~~Confidential~~

Helsinki, 11 February 2022

Addressee
Registrant of TRANS AMYL CINNAMIC ALDEHYDE as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
07/07/2020

Registered substance subject to this decision ("the Substance")
Substance name: Heptanal, 2-(phenylmethylene)-, (2E)-
EC number: 800-696-3
CAS number: 78605-96-6

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 listed below, by the deadline of ***19 August 2024***.

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

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

1. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105)

2. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method)

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

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

B. Information required from 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)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

   The study is already available in the jointly submitted registration for the Substance. Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the same substance.

4. Activated sludge respiration inhibition testing (Annex VIII, Section 9.1.4.; test method: EU C.11/ OECD TG 209)

5. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.; test method: OECD TG 121)

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

1. 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)

   The study is already available in the jointly submitted registration for the Substance. Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the same substance.

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

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

   The study is already available in the jointly submitted registration for the Substance. Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the same substance.

4. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: OECD TG 305)

5. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

6. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: EU C.24./OECD TG 308) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

7. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: EU C.23./OECD TG 307) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

8. Identification of degradation products (Annex IX, 9.2.3.; test method: using an appropriate test method)

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 VII to IX 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, VIII and IX to REACH, for registration at 100-1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

The studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes".

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.

Authorised[1] under the authority of Mike Rasenberg, 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

1. Assessment of your 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:

- 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- 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.)
- Activated sludge respiration inhibition testing (Annex VIII, Section 9.1.4.)

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.

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].

You have not provided any read-across justification document in your registration dossier. However, in your comments to the draft decision you provided a read-across justification document and indicated your intention to update the registration dossier accordingly.

You read-across between the following:

- 2-(4-tert-butylbenzyl)propionaldehyde, EC No. 201-289-8, (CAS No. 80-54-6)
- 2-benzylideneoctanal, EC No. 202-983-3 , (CAS No.101-86-0),
- Cinnamyl alcohol, EC No. 203-212-3, (CAS No. 104-54-1),
- Cinnamaldehyde, EC No. 203-213-9, (CAS No.104-55-2),
- (2E)-3-phenylprop-2-enal, EC No. 604-377-8, (CAS No. 14371-10-9),

as source substances and the Substance as target substance.

A. Predictions for toxicological properties

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

[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)

[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

justification for the read-across including a hypothesis, explanation of the rationale for the 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. In your dossier, you have not provided documentation as to why this information is relevant for your Substance.However, the justification provided in your comments on the draft decision is based on the hypothesis that the Substance and the source substances have similar toxicological properties because they biotransform to common products predicted to have no toxicological effect. You claim that this prediction is supported by toxicological data on the substances themself and by a QSAR analysis.

ECHA notes the following shortcoming with regards to predictions of toxicological properties.

1) Supporting information

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*" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). 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 toxicokinetic information on the formation of the common compound.

<u>Missing information on the formation of common compound</u>

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substances to a common compound. In this context, information characterising the rate and extent of the (bio)transformation of the Substance and of the source substances is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds.

In the justification submitted with your comments on the draft decision, you describe the metabolic pathway of cinnamyl alcohol, cinnamaldehyde and cinnamic acid ([redacted], 2005, [redacted] 2000). The [redacted] paper describes how "*cinnamyl alcohol is rapidly converted to aldehyde via alcohol dehydrogenase to cinnamaldehyde, which in turn, is converted to cinnamic acid*". On this basis, you anticipate that the Substance and the source substances follow the same pathway in that the alcohol is transformed into the aldehyde, which then metabolises to acid, because both belong to the class of compound known as cinnamaldehydes. You also mention that the Substance has an additional five-carbon length side chain.

However, you have not provided any reliable supporting information regarding the claim of similar toxicokinetics between the source substances and the Substance. More specifically, you claim that hippuric acid is the final metabolite excreted in the urine for the source susbtances and the Substance but you did not provide experimental evidence of this for the Substance. In addition, you did not discuss the impact of the carbon chain on the prediction of similar metabolism and thereby similar toxicity.

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

In the absence of this information, you have not provided supporting evidence establishing that the proposed common (bio)transformation product is formed as assumed in your read-across hypothesis. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Missing supporting information to compare properties of the substances(s)

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 substances 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).

For in vitro cytogenicity and in vitro gene mutation, you provide studies only on the source substances EC 203-212-3 and EC 203-213-9. You also provide only one chronic study and one screening study for the source substance EC 203-212-3 and one developmental study for the source substance EC 203-213-9. Based on these studies you claim that there is a similar toxicity profile for the source susbtances and the Substance. As there are no bridging studies provided, the suggested similar toxicity of the Substance and the source substances cannot be confirmed.

In the absence of such information, you have not established that the Substance 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.

B. Predictions for ecotoxicological properties

i. Aquatic toxicity

You have provided the following reasoning for the prediction of aquatic toxicity: *"Target and read-across analogues area group of chemicals whose physicochemical, human health and/or environmental/ecotoxicological properties are likely to be similar and show structural as well as functional similarity."*

You read-across between the structurally similar substances, EC No. 203-213-9 (CAS No. 104-55-2) 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 based on a based on a worst-case approach.

ECHA notes the following shortcoming with regards to prediction(s) of aquatic toxicity:

Missing supporting information to compare properties of the substances(s)

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 substances 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).

For the source substance, you provide in your comments to the draft decision four studies used in the prediction: 1) OECD TG 202 (*Daphnia* sp. Acute Immobilisation Test), 2) OECD

TG 201 (*Pseudokirchneriella subcapitata*), 3) Evaluation of Antibacterial Effects on microorganisms, Rui-Song Pei et al. 2009, and 4) Activated sludge test according the ISO 8192.

Supporting aquatic toxicity information bridging effects between the Substance and of the source substance is provided for three information requirements (see A.3, A.4 and B.4). In all cases the information either on the Substance and/or source substance is not complying with the applicable test guidelines and is therefore not considered reliable. As there are no reliable bridging studies provided for any trophic levels in aquatic environment, the suggested similar toxicity of the Substance and the source substance cannot be confirmed.

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

C. 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 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.

2. Assessment of the (Q)SAR adaptation under Annex XI, Section 1.3.

You seek to adapt the following standard information requirements by applying (a) (Q)SAR approach(es) in accordance with Annex XI, Section 1.3:

- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)
- Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)
- Soil simulation testing (Annex IX, Section 9.2.1.3.)
- Sediment simulation testing (Annex IX, Section 9.2.1.4.)

ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

a. the prediction needs to be derived from a scientifically valid model,
b. the substance must fall within the applicability domain of the model,
c. results need to be adequate for the purpose of risk assessment or classification and labelling, and
d. adequate and reliable documentation of the method must be provided.

With regard to these conditions, we have identified the following issues:

1. Modelled endpoint not well defined

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:

- the training set must be obtained from experimental data generated with homogeneous experimental protocols, and
- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement.

The endpoint predicted by the (Q)SAR is not the same as the endpoint measured by the relevant test protocol.

Therefore, the endpoint of the model is not well defined, and you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

2. *Inappropriate measures of goodness-of–fit, robustness and predictivity*

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness using the learning data set) and predictivity (using a test data set) of the model are available.

To have appropriate robustness, a model must be built from a training set which includes a sufficient number of observations (i.e. data). The minimum number of observations depends on the number of variables or descriptors included in the model. The ratio between the number of observations and the number of variables or descriptors must be at least 5.

Since the ratio between the number of observations and the number of variables or descriptors is less than five, you have not established the robustness, and thus the scientific validity, of the model.

3. *Low reliability of the prediction*

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

You have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

4. *Lack of or inadequate documentation of the prediction (QPRF)*

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

You have not provided information about the prediction.

In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

On the basis of issues 1 – 4, the information requirement is not fulfilled.

Therefore, your adaptations are rejected.

Additional issues related to (Q)SAR are addressed under the corresponding Appendices.

3. Assessment of your weight-of-evidence adaptation under Annex XI, Section 1.2

You seek to adapt the following standard information requirements by applying weight of evidence approaches in accordance with Annex XI, Section 1.2:

- 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Soil simulation testing (Annex IX, Section 9.2.1.3.)

ECHA has considered the scientific and regulatory validity of your weight of evidence approach in general before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to a(n) assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

In your dossier nor in your comments on the draft decision, you have not included in your justification for your weight of evidence adaptation, adequate and reliable documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Your adaptation is rejected because lack of adequate and reliable documentation for justification and the information requirement is not fulfilled.

Irrespective of the above mentioned deficiencies on the documentation, which in itself leads to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Your weight of evidence adaptation has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually.

- For all information requirements listed above, except for Soil simulation testing (Annex IX, Section 9.2.1.3.), we understands that you intend to predict the toxicological properties of the Substance from data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation.

  However, for the reasons explained in section 1 above, your read across adaptation is rejected.

While the deficiency common to several information requirements is set out above, specific deficiencies affecting the reliability of the sources of information are also set out under the information requirement concerned in the Appendices below.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Water solubility

Water solubility is an information requirement under Annex VII to REACH (Section 7.7.).

You have provided a key study using OECD TG 105 (flask method), Water solubility, [redacted], 2017.

We have assessed this information and identified the following issue:

To be considered adequate, the study has to meet the requirements of EU test method A.6 or OECD TG 105, and the key parameters of this test guideline include: for the flask method, reporting of the following (among others):

- the results of the preliminary test,
- precise specification of the substance (identity and impurities),
- the individual analytical determinations and the average where more than one value was determined for each flask,
- the pH of each sample,
- the average of the value for the different flasks which were in agreement,
- evidence of any chemical instability of the substance during the test and the method used,
- all information relevant for the interpretation of the results, especially with regard to impurities and physical state of the substance.

You have not reported any of the parameters listed above.

Therefore, the provided information does not fulfil the information requirement.

In the comments to the draft decision you agree with the request.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

2. Partition coefficient n-octanol/water

Partition coefficient n-octanol/water is an information requirement under Annex VII to REACH (Section 7.8.).

You have provided a key study OECD TG 117, (Partition Coefficient, HPLC Method), [redacted], 2017.

We have assessed this information and identified the following issue:

To be considered adequate, the study has to meet the requirements of OECD TG 117, and the key parameters of this test guideline include:

- at least 6 data points are needed for a calibration curve to be established:
- at least one reference substance should have a partition coefficient value below the test material's partition coefficient value, and one above it.

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

- the reference substances should be structurally similar to the test material.

You have provided a study, where you have used 10 reference substances to generate a calibration curve. However, your reported partition coefficient value falls outside the calibration curve. The reference substances are polyaromatic hydrocarbons, while your registered substance does not contain these chemical groups.

Therefore, the provided study does not fulfil the information requirement.

In the comments to the draft decision you agree with the request.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

3. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

You have provided the following information in your dossier:

i. OECD Guideline 202 (*Daphnia* sp. Acute Immobilisation Test), Japan chemicals collaborative knowledge database (J-check), 2017) National Institute of Technology and Evaluation, 2018;
ii. Non-guideline test (D. magna 48h), USEPA, 2017;
iii. Non-guideline test (*D. magna* 48h), Inventory Multitiered Assessment and Prioritisation, NICNAS, 2017.

In your comments to the draft decision you have provided a new study:

iv. OECD Guideline 202 (*Daphnia* sp. Acute Immobilisation Test) with an analogue substance Cinnamaldehyde (CAS no. 104-55-2; EC no. 203-213-9)

We have assessed this information and identified the following issues:

A. Incompliance of the studies with the specification of the applicable OECD TG

To fulfil the information requirement, a study must comply with OECD TG 202 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

- The test design is reported (*e.g.* static or semi-static test, number of replicates).

  However, you have not specified number of replicates and the test substance purity in studies i and iii.

- The test procedure is reported (*e.g.* composition of the test medium, loading in number of *Daphnia* per test vessel).

  However, you have not specified composition of the test medium, loading in number of *Daphnia* per test vessel in studies (i) and (iii).

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

- The methods used to prepare stock and test solutions is reported.

  However, the methods used to prepare stock and test solutions are not reported in any of the studies.

- The number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation.

  However, tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported in any of the studies.

- The dissolved oxygen and pH measured at least at the beginning and end of the test is reported.

  However, the dissolved oxygen and pH measured at least at the beginning and end of the test is not reported in studies (i) and (iii).

- Adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;

  However, you have not provided in any of the studies details on the analytical method (e.g. level of quantification) of exposure concentrations.

Based on the above, there are critical deficiencies in reporting the study methods and results. More specifically, relevant test methods and procedures including preparation of the test solutions and composition of the test medium were not reported. Also the test substance identity is limited to the EC-number and the test substance identity including impurities should also be provided to allow independent assessment of its suitability as the test substance. Furthermore, the number of immobilised daphnids during the course of the test was not reported and reliability of the reported results cannot be assessed independently. In addition, the performance parameters of the analytical method and details on what was analysed are not provided and therefore, analytical results of the test substance and its components at different concentrations and reliability of the test setup cannot be assessed.

Therefore, the requirements of OECD TG 202 are not met.

B. Invalid read-across adaptation

In your comments to the draft decision you have provided study iv. as well as an adaptation for information requirements according to Annex XI, Section 1.5 (read across). ECHA has assessed the provided adaptation, however, for the reasons explained in section "Appendix on Reasons common to several requests", your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5 (read-across).

On this basis, the information requirement is not fulfilled.

Study design

The Substance is possibly difficult to test due to the non-reliable water solubility and partitition coefficient tests. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for

your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

4. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

You have provided the following information in your dossier:

i. TG 201, *Desmodesmus subspicatus, key study,* [redacted] AB, 2017;
ii. TG 201, green algae (species not specified), *key study,* Japan chemicals collaborative knowledge database (J-check), 2017;
iii. TG 201, *Selenastrum capricornutum*, *supporting study***,** Ward et al. 2003;
iv. TG 201, *Pseudokirchneriella subcapitata*, *supporting study,* Environment Tier II Assessment for Cinnamic Aldehydes, NICNAS, 2017.

In your comments to the draft decision you provided the following:

v. TG 201, *Pseudokirchneriella subcapitata*, with an analogue substance Cinnamaldehyde (CAS no. 104-55-2; EC no. 203-213-9).

We have assessed this information and identified the following issues:

A. Incompliance of the studies with the specification of the applicable OECD TG

To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

- Exponential growth in the control cultures is observed over the entire duration of the test and at least 16-fold increase in biomass is observed in the control cultures by the end of the test;

  However, you have not reported in any of the studies details of the growth in the control cultures.

- The mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35% and the coefficient

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with *Pseudokirchneriella subcapitata* / *Desmodesmus subspicatus*. For other less frequently tested species, the value is ≤ 10%;

However, you have not reported in any of the studies coefficients of variation for the growth rates specified above.

- The results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;

  However, tabulated data on the algal biomass determined daily for each treatment group and control are not reported in any of the studies;

- Microscopic observation performed to verify a normal and healthy appearance of the inoculum culture are reported. Any abnormal appearance of the algae at the end of the test is reported;

  However, you have not reported normal and healthy appearance of the inoculum culture in studies (i), (ii) and (iv).

- Adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

  However, you have not reported analytical method including performance parameters of the method in any of the studies.

Based on the above, the validity criteria of OECD TG 201 are not met as the exponential growth rate and biomass growth cannot be verified. In addition, coefficients of variation for section-by-section specific and average specific growth rates during the whole test period in replicate control cultures cannot be verified.

There are critical methodological deficiencies resulting in the rejection of the study results. More, specifically normal and healthy inoculum culture cannot be confirmed. Also analytical method and the results of the analytical determination are not provided and therefore, the applied exposure concentration of the test substance cannot be confirmed. In addition, the reporting of the test results in all studies is not sufficient and does not allow confirming that certain validity criteria of the tests are met. As a result, the reporting of the studies are not sufficient to conduct an independent assessment of their reliability.

Therefore, the requirements of OECD TG 201 are not met.

B. Invalid read-across adaptation

In your comments to the draft decision you have provided study v. as well as an adaptation for information requirements according to Annex XI, Section 1.5 (read across). ECHA has assessed the provided adaptation, however, for the reasons explained in section "Appendix on Reasons common to several requests", your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5 (read-across).

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is potentially difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

You have adapted this standard information requirements by applying weight-of-evidence approaches in accordance with Annex XI, Section 1.2.

In support of your adaptation you have provided the following sources of information with the Substance and the analogue substances:

i) An *in vitro* cytogenicity / chromosome aberration study in mammalian cells (no guideline, not GLP, [redacted], 2018), with the Substance
ii) An *in vitro* cytogenicity / chromosome aberration study in mammalian cells (no guideline, not GLP, Galloway et al., 1987) with the analogue substance Cinnamaldehyde, EC No. 203-213-9, (CAS No.104-55-2),
iii) An *in vitro* cytogenicity / chromosome aberration study in mammalian cells (equivalent or similar to TG 473, no GLP, NTP, 2018) with the analogue substance (2E)-3-phenylprop-2-enal, EC No. 604-377-8, (CAS No. 14371-10-9),

As explained in section 3 of the Appendix on Reasons common to several requests, it is sufficient to reject your weight-of-evidence adaptation based on the fact that you have not submitted any justification of your adaptation.

ECHA has nevertheless assessed the provided sources of information and we identified the following issues:

To fulfil the information requirement, normally a study performed according to OECD TG 473/487 must be provided. OECD TG 473/487 investigate the following:
- Detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

The source information (i) to (iii) provide limited information on structural or numerical chromosomal aberrations in cultured cells.

In addition, the reliability of these sources of information is significantly affected by the following deficiencies:

1) Information from source substance(s) can contribute to weight of evidence adaptation only if the read-across is acceptable. Studies (ii.), and (iii.) are performed with analogue substances. However, for the reasons explained under section 1 of the Appendix on Reasons common to several requests, the provided studies performed on analogue substances cannot be considered reliable sources of information that could contribute to the conclusion on the key parameters investigated by the required OECD TG 473/487.

2) The specifications of OECD TG 473/487, include the following:
   iv) At least 300 well-spread metaphases (OECD TG 473) or 2000 cells (OECD TG 487) must be scored per concentration
   v) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberrations / micronuclei for the treated and control cultures must be reported.

However, the reported data for all studies you have provided do not include:

a) the scoring of at least 300 metaphases per concentration (OECD TG 473) and the scoring of at least 2000 cells per concentration (OECD TG 487).
b) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures (OECD TG 473) and data on the cytotoxicity and/or the frequency of micronuclei for the treated and control cultures (OECD TG 487).

As indicated in OECD TG 473 this information is required to conclude whether a test chemical is clearly negative. Therefore the acceptability criteria of the OECD TG 473 are not met and the provided study cannot be considered as a reliable source of information that could contribute to the conclusion on this information investigated by the required study.

In the absence of reliable information on all key elements and key investigations, no conclusion can be drawn on structural or numerical chromosomal aberrations in cultured mammalian cellsas required by the information requirement.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 473 or 487 study.

Therefore, your adaptation is rejected and the information requirements is not fulfilled.

In the comments to the draft decision you agree with the request.

Study design

To fulfil the information requirement for the Substance, either in vitrocytogenicity study in mammalian cells (OECD TG 473) or in vitromicronucleus study (OECD TG 487) are considered suitable.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

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

An in vitro gene mutation study in mammalian cells is an 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.

Triggering of the study

Your dossier contains data for an *in vitro* gene mutation study in bacteria and an adaptation (weight-of-evidence) for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

The information for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in section B.1 of this draft decision.

The result of the request for information in B.1 of this decision will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

Information in dossier

You have adapted this standard information requirements by applying weight-of-evidence approaches in accordance with Annex XI, Section 1.2.

In support of your adaptation you have provided the following source of information with the Substance and the analogue substances:

i) *in vitro* gene mutation study in mammalian cells (no guideline, not GLP, [redacted], 2018), with the Substance,
ii) *in vitro* gene mutation study in mammalian cells (Fiorio and Bronzetti, 1994), with the analogue substance Cinnamaldehyde, EC No. 203-213-9, (no guideline, not GLP, CAS No.104-55-2),
iii) *in vitro* gene mutation study in mammalian cells (no guideline, not GLP, ACToR, 2011), with the analogue substance Cinnamyl alcohol, EC No. 203-212-3, (CAS No. 104-54-1),

As explained in section 3 of the Appendix on Reasons common to several requests, it is sufficient to reject your weight-of-evidence adaptation based on the fact that you have not submitted any justification of your adaptation.

ECHA has nevertheless assessed the provided sources of information and we identified the following issues:

In any case, to fulfil the information requirement, the study has to be an *in vitro* gene mutation study conducted in mammalian cells in accordance with OECD TG 476 or OECD TG 490, respectively. OECD TG 476/490 investigate the following: Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) in cultured mammalian cells including data on the frequency of mutant colonies.

The source information (i.) to (iii.) provide limited information on gene mutation in cultured cells.

In addition, the reliability of these source of information is significantly affected by the following deficiency:

1) Information from source substance(s) can contribute to weight of evidence adaptation only if the read-across is acceptable. The studies (ii) and (iii) is performed with an analogue substance. However, for the reasons explained under section 1 of the Appendix on Reasons common to several requests, the provided studies performed on a source substance cannot be considered a reliable source of information that could contribute to the conclusion on the key parameters investigated by the required OECD TG 476/490.

2) One of the key parameters of the OECD TG 476/490 includes at least 4 concentrations to be evaluated, in each test condition. The studies (i) and (ii) were conducted with 2 doses only. The study (iii) does not specify the test

concentration. Therefore, the three sources of information have significant deficiencies.

On the basis of the information provided, it is not possible to conclude whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 476 or 490 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

In the comments to the draft decision you agree with the request.

Study design

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

3. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 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 adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following study records in your dossier:

(i) One automated report generated from the OECD QSAR Toolbox software with NOAEL values for source substances.
(ii) a Subchronic study, in rats (no guideline, no GLP, NICNAS 2017),with the substance
*(iii)*one-generation reproductive toxicity in rats (equivalent or similar to TG 421 no GLP, Secondary source: NICNAS, 2017) with the substance analogue 2-benzylideneoctanal, EC No. 202-983-3 , (CAS No.101-86-0),
*(iv)*a reproductive and developmental toxicity study in rats via gavage (no guideline, no specified GLP, Api *et al*., 2015), with the substance analogue 2-benzylideneoctanal, EC No. 202-983-3 , (CAS No.101-86-0),
(v) a reproductive study, in dogs, (no guideline, no specified GLP, USEPA 2009) with the substance analogue 2-(4-tert-butylbenzyl)propionaldehyde, EC No. 201-289-8, (CAS No. 80-54-6)
*(vi)*a reproductive and developmental toxicity study, in mice, gavage (no guideline, no specified GLP, NTRL 1983, NTP 2004) with the analogues substance (2E)-3-phenylprop-2-enal, EC No. 604-377-8, (CAS No. 14371-10-9),

In your comments to the draft decision you provide information on two additional studies:

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

(vii) a reproductive/developmentaltoxicity study performed according to OECD 421 in Sprague Dawley rats with the analogue subtance cinnamyl alcohol, EC. No. 203-212-3, (CAS 104-54-1),

(viii) a Pre-natal developmental toxicity study performed according to OECD 414 in Wistar rats with the analogue subtance cinnamaldehyde EC. No. 203-213-9, (CAS 104-55-2);

You state that the registration dossier will be updated to include the results of these studies However, the information currently available from your comments is not sufficient for ECHA to make an independent assessment of the studies because you did not provide any robust study summary . Therefore, it can not contribute to the consolidation of the weight of evidence adaptation submitted in the dossier. In the case where those studies would be used in the context of the weight of evidence adaptation, they would nevertheless be vitiated by the deficiencies regarding read across already identified under section 1.A.

Please also note 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 (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude that the substance does not induce reproductive toxicity.

As explained in section 3 of the Appendix on Reasons common to several requests, it is sufficient to reject your weight of evidence adaptation based on the fact that you have not submitted any justification of your adaptation.

ECHA has nevertheless assessed the provided sources of information and we identified the following issues:

Relevant information that can be used to support a weight of evidence adaptation for the information requirement of Section 8.7.3 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At a general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

a) Sexual function and fertility

Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The source of information (i) does not provide information on this key element.

The sources of information (ii-vi) only provide very limited information on these key investigations. More specifically, they provide only statements such as for source (iii) "*No effects observed for the oestrous cycle and reproductive performance*" and no detailed and numerical information on results. Source (iii) refers to OECD TG 421 (equivalent or similar), and therefore it can be assumed, but cannot be concluded, that all the relevant key parameters have been investigated. The sources (ii, iv-vi) are even less informative on the investigations conducted and give also only a high level statement on the results not allowing an independent assessment. Therefore, it is not possible to assess the sexual function and fertility.

In addition, the reliability of these sources of information is significantly affected by the following deficiency:

1) Information from source substance(s) can contribute to weight of evidence adaptation only if the read-across is acceptable. Studies (ii-vi) are performed with analogue substances. However, for the reasons explained under section 1 of the Appendix on Reasons common to several requests, the provided studies performed on source substances cannot be considered reliable sources of information that could contribute to the conclusion on the key investigations of the required OECD TG 421/422.

2) At least one of the sources of information addressing the key investigations must follow the rules for setting the dose levels as required in the information requirement (OECD TG 421, paragraph 24; OECD TG 422, paragraph 29) and be adequate for hazard classification and/or risk assessment as required by REACH. The sources show the following defiences in dose level setting: only one dose below the limit dose (ii, iv), too wide dose spacing between the top dose and the mid dose (iii), likely too low top dose (iv, v). In addition, inconsistent findings were recorded at limit dose (1000 mg/kg bw/day): toxicity in rats (iii) but not in mice (vi). Therefore, a limit dose approach seems not appropriate.

   None of the sources of information (ii – vi) investigate the dangerous (hazardous) properties following the rules for setting the dose levels as required in the OECD TG 421 or OECD TG 422 as explained above. Therefore, the sources of information have significant deficiencies.

Taken together, there is only limited information provided by source studies (ii-vi), and they cannot contribute to the conclusion on this key element due to the significant reliability issues.

b) Toxicity to offspring

Information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

The sources of information (i,ii and v) do not provide information on this key element (no mating, no pups).

The sources of information (iii, iv and vi) only provide very limited information on these key investigations. More specifically, they provide only statements such as for source (iii) "*No clinical signs"* in F1 and no detailed and numerical information on results. Source (iii) refers to OECD TG 421 (equivalent or similar), and therefore it can be assumed, but cannot be concluded, that all the relevant key parameters have been investigated. The sources (iv and vi) are even less informative on the investigations conducted and give also only a high level statement on the results not allowing an independent assessment. Therefore, it is not possible to assess the toxicity to offspring.

In addition, the reliability of these sources of information is significantly affected by the reliability issues as explained above under sub-sections 1) and 2) of section a) above. Therefore, they cannot contribute to the conclusion on this key element.

Taken together, there is only limited information provided by source studies (iii, iv and vi), and they cannot contribute to the conclusion on this key element due to the significant reliability issues

Systemic toxicity

As a minimum, information on systemic toxicity include clinical signs, survival, body weights, food consumption and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

The source of information (i) does not provide information on these key elements.

The sources of information (ii-vi) only provide limited information on clinical signs, survival, body weights, food consumption, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13. Only high level statement on the results are provided not allowing an independent assessment of results.

In addition, the reliability of these sources of information is significantly affected by the reliability issues as explained above under sub-sections 1) and 2) of section a) above. Therefore, they cannot contribute to the conclusion on this key element.

Conclusion

Taken together, the sources of information (i-vi) only provide limited information on the key elements: sexual function and fertility, toxicity to offspring and systemic toxicity and due to significant reliability issues, they cannot contribute to the conclusion on the potential of the Substance to cause reproductive toxicity. It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 421/422. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[5] administration of the Substance.

Information on data sharing for studies involving vertebrate animals

The jointly submitted registration for the Substance contains data that may be relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report."

4. Activated sludge respiration inhibition testing

Activated sludge respiration inhibition testing is an information requirement under Annex VIII to REACH (Section 9.1.4.).

You have provided the following information in your dossier:

i. Non-guideline test, *key study*, Toxicity of test chemical on the growth of microorganism, Journal of Society of Cosmetic Chemists, Sawano et al. 1993,
ii. Non-guideline test, *supporting study*, Evaluation of Antibacterial Effects on microorganisms, Journal of Food Science, Rui-Song Pei et al. 2009.

[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

In your comments to the draft decision you have provided the following new studies:

iii. ISO 8192 (Water quality - Test for inhibition of oxygen consumption by activated sludge for carbonaceous and ammonium oxidation) with the analogue substance Cinnamaldehyde (CAS no. 104-55-2; EC no. 203-213-9)

iv. Non-guideline test, *Escherichia coli*, with the analogue substance Cinnamaldehyde (CAS no. 104-55-2; EC no. 203-213-9), [redacted] 2009.

We have assessed this information and identified the following issues:

A. Compliance of the studies with the specification of the applicable OECD TG

To fulfil the information requirement, a study must comply with OECD TG 209 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

- Pre-treatment and maintenance of the activated sludge is reported, including concentration, source, conditions of operation of the wastewater treatment plant and influent it receives.

  However, no details on the activated sludge were provided in study (i).

- Test temperature, pH during the test and duration of the exposure phase(s) are reported.

  However, no details on the test conditions were provided in study (i).

- Specific oxygen consumption of the controls are reported.

  However, no details on the oxygen consumption of the controls were provided (in studies (i), (ii) and (iv).

- All measured data, inhibition curve(s) and method for calculation of EC50 are reported.

  However, no details on the measured data were provided in any of the studies.

- Results for total, and if appropriate, heterotrophic and nitrification inhibition are reported;

  However, no details on the heterotrophic and nitrification inhibition were provided in any of the studies.

- Name of the reference substance and results with this substance are reported.

  However, no details on the reference substance and results with this substance were provided (in studies (i), (ii) and (iv).

- All observations and deviations from the standard procedure, which could have influenced the result are reported.

  However, existing deviations of the reported non-guideline tests to the standard test protocols were not provided.

  Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the applied test protocol and their differences to the standard test requirements were not provided. Also procedure and

test consitions are not reported in sufficient detail. In addition the measured data, bacterial inhibition, information on the reference substance are not reported. As a result, the reporting of the studies is not sufficient to conduct independent assessment of their reliability.

B. Invalid read-across adaptation

In your comments to the draft decision you have provided studies (iii) and (iv) as well as an adaptation for information requirements according to Annex XI, Section 1.5 (read across). ECHA has assessed the provided adaptation, however, for the reasons explained in section "Appendix on Reasons common to several requests", your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5 (read-across).

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is potentially difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

5. Adsorption/ desorption screening

Adsorption/desorption screening is an information requirement under Annex VIII to REACH (Section 9.3.1.).

You have provided the following information:

i. OECD TG 121, (Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)) [redacted] (2017)
ii. Estimated value. Determination of adsorption value (Koc) of chemical (2E)-2-(phenylmethylidene)heptanal. U.S. National Library of Medicine (HSDB), 2017 HSDB

We have assessed this information and identified the following issues:

A. *Assessment of experimental data*

To fulfil the information requirement, a study must comply with OECD TG 121 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

- the measured HPLC-retention data of a test substance correlates with its adsorption coefficient Koc, a calibration graph of log Koc versus log k' has to be established with minimum of six reference points, at least one above and one below the expected value of the test substance should be used.

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

However, you have used six reference substances that had the Koc value in the range from 1.239 to 2.7 that is lower than the determined Koc value (i.e. 2.989) of the Substance.

Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the adsorption coefficient of the references substances do not overlap the adsorption coefficient of the test Substance and as a result, the applied reference substances do not provide reliable calibration data for the Substance.

Therefore, the requirements of OECD TG 121 are not met and the study i) you provided must be considered not compliant.

B. *Assessment of your (Q)SAR adaptation*

As explained in section 3 of the Appendix on reasons common to several requests, your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your (Q)SAR adaptation:

Lack of or inadequate documentation of the prediction (QPRF)

There is no QPRF or equivalent information provided. The information ii) you submitted must therefore be considered not compliant.

On the basis of the above, the information requirement is not fulfilled.

In the comments to the draft decision you agree with the request.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

Appendix C: Reasons to request information required under Annex IX of REACH

1. Pre-natal developmental toxicity study 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 adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following study records with analogue substances in your dossier:

(i) A developmental toxicity study on CD1 mice, oral gavage (no guideline, no specified GLP, Hardin *et al.* 1987/ Bickers *et al*. 2005)) with Cinnamaldehyde, EC No. 203-213-9, (CAS No.104-55-2),

(ii) One-generation reproductive toxicity in rats (equivalent or similar to TG 421, no GLP, Secondary source: NICNAS, 2017) with the substance analogue 2-benzylideneoctanal, EC No. 202-983-3 , (CAS No.101-86-0),

*(iii)*A reproductive and developmental toxicity study, in mice, gavage (equivalent or similar to TG 414, no specified GLP, NTRL 1983, NTP 2004) with the analogues substance (2E)-3-phenylprop-2-enal, EC No. 604-377-8, (CAS No. 14371-10-9),

In your comments to the draft decision you provide information of two additional studies:

*(iv)*a reproductive/developmentaltoxicity study performed according to OECD 421 in Sprague Dawley rats with the analogue subtance cinnamyl alcohol, EC. No. 203-212-3, (CAS 104-54-1),

(v) a Pre-natal developmental toxicity study performed according to OECD 414 in Wistar rats with the analogue subtance cinnamaldehyde EC. No. 203-213-9, (CAS 104-55-2);

You state that the registration dossier will be updated to include the results of these studies However, the information currently available from your comments is not sufficient for ECHA to make an independent assessment of the studies because you did not provide any robust study summary . Therefore, it can not contribute to the consolidation of the weight of evidence adaptation submitted in the dossier. In the case where those studies would be used in the context of the weight of evidence adaptation, they would nevertheless be vitiated by the deficiencies regarding read across already identified under section 1.A.

Please also note 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 (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the 1st species prenatal developmental toxicity.

As explained in section 2 of the Appendix on Reasons common to several requests, it is sufficient to reject your weight of evidence adaptation based on the fact that you have not submitted any justification of your adaptation.

ECHA has nevertheless assessed the provided sources of information and we identified the following issues:

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is

produced by the OECD TG 414 on one species. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

a) Prenatal developmental toxicity

Prenatal developmental toxicity includes information after prenatal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

All sources of information provide limited information on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) . However, they do not inform on structural malformations and variations (external, visceral and skeletal) as foreseen to be investigated in OECD TG 414. Source (iii) is claimed to be equivalent or similar to OECD TG 414, but this cannot confirmed from the method and results provided. It seems that the dams were terminated after the parturition and not at the end of pregnancy, and no investigations of foetuses according to OECD TG 414 have been reported. Similarly, both sources (i and ii) did not perform a detailed investigations on malformations and variations in foetuses.

In addition, the reliability of these sources of information is significantly affected by the following deficiency:

> Information from source substance(s) can contribute to weight of evidence adaptation only if the read-across is acceptable. Studies (i -iii) are performed with analogue substances. However, for the reasons explained under section 1 of the Appendix on Reasons common to several requests, the provided studies performed on source substances cannot be considered reliable sources of information that could contribute to the conclusion on the key parameters investigated by the required OECD TG 414.

Taken together, critical information on prenatal developmental toxicity, external, visceral and skeletal malformations and variations is missing from the sources of information (i-iii), and they cannot contribute to the conclusion on this key element also due to the significant reliability issues.

b) Maternal toxicity

Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

All sources of information only provide limited information on maternal survival, body weight and clinical signs. However, the reliability of all sources of information is significantly affected by reliability issues as explained above under section a) above. Therefore, they cannot contribute to the conclusion on this key element.

Taken together, there is only limited information provided by source studies (i-iii), and they cannot contribute to the conclusion on this key element due to the significant reliability issues.

c) Maintenance of pregnancy

Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

All sources of information do not sufficiently inform on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy due to insufficient reporting.

In addition, the reliability of all sources of information is significantly affected by reliability issues as explained above under a). Furthermore, sources (i, iii) do not follow the exposure duration criteria of OECD TG 414 (paragraph 13) and are deficient.Therefore, they cannot contribute to the conclusion on this key element.

Taken together, there is only limited information provided by source studies (i-iii), and they cannot contribute to the conclusion on this key element due to the significant reliability issues.

Conclusion

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 414, prenatal developmental toxicity study. Therefore, your adaptation is rejected and 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.

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[7] administration of the Substance.

Information on data sharing for studies involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report."

2. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided the following information:

i. OECD Guideline 211 (*Daphnia magna* Reproduction Test), Japan chemicals collaborative knowledge database (J-check), National Institute of Technology and Evaluation, 2017.

We have assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with the OECD TG 211 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

[6] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[7] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

- parental mortality may only be excluded from the data analysis of the test result if it can be demonstrated that mortality does not follow concentration-response pattern.

  However, you have not provided information on parental mortality.

- the test design is reported (*e.g.* number of replicates, number of parents per replicate).

  However, you have not provided sufficient details on number of replicates and parents per replicate.

- the test procedure is reported (*e.g.* loading in number of *Daphnia* per litre, test medium composition).

  However, you have not provided required details on the loading rate of Daphnia or test medium composition.

- the methods used to prepare stock and test solutions is reported.

  However, you have not provided required details on preparation of the stock and test solutions.

- detailed information on feeding, including amount (in mgC/daphnia/day) and schedule is reported.

  However, you have not provided any details on feeding.

- results from any preliminary studies on the stability of the test substance is reported.

  However, you have not provided required details on any preliminary studies.

- water quality monitoring within the test vessels (*i.e.* pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) is reported.

  However, you have not provided any details on water quality monitoring.

- the full record of the daily production of living offspring during the test by each parent animal is provided.

  However, you have not provided any information on the daily production of living offspring.

- the coefficient of variation for control reproductive output is reported.

  However, you have not reported the required coefficient of variation.

  Based on the above, there are critical deficiencies in reporting the study methods and results. More, specifically the applied test design, procedure and preparation of test solutions are not reported in sufficient detail. In addition the monitoring of the water quality, feeding of Daphnia, mortality rate and production of living of offspring including variability of the reproductive output (coefficient of variation) are not reported. As a result, the reporting of the study is not sufficient to conduct an independent assessment of its reliability.

  Therefore, the requirements of OECD TG 211 are not met.

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision you agree with the request.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

3. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided the following information:

i. QSAR estimate of long-term toxicity to fish, ECOSAR Version 1.11

We have assessed this information and identified the following issue[s]:

As explained in section 2 of the Appendix on reasons common to several requests, your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your (Q)SAR adaptation:

The (Q)SAR estimate is based on ECOSAR 1.11, model Fish ChV - Allyl/Vinyl aldehydes, to predict LT toxicity to fish. The input structure for the prediction is: c1(\C=C(\CCCCC)C=O)ccccc1. The NOEC is reported as 0.169 mg/l. The Substance used as input for the prediction is identified as CAS 122-40-7.

1. *Inappropriate measures of robustness of the model*

   The ECOSAR model Allyl/Vinyl aldehydes is not based on training set data, but on extrapolation from acute fish data via the ACR method. The model is not sufficiently valid.

2. *Low reliability of the prediction*

   The prediction for the Substance used as input is not reliable because the training set does not contain long term fish toxicity data.

3. *Lack of or inadequate documentation of the prediction (QPRF)*

   There is no QPRF or equivalent information provided.

On this basis, the information requirement is not fulfilled.

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

In the comments to the draft decision you agree with the request.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is possibly difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

Information on data sharing for studies involving vertebrate animals

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report.

4. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is an information requirement under Annex IX to REACH (Section 9.3.2.).

You have provided the following information:

i. Calculated BCF estimate. *Supporting study.* Data generated using the EPI Suite program developed by the USEPA. BCFBAF Program (v3.00), [redacted] – 2019.
ii. Calculated BCF estimate from the ACS database. *Supporting study.* Biological properties, SciFinder, American Chemical Society (ACS), 2017.
iii. Experimental BCF estimate from the HSDB database. *Key study.* Determination of bioaccumulation value (BCF) of chemical (2E)-2-(phenylmethylidene)heptanal. HSDB (Hazardous Substances Data Bank); US national Library of Medicine reviewed by SRC, 2017.
iv. Experimental BCF estimate from the HSDB database. Determination of bioaccumulation value (BCF) of test chemical. *Supporting study.* HSDB (Hazardous Substances Data Bank); US national Library of Medicine reviewed by SRC, 2017.
v. Experimental BCF estimate from the HSDB database. *Supporting study.* Determination of bioaccumulation value (BCF) of test chemical. HSDB (Hazardous Substances Data Bank); US national Library of Medicine reviewed by SRC, 2017.
vi. Experimental data from the J-check database. *Supporting study.* Bioaccumulation: aquatic/sediment, National Institute of Technology and Evaluation. Japan chemicals collaborative knowledge database (J-check), 2017.

We have assessed this information and identified the following issues:

1) BCF data based on experimental tests on fish (study vi)

To fulfil the information requirement, a study must comply with the OECD TG 305 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- the analytical method used for the quantification of the test material in the test

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

solutions and in fish tissues is described. The recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range are reported;
- individual fish wet weights and total lengths for all sampling intervals are provided, and be linked to the analysed chemical concentration for that individual. The data are used to correct the BCF for growth dilution;
- tabulated test material concentration data in individual fish and water (including mean values for test group and control, standard deviation and range, if appropriate) for all sampling times are provided.

However, you have not provided any of the information specified above.

Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. Therefore, the requirements of OECD TG 305 are not met in study (vi).

2) Assessment of your (Q)SAR adaptation (studies i-v)

As explained in section 2 of the Appendix on reasons common to several requests, your adaptation is rejected.

In relation to given information on studies iii-v we note, that even though you indicate in the dossier that the studies are considered as *"experimental"*, we understand that the provided values for studies iii-v are rather based on estimated values and therefore, we have requalified the tests as (Q)SAR studies and assessed them in this section.

The following endpoint-specific deficiencies have been identified in your (Q)SAR adaptation:

1. Low reliability of the prediction (study i)

The registrant used BCFBAF v3.00 software to predict a BCF value of 334 L/kg (regression based estimate). Log Kow used by BCF estimates: 4.33 (calc). The ESR only includes reporting of results, but no assessment of the applicability of the model for the substance. The test material is identified with CAS 122-40-7

The training set does not cover well the structural features of the substance. When running the BCF Models Meylan and Arnot-Gobas in VEGA (v. 1.1.5) (which are derived from the Episuite BCFBAF models), VEGA highlights the following issues with the predictions:
- only moderately similar compounds with known experimental value in the training set have been found;
- reliability of logP value used by the model is not adequate;
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

2. Lack of or inadequate documentation of the prediction (QPRF) studies *(i-v)*

- There is no QPRF or equivalent information provided.

Therefore, the adaptation is rejected in studies (i-v).

In the comments to the draft decision you state that "*we have considered to initiate the partition coefficient study of the target chemical (2E)-2-(phenylmethylidene)heptanal (CAS*

no. 78605-96-6; EC no. 800-696-3) and on the basis of partition coefficient result, will further decide for the Bioaccumulation in aquatic species study."

We understand that your intention is to adapt this information requirement based on Annex IX section 9.3.2. Column 2: *The study need not be conducted if the substance has a low potential for bioaccumulation (for instance a log Kow ≤ 3).* However, the information in your comments is not sufficient for ECHA to make an assessment because you have only provided an intention to adapt without supporting information. Please note 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 (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation). You remain responsible for complying with this decision by the set deadline."

On this basis, the information requirement is not fulfilled.

Study design

Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (ECHA Guidance R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test substance in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

5. Simulation testing on ultimate degradation in surface water

Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

You have provided the following information:

i. QSAR estimate. Bio-degradation in water and sediment by EPI (Estimation Programs Interface) Suite Sustainability Support Service (Europe) AB – estimated, 2018.

We have assessed this information and identified the following issues:

As explained in section 2 of the Appendix on reasons common to several requests, your adaptation is rejected.

In addition, the following endpoint-specific deficiencies have been identified in your (Q)SAR adaptation:

Modelled endpoint not well defined

You specify that the property that is modelled is the half-life of the test chemical in water.

You have provided a (Q)SAR model *Fugacity Model by EPI Suite* which is based on data generated using the following methodology: MITI 28 day biodegradability data (biodegradation screening test data).

The endpoint predicted by the (Q)SAR is not the same as the endpoint measured by the relevant test protocol.

In the comments to the draft decision you have provided the following:

> *"For fulfilling the requirement of Simulation testing on ultimate degradation in surface water (Annex IX) and to overcome the above reported issues; we have reviewed the study conducted in accordance with the principles of OECD TG 301 & other available information of Biodegradability of target chemical (2E)-2-(phenylmethylidene)heptanal (CAS no. 78605-96-6; EC no. 800-696-3) in water.*
>
> *On the basis of the overall biodegradability results and as per the reviewer judgement, target chemical (2E)-2-(phenylmethylidene)heptanal (CAS no. 78605-96-6; EC no. 800-696-3) was considered to be readily biodegradable in water.*
>
> *Considering the ready biodegradability in water results; we adapted the waiver for this endpoint considering the specific rules for adaptation from column 1 as specified in the REACH regulation –*
>
> *''The study need not be conducted if: — the substance is readily biodegradable''*
>
> *Thus, the adaptation taken for the Simulation testing on ultimate degradation in surface water (Annex IX) is considered to be valid."*

We understand that you are referring to adaptation in Annex IX Sections 9.2.1.2 (request C.5 Simulation testing in water), 9.2.1.3 (request C.6 Simulation testing in soil), 9.2.1.4. (request C.7 Simulation testing in sediment) or 9.2.4. (request C.8 Identification of degradation products) in column 2 stating that the simulation testing study need not be conducted if the substance is readily biodegradable.

We have assessed your comment and identified the following issue:

> ECHA Guidance R.7.9.4.1. specifies that a substance may be regarded as readily biodegradable if 60% degradation is achieved in a respiratory test within 28 days. Further, for mono-constituent substance, the pass level needs to be reached in a 10-day window within the 28-day period of the test.
>
> Under section 5.2.1. of your technical dossier, you provide a respiratory test according to OECD TG 301D. Only 41.19% biodegradation was achieved after 42 days.
>
> On this basis, the Substance is not regarded as readily biodegradable and your adaptation is rejected.

Therefore, the adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (ECHA Guidance R.11.4.1.1.3.).

The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

As specified in ECHA Guidance R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test substance concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; ECHA Guidance R.11.4.1.).

6. Sediment simulation testing

Sediment simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.4.) for substances with a high potential for adsorption to sediment.

The Substance does not have reliable water solubility, partition coefficient and adsorption coefficient values available and therefore may possess high potential for adsorption to sediment.

You have provided the following information:

i. QSAR estimate. Biodegradation in water: screening tests. U.S. Environmental Protection Agency, 2017

We have assessed this information and identified the following issues:

As explained in section 2 of the Appendix on reasons common to several requests, your adaptation is rejected.

In addition, the following endpoint-specific deficiencies have been identified in your (Q)SAR adaptation: *Modelled endpoint not well defined*

You specify that the property that is modelled is the half-life of the test chemical in sediment.

You have provided a (Q)SAR model *Mackay EQC Fugacity Level III* which is based on data generated using the following methodology: MITI 28 day biodegradability data (biodegradation screening test data).

The endpoint predicted by the (Q)SAR is not the same as the endpoint measured by the relevant test protocol.

Therefore, the adaptation is rejected.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision you have provided an adaptation similar to the one already analysed under section C.5. We reject your adaptation for the same reasons as the ones provided under section C.5.

Study design

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

In accordance with the specifications of OECD TG 308, you must perform the test using two sediments. One sediment should have a high organic carbon content (2.5-7.5%) and a fine texture, the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture. If the Substance may also reach marine waters, at least one of the water-sediment systems should be of marine origin.

The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 308.

In accordance with the specifications of OECD TG 308, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (ECHA Guidance R.7.9.4.1.). By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 308; ECHA Guidance R.11.4.1.).

7. Soil simulation testing

Soil simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.3.) for substances with a high potential for adsorption to soil.

The Substance does not have reliable water solubility, partition coefficient and adsorption coefficient values available and therefore has high potential for adsorption to soil.

You have adapted this standard information requirement according to Annex XI, Section 1.2. of REACH (weight of evidence). In support of your adaptation, you have provided the following sources of information:

i. (Q)SAR prediction of biodegradation half-life of test chemical in soil based on Fugacity Model level III by EPI Suite v 4.1 estimation database, and
ii. (Q)SAR estimation of half-life of the chemical in soil by using Mackay EQC Fugacity Level III.

As explained in section 2 of the Appendix on reasons common to several requests, your adaptation is rejected as you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation and identified the following issues.

To fulfil the information requirement, normally a study performed according to OECD TG 307 must be provided. OECD TG 307 requires the study to investigate the following key investigations:

1) the rate of aerobic and anaerobic transformation of the test material in four soil types, and
2) the identity and rates of formation and decline of transformation products in at least one soil type.

The sources of information (i) and (ii) may provide some relevant information on degradation of the test material in soil.

However, the reliability of these sources of information is significantly affected by the following deficiencies:

1. As explained in section 2 of the Appendix on reasons common to several requests, your (Q)SAR adaptation has significant deficiencies.

2. In addition, the following endpoint-specific deficiency has been identified in your (Q)SAR adaptation:

   Modelled endpoint not well defined

   You specify that the property that is modelled is the half-life of the test chemical in soil.

   You have provided two (Q)SAR models (i) *Fugacity Model by EPI Suite* and (ii) *Mackay EQC Fugacity Level III* which are based on data generated using the following methodology: MITI 28 day biodegradability data (biodegradation screening test data).

   In conclusion, the reported information is considered insufficient to estimate degradation of the Substance in soil, since the endpoint in the selected model is not the same as the endpoint measured by the relevant test protocol.

As a result, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance is degraded in soil foreseen to be investigated in an OECD TG 309 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments to the draft decision you have provided an adaptation similar to the one already analysed under section C.5. We reject your adaptation for the same reasons as the ones provided under section C.5.

Study design

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

In accordance with the specifications of OECD TG 307, you must perform the test using at least four soils representing a range of relevant soils (*i.e.* varying in their organic content, pH, clay content and microbial biomass).

The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 307.

In accordance with the specifications of OECD TG 307, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (ECHA Guidance R.7.9.4.1.). By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 307; ECHA Guidance R.11.4.1.).

8. Identification of degradation products

Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

The Substance is not readily biodegradable and you have provided no information on the identity of transformation/degradation products for the Substance.

Therefore, this information requirement is not met.

This information is required for the purpose of the PBT/vPvB assessment (Annex I, Section 4) and the risk assessment (Annex I, Section 6) of the Substance.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision you have provided an adaptation similar to the one already analysed under section C.5.We reject your adaptation for the same reasons as the ones provided under section C.5.

Study design

Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation studies requested in Appendices C.5 to C.7 or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Appendix C.5) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, *e.g.* 20°C) and at higher application rate (*i.e.* > 100 µg/L).

To determine the degradation rate of the Substance, the requested studies according to OECD TG 308/307 (Appendices C.6 and C.7) must be conducted at 12°C and at test material application rates reflecting realistic assumptions. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline) and at higher application rate (*e.g.* 10 times).

Appendix D: 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[8].

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 dossiers[9].

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

Appendix E: General recommendations when conducting and reporting new tests for REACH purposes

A. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult ECHA Guidance R.7b (Section R.7.9.), R.7c (Section R.7.10) and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

Appendix F: Procedure

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 13 January 2021.

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

ECHA took into account your comments and 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 G: List of references - ECHA Guidance[10] 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)[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 documents[13]

[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 H: 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
[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.