

Helsinki, 12 November 2021

Addressees

Registrant(s) of EC_250-954-9 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision

16/10/2019

Registered substance subject to this decision ("the Substance")

Substance name: 4-tert-butylcyclohexyl acetate

EC number: 250-954-9

CAS number: 32210-23-4

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

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information for A.1. listed below, by the deadline of **17 August 2023** and all other information listed below by **20 November 2023**.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats
2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

B. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat/rabbit)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes IX to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to <http://echa.europa.eu/regulations/appeals> for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised¹ 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.

Appendix on Reasons common to several requests

Assessment of the Grouping of substances and read-across approach under 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:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

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^{2,3}.

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.

You read-across between the structurally similar substance, D-menthol, 2-isopropyl-5-methylcyclohexanol, EC No. 201-939-0, (CAS No. 89-78-1) as source substance and the Substance as target substance.

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 the following shortcomings with regards to predictions of toxicological properties.

Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the

² Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: [Read-Across Assessment Framework \(https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across\)](https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

³ Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: <https://doi.org/10.2823/794394>

prediction of properties and robust study summary(ies) of the source study(ies).⁴

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s).

Missing supporting information to compare toxic properties of the substances

Annex XI, Section 1.5 of the REACH Regulation states that “*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*”. For this purpose “*it is important to provide supporting information to strengthen the rationale for the read-across*”⁵. 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). Supporting information must include bridging studies to compare properties of the Substance and source substance.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) 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 Substance and of the source substance(s).

The data set reported in the technical dossier does not include relevant, reliable and adequate toxicological information for the Substance and of the source substance(s) to support your read-across hypothesis.

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

A. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Additional deficiencies are addressed in the corresponding Appendices. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

⁴ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1

⁵ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

Appendix A: Reasons to request information required under Annex IX of REACH**1. Sub-chronic toxicity study (90-day)**

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

You have provided an adaptation according to Column 2 of Annex IX, Section 8.6.2./ Annex XI, Section 1.5. using the following key study for this endpoint in your dossier:

- A combined chronic toxicity/carcinogenicity study TG 453, (1979), with the analogue substance D-menthol, 2-isopropyl-5-methylcyclohexanol, EC No. 201-939-0, in rats and mice, reliability 1, GLP not specified.

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

As explained in the Appendix on common reasons your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read-across must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 408, which include, among others:

1. testing of at least three dose levels and a concurrent control, and
2. Clinical observations, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, Recording of body weight, haematology, clinical biochemistry, and pathology of sexual (male and female) organs.

The study you have provided:

- was conducted with less than three dose levels,.
- is missing the following key parameters: ophthalmology, haematology, clinical biochemistry and urinalysis.

Therefore, your adaptation is rejected.

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

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

Referring to 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, because although the information indicate that human exposure to the Substance by the inhalation route is likely, according to the exposure scenarios, the exposure via inhalation is low.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration 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 key study for this endpoint in your dossier:

- A prenatal developmental toxicity study similar to OECD TG 414 (1973), in mice and rats, made with the analogue substance DL-Menthol EC No. 201-939-0 (CAS No. 89-78-1), reliability 1, GLP not specified.

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

As explained in the Appendix on common reasons your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 414, which include, among others:

- testing of at least three dose levels and a concurrent control,
- dosing of the Substance from implantation until the day prior to scheduled caesarean section,
- examination of the dams for weight and histopathology of the thyroid gland,
- examination of external, skeletal and soft tissue alterations (variations and malformations)

The study you have provided:

- was conducted with two dose levels. Therefore it does not fulfil the criterion of at least three dose levels set in OECD TG 414.
- the animals were exposed during GD6-15.
- the weight and histopathology of the thyroid gland has not been examined in dams.
- soft tissue alterations (variations and malformations) have not been examined.

Therefore, your adaptation is rejected.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral⁶ administration of the Substance.

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

Appendix B: Reasons to request information required under Annex X of REACH**1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species**

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

You have provided a key study for this endpoint in your dossier:

- A prenatal developmental toxicity study similar to OECD TG 414 (1973), in hamsters and rabbits, made with the analogue substance DL-Menthol EC No. 201-939-0 (CAS No. 89-78-1), reliability 1, GLP not specified.

As explained in the Appendix on common reasons your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 414, which include, among others:

- testing of at least three dose levels and a concurrent control,
- dosing of the Substance from implantation until the day prior to scheduled caesarean section,
- examination of the dams for weight and histopathology of the thyroid gland,
- examination of external, skeletal and soft tissue alterations (variations and malformations).

The study you have provided:

- was conducted with two dose levels
- the animals were exposed during GD6-18
- the weight and histopathology of the thyroid gland has not been examined in dams.
- soft tissue alterations (variations and malformations) have not been examined.

Therefore, your adaptation is rejected.

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

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request [A.2] in this decision).

The study shall be performed with oral⁷ administration of the Substance.

⁷ ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. 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 on How to report robust study summaries⁸.

B. Test material

1. Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

- 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.
2. Information on the Test Material needed in the updated dossier
 - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
 - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers⁹.

⁸ <https://echa.europa.eu/practical-guides>

⁹ <https://echa.europa.eu/manuals>

Appendix D: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 25 November 2020.

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

ECHA did not receive any comments within the notification period.

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: List of references - ECHA Guidance¹⁰ and other supporting documentsEvaluation 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 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)¹¹

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)¹²

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.

Data sharing

Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents¹³

¹⁰ <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

¹¹ <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

¹² https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

¹³ <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you

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.