

Helsinki, 12 November 2021

**Addressees**

Registrants of EC\_250-954-9 listed in the last Appendix of this decision

**Date of submission for the jointly submitted dossier subject of a decision**

30/10/2019

**Registered substance subject to this decision, hereafter '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 TPE-D-XXXXXXXXXX-XX-XX/F)**DECISION ON A TESTING PROPOSAL**

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of **17 August 2023**.

The requested information must be generated using the Substance unless otherwise specified.

**A. 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 .

Whilst your originally proposed test(s) using an analogue substance cis-4-tert-butylcyclohexyl acetate (EC No 233-881-7) is rejected, according to Article 40(3)(d):

**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 Annex VII - Annex IX REACH, for registration at 100 – 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 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<sup>1</sup> under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

---

<sup>1</sup> 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 A: Reasons to request information required under Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted.

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

#### *Examination of the testing proposal*

A sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX, Section 8.6.2. to REACH.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the analogue substance cis-4-tert-butylcyclohexyl acetate (EC No 233-881-7).

ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

You proposed testing by the oral route, in rats. ECHA agrees with your proposal.

ECHA has evaluated your proposal to perform the test with the analogue substance cis-4-tert-butylcyclohexyl acetate (EC No 233-881-7). As explained under Grouping of substances and read-across approach, below, your adaptation according to Annex XI, Section 1.5 is rejected, and therefore your proposal to test the analogue substance, cis-4-tert-butylcyclohexyl acetate (EC No 233-881-7), is also rejected according to Article 40(3)(d).

#### **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<sup>2</sup> and related documents<sup>3, 4</sup>.

#### **A. Predictions for toxicological properties**

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

You read-across between the structurally similar substances, cis-4-tert-butylcyclohexyl acetate (EC No 233-881-7) as source substance and the Substance as target substance.

<sup>2</sup> Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: [https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r6\\_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9](https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9)

<sup>3</sup> 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)

<sup>4</sup> 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>

You have provided the following reasoning for the prediction of toxicological properties: *"This read-across is based on the hypothesis that source and target substances have similar physicochemical, (eco)toxicological and environmental fate properties because of their structural similarity. Source substance and the target substance are isomers. Based on acute toxicity data, the source substance is expected to be a worst-case compared to the target substance considering the acute toxicological property"*.

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.

#### *Read-across hypothesis contradicted by existing data*

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance<sup>5</sup> indicates that *"it is important to provide supporting information to strengthen the rationale for the read-across"*. 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).

The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

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).

The results of the sub-acute toxicity studies (OECD TG 407) show that the Substance, which also contains the trans-isomer, is significantly more toxic (LOAEL is below 300 mg/kg) than the cis-isomer (NOAEL is 1000 mg/kg), which is the source substance. No toxicity was observed in the sub-acute study with the source substance. The Substance contains cis- and trans- isomers as well as an unidentified isomer (IUCLID section 13.2.).

Moreover, the NOAEL derived from the pre-natal developmental toxicity study with the Substance is 160 mg/kg (maternal toxicity), which confirms the higher toxicity of the Substance as compared with the source substance.

The available set of data on the Substance and source substance(s) indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

## **B. 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. Therefore, your adaptation does not

---

<sup>5</sup> Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

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.

*Outcome*

Under Article 40(3)(d) and (c) of REACH, your proposed test is rejected and you are requested to carry out additional test(s) with the **Substance**:

Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats

## **Appendix B: 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 summaries<sup>6</sup>.

### **B. Test material**

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 is known to have or could have 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"<sup>7</sup>.

---

<sup>6</sup> <https://echa.europa.eu/practical-guides>

<sup>7</sup> <https://echa.europa.eu/manuals>

**Appendix C: Procedural history**

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 30 October 2019,

ECHA held a third party consultation for the testing proposal from 24 February 2020 until 9 April 2020. ECHA did not receive information from third parties.

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 REACH.

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

ECHA did not receive any comments within the commenting 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 D: List of references - ECHA Guidance<sup>8</sup> and other supporting documents**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 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)<sup>9</sup>

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)<sup>9</sup>

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 documents<sup>10</sup>

<sup>8</sup> <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

<sup>9</sup> <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

<sup>10</sup> <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 E: Addressees of this decision and the corresponding information requirements applicable to them**

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

<b>Registrant Name</b>	<b>Registration number</b>	<b>(Highest) Data requirements to be fulfilled</b>
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.