation, acute toxicity, DNA alerts, and on mutagenicity, etc. While this information has relevance in providing evidence on similarity, ECHA notes that this information is not sufficient because it does not address all those endpoints for which you rely on a read across adaptation to fulfil the respective information requirements, more notably the alerts do not concern repeated dose toxicity and reproductive toxicity. Concerning the (eco)toxicity endpoints addressed in the draft decision, we note that QSAR modelling results provided in registrants comments are based on structural similarities and provide alerts of certain effects and modes of action. However, there may be other modes of action and other effects that QSAR modelling is unable to identify, e.g. due to limitations of the domain of that QSAR. Therefore, QSAR modeling results cannot be used as binding studies, to support the read-across.

Quality of the human health and enviroment studies with source substance(s)

As required in Annex XI, Section 1.5. of the REACH Regulation, source studies should be adequate for the purpose of classification and labelling and/or risk assessment, have adequate and reliable coverage of the key parameters and cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3), and adequate and reliable documentation of the applied method shall be provided.

Full composition of the tested substance in the short-term aquatic toxicity studies with fish and Daphnia performed with source substance [1] was not provided, as explained in Appendix A and B. Therefore, ECHA considers the study not reliable to describe the ecotoxicological profile of the analogous substance.

In addition, as specified in Appendix C, the sub-chronic study made with alpha-Terpinyl Acetate (CAS No. 80-26-2) is of unacceptable quality, because the following key parameters are missing: histopathology of the tissues and clinical biochemistry.

To support your predictions for repeated dose toxicity and reprotoxicity, you have provided automated reports for alpha, gamma- and beta-terpinyl acetate generated from the OECD QSAR Toolbox software. These reports does not contain any no observed (adverse) effect level NO(A)EL values for the substances.

In the absence of such documentation, ECHA cannot verify that the results to be read across meet the criteria above.

Missing supporting information on the toxicokinetics for human health

Your read-across hypothesis is partly based on the (bio)transformation of the target and source substances to a common compound(s). In this context, information characterising the rate and extent of the metabolism of the target substance and of the source substance is necessary to confirm the formation of the proposed common hydrolysis product and to assess the impact of the exposure to the parent compounds.

You claim that "***terpineol multi*** *has* ***a similar backbone*** *compared to Terpinyl Acetate multi and the latter acetic ester will metabolise into Terpineol multi when passing the gut and the liver, resulting in a similar reproductive and developmental toxic potential.*"

You have not, however, provided any *experimental* data or other adequate and reliable information to document that these metabolic pathways/steps take place.

In the absence of this information, you have not demonstrated that there is common metabolism as assumed/claimed in your read-across hypothesis.

The Substance, terpinyl acetate multi constitutes of acetates, while Terpineol multi constitutes of terpineols. According to your comments on the draft decision, you intend to show that due to transformation of the Substance, systemic exposure is solely to the (components of) Terpineol multi. Such evidence of rapid transformation is however not yet available, and it is considered by ECHA as a preliminary hypothesis without experimental support. Therefore, there is at present no data on transformation to provide further evidence to substantiate the read-across.

Missing the supporting information on toxicokinetics for environment

According to the ECHA Guidance *"it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals"*.

In order to support your claim that the target and source substances have similar properties for the ecotoxicological endpoints under consideration in the read-across approach, you refer to their toxicokinetic properties under Section 7.1 of IUCLID

Section 7.1 of IUCLID does not provide experimental toxicokinetic studies, nor is this information related to aquatic toxicity endpoints. No justification can be found in this section for the read-across of aquatic toxicity endpoints.

ECHA did not consider this documentation to be relevant for the read-across for aquatic toxicity endpoints because it does not address read-across for aquatic toxicity endpoints.

B. Conclusions on the grouping of substances and read-across approach for (eco)toxicological properties

As explained above, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation for (eco)toxicological properties is rejected and it is necessary to perform testing on your Substance.

Appendix A: Reasons for the requests to comply with Annex VII of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have provided a key study in your dossier:

i. Ames test OECD 471 with analogue substance, alpha-Terpinyl Acetate (CAS No. 80-26-2), according to GLP, [redacted] 2012.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations above, your adaptation is rejected.

In your comment on the draft decision, you have indicated that you agree to perform the requested study.

Consequently, you are required to provide information on the Substance for this endpoint.

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided one short-term toxicity to aquatic invertebrates key study performed with the analogue substance [1 alpha -terpinyl acetate (1-methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl acetate) 80-26-2] (which had an analyitical purity=[redacted], and no information of the composition of the other [redacted] of the tested substance is provided) in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected. Therefore, the information requirement is not fulfilled.

You provided comments on the draft decision for this endpoint according to Article 50(1) of the REACH Regulation. Here you agree to update in the dossier the description of the test material for the substance and the used analogue alpha Terpinyl acetate. ECHA indicates that as QSAR modelling is based on structural similarities, there may be other modes of action and other effects that QSAR modelling is unable to identify. Therefore, QSARs cannot be used as binding studies. You further indicate in your comments that analytical monitoring was performed. ECHA has modified the decision accordingly.

Consequently, there is a data gap that needs to be filled in.

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided one algal inhibition key study performed with the analogue substance [1 **test material/source substance:** alpha -terpinyl acetate (1-methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl acetate) 80-26-2; Analyitical purity=[redacted] **Batch** [redacted] in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected. Therefore, the information requirement is not fulfilled.

You provided comments on the draft decision for this endpoint according to Article 50(1) of the REACH Regulation. Here you agree to update in the dossier the description of the test material for the substance and the used analogue alpha Terpinyl acetate. ECHA indicates that as QSAR modelling is based on structural similarities, there may be other modes of action and other effects that QSAR modelling is unable to identify. Therefore, QSARs cannot be used as binding studies.

Consequently, there is a data gap that needs to be filled in.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.)

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided two studies in your dossier:

i. Cytogenicity assay according to OECD TG 473, according to GLP, with the source substance Terpineol multi (CAS No. 8000-41-7), [redacted] 2010.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.

In your comments on the draft decision, you have indicated that you agree to perform the requested study.

To fulfil the information requirement for the Substance, both *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered appropriate/ adequate.

2. Only if both studies under sections A.1 and B.1 have negative results, *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

You have provided two studies in your dossier:

i. In vitro gene mutation study in mammalian cells according to OECD TG 476, with analogue substance "alpha-Terpineol: 98-55-5", not according to GLP, [redacted] 2006;

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.
In your comments on the draft decision, you have indicated that you agree to perform the requested study.

Consequently, you are required to provide information on the Substances for this endpoint, if the *in vitro* gene mutation study in bacteria *and* the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

3. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (OECD TG 421 or 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have provided two studies for this endpoint in your dossier:

i. A screening study 422, made in 2010 with an analogue substance, Terpineol multi (CAS No. 8000-41-7), GLP compliant, [redacted] 2010.
ii. A 90-day oral study according to OECD TG 408, with the analogue substance; alpha-Terpinyl Acetate (CAS No. 80-26-2), feeding, not according to GLP, [redacted] 1967.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.
Consequently, you are required to provide information for this endpoint.

According to your comment on the draft decision, you intend to show that due to transformation of the Substance, systemic exposure is solely to the Terpineol multi. In the "Appendix on general considerations" above, we have addressed this claim. Furthermore, you suggest that for the reproductive toxicity screening study, the quantitative difference between alcohol and acetate could be accounted with molecular weight conversion. ECHA finds that also this approach is based on theoretical assumption on the transformation, which has not yet been documented with experimental and substance-specific information. ECHA notes that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH.

Therefore, a study according to the test method OECD TG 421/422 should be performed in rats with oral[4] administration of the Substance.

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided one short-term toxicity to fish studies, all performed with the analogue substance [1 **test materia/source substance:** alpha -terpinyl acetate (1-methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl acetate) 80-26-2; Analyitical purity=[redacted] **Batch** [redacted] (which had an analyitical purity=[redacted] and no information of the composition of the other [redacted] of the tested substance is provided), in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Annex XI, Section 1.5 is rejected. Therefore, the information requirement is not fulfilled.

You provided comments on the draft decision for this endpoint according to Article 50(1) of the REACH Regulation. Here you agree to update in the dossier the description of the test material for the substance and the used analogue alpha Terpinyl acetate. ECHA indicates that as QSAR modelling is based on structural similarities, there may be other modes of action and other effects that QSAR modelling is unable to identify. Therefore, QSARs cannot be used as binding studies. You further indicate in your comments that one short term fish study was performed only, and that analytical monitoring was performed. ECHA has modified the decision accordingly.

Consequently, there is a data gap that needs to be filled in.

Appendix C: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to REACH.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided two studies for this endpoint in your dossier:

i. A screening study 422, made in 2010 with an analogue substance, Terpineol multi (CAS No. 8000-41-7), GLP compliant, [redacted] 2010.
ii. A 90-day oral study according to OECD TG 408, with the analogue substance; alpha-Terpinyl Acetate (CAS No, 80-26-2), feeding, not according to GLP, [redacted] 1967.

We have assessed this information and identified the following issue(s):

A. Inadequate studies

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others

- clinical biochemistry and histopathology of the relevant tissues,
- required exposure duration is 90 days as required in OECD TG 408.

In the assessment of these studies ECHA found the following:

- The sub-chronic toxicity study TG 408 you have provided did not cover histopathology of the tissues and clinical biochemistry.
- The duration of the screening study TG 422 study was only 28 days.

Therefore, the studies did not fulful the key parameters according to the sub-chronic study.

B. Adaptation

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.

In your comment to the draft decision, you have indicated that you consider adapting the standard information requirement according to Annex XI, Section 1.2. Weight of evidence (WoE) of REACH. You intend to provide a 90-day inhalation study on Terpineol multi to the dossier.

However, irrespective of this information, ECHA can already note that as explained above, in the "Appendix on general consideration", the reported read-across approach does not fulfil the criteria in Annex XI, Section 1.5. Therefore, it cannot be used as part of weight of evidence adaptation according to Annex XI, Section 1.2.

Based on the above, the information you provided do not fulfil the information requirement.

Information on the design of the study to be performed (route/ species)

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity[5]. The sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance, because although the information indicate that human exposure to the Substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route are low compared to the toxicity profile of the substance.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided

- A screening study according to OECD TG 422, made in 2010 with an analogue substance, Terpineol multi (CAS No. 8000-41-7), according to GLP, and
- An adapation according to Annex XI, 1.5

We have assessed this information and identified the following issue(s):

A. OECD TG 422 study

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in one species.

You have not provided information following OECD TG 414. Instead, you have provided a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (OECD TG 422). In this study, structural malformations and variations are not investigated as required in the PNDT study (OECD TG 414).

Therefore, this study does not fulfil the information requirement.

B. Adaptation

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

Additionally, in your comments to the draft decision, you have indicated that in your dossier you will include an OECD TG 414 study on Terpineol multi, that is a source substance of the proposed read-across.

However, as explained in the Appendix on general considerations, your read-across adaptation is rejected. Moreover, ECHA notes that the source study with Terpineol multi is not submitted in the dossier. In addition, in the chapter "Appendix on general considerations"

[5] ECHA Guidance R.7a, Section R.7.5.4.3.

above, we have addressed your claim that Terpinyl acetate multi transforms to Terpineol multi. ECHA notes that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH.

Therefore, the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[6] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Long-term aquatic toxicity standard text is a standard information requirement in Annex IX to REACH.

You have provided adaptation based on column 2 of Annex IX, section 9.1., summarised as follows: "*Terpinyl Acetate multi is readily biodegradable, which diminishes long-term exposure in the environment. In addition, the available aquatic toxicity data do not reveal a need for further investigation (the environmental risk assessment for all intended uses shows that the risk is controlled).*"

In order to adapt the information requirement for long-term toxicity to aquatic invertebrates based on Annex IX, Section 9.1, Column 2, the Chemical Safety Assessment (CSA) needs to demonstrate that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1).The Chemical Safety Assessment (CSA) needs to assess and document that risks arising from the Substance are controlled and demonstrate that there is no need to conduct further testing (Annex I, Section 0.1; Annex IX, Section 9.1, Column 2).

In particular, you need to take into account of the following elements in your justification:
- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

As specified in requests Appendix A 2-4 and Appendix B 3, the data on Short-term toxicity testing on aquatic invertebrates, Growth inhibition study aquatic plants and Short-term toxicity testing on fish, are not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance.

Therefore your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., Column 2.

You provided comments on the draft decision for this endpoint according to Article 50(1) of the REACH Regulation. Here you address that based on your comments regarding the acute toxicity to aquatic organisms, a base set for aquatic toxicity is available, and that you will adapt the waiver in a dossier update. You may, under your own responsibility, provide a new justification for waiving this information requirement. If it fails you remain responsible for complying with this decision by the set deadline. ECHA notes that this decision does not take

[6] ECHA Guidance R.7a, Section R.7.6.2.3.2.

into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH.

Consequently, there is a data gap that needs to be filled in.

As reliable information neither on the short-term toxicity to fish nor to invertebrates is available, neither fish nor invertebrates are shown to be substantially more sensitive than other trophic levels (i.e., fish, invertebrates, algae). According to the integrated testing strategy (ITS) (ECHA Guidance R.7b,Section R.7.8.5 including Figure R.7.8-4), if necessary, the long-term *Daphnia* toxicity study is to be conducted first. If based on the results of that study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), the long-term fish study may not need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Long-term toxicity testing on fish is a standard information requirement in Annex IX to REACH.

You have provided adaptation based on column 2 of Annex IX, section 9.1., summarised as follows: "*...Terpinyl Acetate multi is readily biodegradable, which diminishes long-term exposure in the environment. In addition, the available aquatic toxicity data do not reveal a need for further investigation (the environmental risk assessment for all intended uses shows that the risk is controlled).*".

In order to adapt the information requirement for long-term toxicity to fish based on Annex IX, Section 9.1, Column 2, the Chemical Safety Assessment (CSA) needs to demonstrate that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1).The Chemical Safety Assessment (CSA) needs to assess and document that risks arising from the Substance are controlled and demonstrate that there is no need to conduct further testing (Annex I, Section 0.1; Annex IX, Section 9.1, Column 2).

In particular, you need to take into account of the following elements in your justification:
- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

As specified in requests Appendix A 2-4 and Appendix B 3, the data on Short-term toxicity testing on aquatic invertebrates, Growth inhibition study aquatic plants and Short-term toxicity testing on fish are not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance.

Therefore your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., Column 2.

You provided comments on the draft decision for this endpoint according to Article 50(1) of the REACH Regulation. Here you address that based on your comments regarding the acute toxicity to aquatic organisms, a base set for aquatic toxicity is available, and that you will adapt the waiver in a dossier update. You may, under your own responsibility, provide a new

justification for waiving this information requirement. If it fails you remain responsible for complying with this decision by the set deadline. ECHA notes that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH.

Consequently, there is a data gap that needs to be filled in.

As reliable information neither on the short-term toxicity to fish nor to invertebrates is available, neither fish nor invertebrates are shown to be substantially more sensitive than other trophic levels (i.e., fish, invertebrates, algae). According to the integrated testing strategy (ITS) (ECHA Guidance R.7b,Section R.7.8.5 including Figure R.7.8-4), if necessary, the long-term *Daphnia* toxicity study is to be conducted first. If based on the results of that study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), the long-term fish study may not need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 14 January 2019.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments. The information you provided in your comments did not fulfil the information requirements. ECHA did not amend the requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[7].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[9]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[10]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document supporting the OECD TG 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD151.

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.