~~Confidential~~

Helsinki, 13 April 2022

Addressees
Registrants of JS_112-45-8_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
28/11/2018

Registered substance subject to this decision ("the Substance")
Substance name: Undec-10-enal
EC number: 203-973-1
CAS number: 112-45-8

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 July 2023***.

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

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

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

4. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: OECD TG 301B/C/D/F or OECD TG 310)

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

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG

203)

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

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

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

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

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

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 and VIII to REACH, for registration at 10-100 tpa;
- 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".

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. from your registration dossier**

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

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

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

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Predictions for toxicological and ecotoxicological properties

You read across between the structurally similar substances,

- Decanal (CAS: 112-31-2; EC: 203-957-4),
- Nonanal (CAS: 124-19-6; EC: 204-688-5),
- 2,6-Dimethyl-5-heptenal (CAS: 106-72-9; EC: 203-427-2),
- heptanoic acid (CAS: 111-14-8; EC: 203-838-7),
- 1-Tetradecene (CAS: 1120-36-1; EC: 214-306-9),
- 1-Hexene (CAS: 592-41-6; EC: 209-753-1),
- 2-Undecanone (CAS: 112-12-9; EC: 203-937-5),
- Docosanoic acid (CAS: 112-85-6; EC: 204-010-8),
- Tridecan-1-ol (CAS:112-70-9; EC:203-998-8),
- 2-Octanone (CAS: 111-13-7; EC: 203-837-1),
- Oct-1-ene (CAS: 872-05-9; EC: 203-893-7), and
- 1-Decene (CAS: 872-05-9; EC: 212-819-2)

as source substances 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

[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

properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following deficiency with regards to predictions:

1) Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the study(ies) on the source substance(s) (Guidance on IRs and CSA, Section R.6.2.6.1.).

You have provided robust study summaries for studies conducted with other substances than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance.

In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance(s).

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not 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 read-across approach under Annex XI, Section 1.5. from your comments to the draft decision

In your comments to the draft decision, you submitted a different read-across adaptation from the one submitted in your dossier, relying on different source substances to adapt the following standard information requirements:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1., column 2)

ECHA has considered the scientific and regulatory validity of your read-across adaptations 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[4,5].

A. Predictions for toxicological properties

You provide a read-across justification document attached to your comments to the draft decision (entitled "[redacted]")

You predict the properties of the Substance from information obtained from the following source substance:

Undecanal (CAS: 112-44-7; EC: 203-972-6)

You provide the following reasoning for the prediction of toxicological properties:

- "*the target and the source substances, i.e., Undec-10-enal (CAS: 112-45-8; EC: 203-973-1) and Undecanal (CAS: 112-44-7; EC: 203-972-6), share structural similarity with common functional groups (alkyl and aldehyde groups) and an aliphatic methylene chain (11 carbon atom-length)*" and "*The target is an unsaturated aldehyde and has a double covalent bond at the 10th position. The read-across analogue is a saturated aldehyde*".
- *"The physicochemical profiles of the target and source substances are similar"*
- "*The target and the source substances* […] *are straight-chain, aliphatic primary aldehydes that are biotransformed to the same metabolites*"
- "*Metabolites of the target and source substances are simple structures that have no structural alert for toxicity, and they are closely related to substances of known low toxicity*"
- "*The target and source substances are characterised by a similar degree of impurities. The impurities present in the target and source substances have not been identified*"
- "*No experimental data on absorption, distribution and excretion is available for the source and target substances and their metabolites*". However, based on general knowledge you consider that ADME properties are expected to be similar.
- You consider that both the target and source substance have low oral and dermal acute toxicity, have similar irritation properties, were found to be non-clastogenic in *in vitro* mammalian chromosomal aberration tests and showed similar (lack of) toxicity in short-term repeated-dose toxicity studies.
- "*Overall, the descriptors and various alerts predicted by QSAR toolbox v.3.4 indicate that the target substance and read-across analogue are functionally and structurally similar*".

ECHA understands that your read-across hypothesis is based on the formation of common (bio)transformation products. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

We have identified the following issues with the prediction of toxicological properties:

1) Inadequate read-across hypothesis

[4] 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)

[5] 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

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 include an explanation why the properties of the Substance may be predicted from other substances in the group, i.e. a read-across hypothesis.

This hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.).It should also explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

Your read-across hypothesis is based on structural similarities and similarities in the physico-chemical properties of the source substance and the Substance. You consider that these elements are a sufficient basis for predicting the toxicological properties of the Substance.

You state that "*The presence of unsaturation (double-bond) at 10th carbon in the target likely has no significant influence on the metabolism*." However, you have not substantiated why this structural difference between the source and target substances would have no impact on the prediction. Furthermore, you have not provided any justification that toxicodynamics will be similar enough so that no impact is expected on the formation of the common compound.

Physico-chemical similarity alone does not necessarily lead to predictable or similar toxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances, and thus why the properties of the Substance may be predicted from information on the source substance(s)

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

In your justification document, you list processes via which the source substance and

the Substance are potentially metabolised. However, you also state that: "*Experimental data on the metabolism of the target and source substances in humans and animals are lacking in the scientific literature".* You do not provide information on the rate or extent to which the common metabolite is formed from the parent substances and you do not provide experimental data on absorption, distribution and excretion of the source substance and the Substance. You briefly imply that the source substance may not be metabolized at the same rate as the target, potentially voiding your prediction: "*In general, saturated linear-chain primary aldehydes are better substrates of aldehyde dehydrogenase than unsaturated, branched-chain aldehydes*".

Comparing the toxicokinetic profiles (including experimental evidence on the formation dynamics of the common compound, which may be affected by structural differences between the parent substances) of the target substance and the Substance is crucial to determine whether both substances have similar properties, and in turn cause the same types of effects. In the absence of information addressing this matter, you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis.

3) *Adequacy and reliability of source studies*

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

Specific reasons why the studies on the source substance do not meet these criteria are explained further below under Appendix A.3. Therefore, no reliable predictions can be made for these information requirements.

B. Predictions for ecotoxicological properties

You provide a read-across justification document attached to your comments to the draft decision (entitled "[redacted]")

You predict the properties of the Substance from information obtained from the following source substance:

1-Hexadecene (CAS: 629-73-2; EC: 211-105-8)
1-Octadecene (CAS: 112-88-9; EC: 204-012-9);
1-Tetradecene (CAS: 1120-36-1; EC: 214-306-9)
1-Decene (CAS: 872-05-9; EC: 212-819-2)
1-Dodecanol (CAS: 112-53-8; EC: 203-982-0)
Nonanal (CAS: 124-19-6; EC: 204-688-5)
1-Dodecene (CAS: 112-41-4; EC: 203-968-4)

You provide the following reasoning for the prediction of toxicological properties:

- "*The target and read-across analogues used are all mono-constituent substances* […] *and contains alkene as the common basic moiety*";
- "*The target and most of the read-across analogues have alkene as common basic moiety in their structure. In addition to this, common group shared between target substance and read across analogue Nonanal (CAS no. 124-19-6; EC no. 204-688-5) include aldehyde group*";
- "*OECD (Q)SAR Toolbox v.3.4, it is indicated that the target and the read-across analogues share similar structural alerts*";

- "*The target and the read-across analogues demonstrate the same alerts* […] *by the profilers like acute aquatic toxicity classification by Verhaar (Modified)* [and for] *general mechanistic alerts like DNA binding, and Protein binding alerts*";
- The target and analogues substances have similar physico-chemical properties;
- The target and analogues substances have similar biodegradation potential as predicted by BioWin. You state that "*(Q)SAR analysis and experimental data indicate that the analogue substances will give rise to degradation products with different ecotoxicological profile*".

ECHA understands the read-across hypothesis submitted in your comments to the draft decision assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

We have identified the following issues with the predictions of ecotoxicological 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 bridging studies to compare properties of the Substance and source substances to confirm your claimed worst-case prediction.

   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 provided the study used in the prediction in the registration dossier. Apart from that study, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of data for the target substance that would confirm that both substances cause the same type of effects.

2) *Adequacy and reliability of source studies*

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

   Specific reasons why the studies on the source substance(s) do not meet these criteria are explained further below under the applicable information requirement sections A.2, A.3, B.4 and C.3. Therefore, no reliable predictions can be made for these information requirements.

C. Conclusion on the read-across approach

For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance. Your read-across approach under Annex XI, Section 1.5. proposed as part of your comments to the draft decision is rejected.

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

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

- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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 issue:

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,
- 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 any 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 the issues above, your adaptations are rejected.

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

4. Assessment of the weight of evidence adaptations under the requirements of Annex XI, section 1.2

You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Your weight of evidence adaptation raises the same deficiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, 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 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.

However, for each relevant information requirement, 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.

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

1. *Reliability of the read across approach*

Section 1 of the present Appendix identifies deficiencies of the read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

2. *Reliability of the QSAR information*

Section 2 of the present Appendix identifies deficiencies of the QSARs used in your dossier for some ecotoxicological and environmental fate information requirements. These findings apply equally to the sources of information relating to QSARs submitted under your weight of

evidence adaptations.

Additional issues related to weight of evidence are addressed under the corresponding endpoints.

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

1. In vitro gene mutation study in bacteria

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

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 analogues:

i. an *in vitro* gene mutation study in bacteria, not according to a specific guideline (GLP not specified) with the Substance (Florin, 1980);
ii. an *in vitro* gene mutation study in bacteria according to OECD TG 471 (GLP not specified) with the analogue decanal (CAS: 112-31-2; EC: 203-957-4) (Ishidate 1984).

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

In any case, to fulfil the information requirement, normally a study performed according to OECD TG 471 must be provided. OECD TG 471 investigates gene mutations in bacteria as a key investigation using 5 different bacterial strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The information in your dossier provides relevant information on gene mutations in bacteria. However, it does not cover all essential aspects as defined above. More specifically, the sources of information i. and ii. do not provide information on either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

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

A. *Read-across adaptation (information source ii)*

As explained in the Appendix on reasons common to several requests, you have not demonstrated that the applied read across for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

B. *The specifications of OECD TG 471, include the following:*

a) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 ml/plate.
b) At least 5 doses must be evaluated, in each test condition.
c) Triplicate plating must be used at each dose level.
d) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
e) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
f) The mean number of revertant colonies per plate must be reported for the treated

doses and the controls.

The reported data for the studies you have provided did not include:

a) a maximum dose of 5 mg/plate or 5 ml/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. (studies i and ii)
b) the evaluation of at least 5 doses in each test condition. (studies i and ii)
c) triplicate plating at each dose level. (studies i and ii)
d) a positive control. (studies i and ii)
e) a negative control with a number of revertant colonies per plate inside the historical control range of the laboratory. (study i)
f) data on the number of revertant colonies per plate for the treated doses and the controls. (studies i and ii)

On this basis, the sources of information i. and ii. were conducted at test concentrations that are too low and therefore do not provide reliable information to detect gene mutations in bacteria for the selected test materials. In addition, there are issues with the test conditions and/or reporting of these studies which significantly affect the overall reliability of the reported results. As a result, the provided studies cannot be considered as a reliable source of information that could contribute to the conclusion on the information investigated by the required study.

Taken together, the sources of information provide information on gene mutations but not in all required bacterial strains. In addition, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

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 property foreseen to be investigated in an OECD TG 471. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In the comments to the draft decision, you agree to perform the requested study.

Information on the study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed.

2. 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 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, short-term toxicity to aquatic invertebrates by ECOSAR Version 1.11;
ii. Read across, OECD TG 202, Japan chemicals collaborative knowledge database (J-check), 2018, test substance: 2-Undecanone (CAS: 112-12-9; EC: 203-937-5);
iii. Read across, OECD TG 202, European Food Safety Authority (EFSA), 2008, test substance: undecan-2-one (CAS: 112-12-9; EC: 203-937-5);
iv. Read across, OECD TG 202, Hazardous substance databank U.S National Library of Medicine 2017, test substance: docosanoic acid (CAS: 112-85-6; EC: 204-010-8).

In your comments to the draft decision, you propose to "*further* [to adapt] *the weight of evidence approach in the technical dossier*" by using a new read-across approach. In support of this new adaptation, you provide the following sources of information:

v. OECD TG 202, performed with the analogue substance: 1-octadecene (CAS: 112-88-9; EC: 204-012-9);
vi. OECD TG 202, performed with the analogue substance: 1-tetradecene (CAS: 1120-36-1; EC: 214-306-9).

As explained in section 4 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 for your adaptation.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your weight of evidence adaptation.

To fulfil the information requirement, normally a study performed according to OECD TG 202 must be provided. OECD TG 202 requires the study to investigate the following key investigation:

- the concentration of the substance leading to 50% immobilisation of daphnids after 48 hours.

The sources of information (i-vi) may provide relevant information on the key investigation of short-term toxicity to aquatic invertebrates.

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

A. (Q)SAR adaptation (source of information i)

As explained in the Appendix on reasons common to several requests, you have not demonstrated that the applied (Q)SAR adaptation for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

In addition, we have identified the following endpoint specific issue:

The prediction is not adequate due to low reliability

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 condition must be met:

- the model predicts well substances that are similar to the substance of interest.

Your registration dossier provides the following information: predictions were conducted with the model for neutral organics (baseline toxicity).

The following information is also available for the Substance used as input for the prediction: the Substance is a mono aldehyde and considered as an organic chemical with excess toxicity (i.e. not only as a neutral organic chemical since it possesses more specific mode of toxicity) and you have not used the corresponding model from ECOSAR.

The prediction for the Substance used as input is not reliable because the model you

used has no similar substances in the training set.

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

B. *Read-across adaptations (sources of information ii-vi)*

As explained in the Appendix on reasons common to several requests (Section 1 and 2), you have not demonstrated that the applied read across for the Substance currently included in your registration dossier or the newly proposed read-across proposed as part of your comments to the draft decision is adequate for the purpose of classification and labelling and/or risk assessment.

C. *Insufficient documentation of the additional read-across studies referred to in your comments to the draft decision (sources of information v-vi)*

Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 202. Therefore, the following specifications must be met:

Reporting of the methodology and results

- the number of immobilised daphnids is determined at 24 and 48 hours;
- the data should be summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations must be provided.

However, you have not provided adequate information on these studies in the form of robust study summaries including, for instance, the information listed above.

Independent on the issues identified in the Appendix on reasons common to several requests for the proposed read-across, no conclusion on the reliability of these new studies can be made. Please note that this decision does not consider 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.

As a result of these deficiencies, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance shows short-term toxicity to aquatic invertebrates foreseen to be investigated in an OECD TG 202 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to high adsorptive properties (log Kow of 4.672 based on OECD TG 117). 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 solutions.

3. Growth inhibition study on aquatic plants

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

In your registration dossier you have provided the following information:

i. A growth inhibition study on algae according to OECD TG 201 with the Substance ([redacted], 2015).

In your comments to the draft decision you have requalified study i. as one source of information of a weight of evidence adaption under section 1.2. of Annex XI. In support of your adaptation, you have provided the following additonal sources of information:

ii. OECD TG 201, performed on the analogue substance: nonanal (CAS: 124-19-6; EC: 204-688-5);
iii. OECD TG 201, performed on the analogue substance: 1-Dodecene (CAS: 112-41-4; EC: 203-968-4)

We have assessed this information and identified the following issues:

As explained in section 4 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 documentation for your adaptation.

In spite of this critical deficiency, ECHA has nevertheless assessed the reliability and relevance of the source of information provided.

To fulfil the information requirement, normally a study performed according to OECD TG 201 must be provided. OECD TG 201 requires the study to investigate the following key investigation:

- the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated.

The sources of information (i-iii) may provide information on the inhibition of growth of algae.

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

A. Reliability of the experimental study on the Substance (study i)

To inform on growth inhibition on aquatic plants, normally a study according to OECD TG 201 needs to be conducted. Further, if the substance to be tested is difficult to test the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) must be followed. Accordingly, the following specifications/conditions must be met:

Validity criteria

- 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%.

  However, the mean coefficient of variation for section-by-section specific growth in the control was not reported and based on the provided growth values it is ≥ 35%.

Technical specifications impacting the sensitivity/reliability of the test

- three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included.

  However, the number of replicates was 2 in each test concentration.

- one of the two alternative growth medium (*i.e.* the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified.

  However, the test medium is described as Bold's Basal Medium (BBM) and you have not provided a justification as why you did not use one of the two alternative growth medium of OECD TG 201.

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range must be available. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided.

  However, analytical monitoring of exposure was not conducted and justification that analytical monitoring is not technically feasible was not provided.

Based on the above, the validity criteria of OECD TG 201 are not met, since the mean coefficient of variation for section-by-section specific growth rates is not provided. In addition, there are critical methodological deficiencies. More specifically, only two replicates were used and there is no detailed description of the growth medium and justification why it is used. Also, no analytical monitoring of exposure was provided. All of the listed issues are deviations from the OECD TG and significantly impact the reliability of the test results.

B. *Read-across adaptations (sources of information ii-iii)*

As explained in the Appendix on reasons common to several requests (Section 2), you have not demonstrated that the newly proposed read-across proposed as part of your comments to the draft decision is adequate for the purpose of classification and labelling and/or risk assessment.

C. *Insufficient documentation of the additional read-across studies referred to in your comments to the draft decision (sources of information ii-iii)*

Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 201. Therefore, the following specifications must be met:

Reporting of the methodology and results

- the control cultures of a valid test must report the following: exponential growth of algal biomass, at least 16-fold increase in biomass is observed by the end of the test;
- the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) should be below or equal to 35%;
- the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures should be below or equal to 7% for the tested species
- the results of algal biomass should be determined in each flask at least daily during the test period and reported in a tabular form.

However, you have not provided adequate information on these studies in the form of robust study summaries including, for instance, the information listed above.

Independent on the issues identified in the Appendix on reasons common to several requests for the proposed read-across, no conclusion on the reliability of these new studies can be made. Please note that this decision does not consider 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.

As a result of these deficiencies, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance shows short-term toxicity to aquatic invertebrates foreseen to be investigated in an OECD TG 201 study. Therefore, your adaptation is rejected and 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 difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.2.

4. Ready biodegradability

Ready biodegradability is a standard information requirement under Annex VII to REACH (Section 9.2.1.1.).

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 ready biodegradation, EPI Suite estimate, [redacted];
ii. Read across, OECD TG 301C, experimental study, data is from J-CHECK, EnviChem, HSDB and PubChem authoritative database, 2017. Test substance: Tridecan-1-ol/ CAS:112-70-9/ EC:203-998-8.
iii. Read across, Non-specified guideline test, experimental study, data is from authoritative database J CHECK, National Institute of Technology and Evaluation, 2018. Test substance: Docosanoic acid/ CAS:112-85-6/ EC:204-010-8

As explained in 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 for your adaptation.

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

To fulfil the information requirement, normally a study performed according to OECD TG 301 or 310 must be provided. OECD TG 301 requires the study to investigate the following key investigation:

- The ultimate aerobic biodegradation (as measured by parameters such as DOC removal, CO2 production and oxygen uptake) of the test material under low inoculum concentration is measured at sufficiently frequent intervals to allow the identification of the beginning and end of biodegradation.

The sources of information (i-iii) may provide relevant information on the key investigation of ready biodegeradability.

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

A. *(Q)SAR adaptation (information sources i)*

   As explained in the Appendix on reasons common to several requests, you have not demonstrated that the applied (Q)SAR adaptation for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

B. *Read-across adaptation (information sources ii-iii)*

   As explained in the Appendix on reasons common to several requests, you have not demonstrated that the applied read across for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

In conclusion, the reported information provides information on ready biodegradability but is considered insufficient to estimate ready biodegradability of the Substance due to listed shortcomings and uncertainties in the applied model and read across approach. First, the lack of the Prediction Reporting Format document (QPRF) means there is no adequate and reliable documentation of the applied QSAR method. As a result of this the reliability and applicability of the applied model cannot be assessed. Second, the absence of read-across documentation does not allow independent evaluation of the adaptation and therefore we cannot assess reliability of the read-across approach.

As a result of these, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance is or is not readily biodegradable foreseen to be investigated in an OECD TG 301 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In the comments to the draft decision, you agree to perform the requested study.

You also state that one of the member of the joint submission has "*performed biodegradation study with the target chemical*" and that "[o]*nce* [you] *receive the study reports after [your] internal evaluation, [you] will update dossier accordingly"*.

However, as already explained above, your read-across adaptation is rejected. 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.

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 a standard information requirement in Annex VIII to REACH.

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 analogue substances:

i. A study similar to OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test) (1984) with the analogue decanal (CAS: 112-31-2; EC: 203-957-4);
ii. A sister chromatid exchange and chromosome aberration study, not according to a specific guideline (1990) with the analogue nonanal (CAS: 124-19-6; EC: 204-688-5)

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

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 sources of information (i. and ii.) provide relevant information on structural or numerical chromosomal aberrations in cultured mammalian cells.

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

A. Read-across adaptation (information source ii)

As explained in the Appendix on reasons common to several requests, you have not demonstrated that the applied read across for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

B. The specifications of OECD TG 473/487, include the following:

a) Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
b) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
c) At least 300 well-spread metaphases must be scored per concentration.
d) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
e) The response for the concurrent negative control must be inside the historical control range of the laboratory.
f) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

The reported data for the studies (i and ii) you have provided do not include:

a) two separate test conditions, but only in absence of metabolic activation.
b) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
c) the scoring of at least 300 metaphases per concentration.
d) a positive control.
e) a negative control with a response inside the historical control range of the laboratory.
f) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

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 studies cannot be considered as a reliable source of information that could contribute to the conclusion on this information investigated by the required study.

Taken together, the sources of information provide information on chromosomal aberrations but in the absence of reliable information on all key investigations, no conclusion can be drawn on structural or numerical chromosomal aberrations in cultured mammalian cells as 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 your comments to the draft decision, you provide no comments on the above assessment. You state that you intend to adapt this information requirement based on Annex XI, Section 1.1.2. You refer to a study according to OECD TG 473 by the National Institute of Technology and Evaluation (NITE), Japan and provide a brief summary of this study. You explain that the registration dossier will be updated to contain a robust study summary for that study.

As you have not provided a robust study summary for the study, no conclusion on the compliance of the proposed adaptation can be made. Please note that this decision does not consider 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.

Study design

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

2. 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 an adaptation (weight-of-evidence) 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.

The information for the *in vitro* gene mutation study in bacteria and 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 sections A.1 and B.1 of this draft decision.

The result of the requests for information in A.1 and 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:

- OECD TG 476 with the Substance (2015).

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

In addition, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "*from several independent sources of information*". However, you have only provided one source of information.

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 of information provides relevant information on gene mutation in cultured mammalian cells.

However, the reliability of this source of information is significantly affected by the following deficiencies:

The specifications of OECD TG 476 or OECD TG 490, include the following:

a) Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
b) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
d) The response for the concurrent negative control must be inside the historical control range of the laboratory.
e) Data on the cytotoxicity and the mutation frequency for the treated and control

cultures must be reported.

The reported data for the study you have provided did not include:

a) two separate test conditions, but only in absence of metabolic activation.
b) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
c) one positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
d) a negative control with a response inside the historical control range of the laboratory.
e) data on the cytotoxicity and the mutation frequency for the treated and control cultures.

For these reasons, 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.

Therefore, the source information provides information on gene mutation in mammalian cells but its reliability is affected so significantly that it cannot be taken into consideration in a weight of evidence approach.

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 your comments to the draft decision, you explain that you would like to await the results from the scheduled OECD 471 study before taking a decision on the need to perform an OECD 476 study with the Substance. However, irrespective of your intended preferred testing strategy, you remain responsible for complying with this decision by the set deadline.

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.

3. Screening for reproductive/developmental toxicity

Screening for reproductive/developmental toxicity is an information requirement under Annex VIII to REACH (Section 8.7.1.).

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation, you have provided the following information:

i. a study according to OECD TG 422 with an analogue substance 1-tetradecene (CAS: 1120-36-1; EC: 214-306-9), GLP not specified (2000)

In your comments to the draft decision you have requalified the study as one source of information of the weight of evidence adaption under section 1.2. of Annex XI. In support of your adaptation, you have provided the following additonal sources of information:

ii. Read across, OECD TG 422, test substance: undecanal (CAS No 112-44-7; EC: 203-972-6);

iii. OECD TG 407 with the Substance (1998)
iv. OECD

As explained in section 4 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 documentation for your adaptation.

In spite of this critical deficiency, ECHA has nevertheless assessed the reliability and relevance of the source of information provided.

Relevant information that can be used to support weight of evidence adaptation for 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 general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

1.Key element/key investigations
Sexual function and fertility
Description of information required in more detail (relevance and coverage)
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.

- Study i provides limited information on mating, fertility, gestation (length), parturition and litter sizes.
- Study ii may provide information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, organ weights and histopathology of reproductive organs and tissues, and litter sizes.
- Studies iii and iv may provide information on organ weights and histopathology of reproductive organs and tissues.

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.

- Study i provides limited information on litter sizes, stillborns, and external malformations and postnatal developmental toxicity reflected by survival.
- Study ii may provide information on toxicity to offspring.
- Studies iii and iv do not provide any information on toxicity to the offspring.

Systemic toxicity

Information on systemic toxicity include information on clinical signs with specific observations, survival, body weights, food consumption, haematology, clinical biochemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

- Study i provides limited information on clinical signs with specific observations, organ weights and histopathology of non-reproductive organs (liver only).

- Study ii may provide information on clinical signs with specific observations, survival, body weights and food consumption.
- Studies iii and iv may provide information on systemic toxicity.

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

A. *Reliability of the experimental studies (studies i, iii and iv)*

To inform on screening for reproductive and developmental toxicity, normally a study according to EU B.63/OECD TG 421 or EU B.64/OECD TG 422 needs to be conducted. Accordingly, the following specifications/conditions must be met:

a. at least 10 male and 12-13 female animals for each dose and control group.

Study i: you state that "*A total of 14 animals were used per group in this study"* followed by "*12 females were dosed*" thus suggesting that only 2 males were used.
Study iii and iv: only 5 and 10 rats per dose per sex were used respectively.

The statistical power of the information provided (i, iii and iv) is not sufficient because it does not fulfil the criterion of at least 10 male and 12-13 female animals for each test group.

b. Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation.

Study i: the animals were exposed 42-51 consecutive days.
Study iii: the dosing period was limited to 28 days

The studies (i and iii) do not have the required exposure duration according to OECD TG 421 because the exposure does not cover two weeks of premating, pregnancy and at least 13 days of lactation.

Based on the above, the studies (i, iii and iv) do not provide reliable coverage of the key parameter(s) addressed by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422 and as such these studies cannot reliably contribute to your weight of evidence adaption under section 1.2. of Annex XI.

B. *Read-across adaptations (sources of information i and ii)*

As explained in the Appendix on reasons common to several requests (Sections 1 and 2), you have not demonstrated that the newly proposed read-across proposed as part of your comments to the draft decision is adequate for the purpose of classification and labelling and/or risk assessment.

C. *Insufficient documentation of the additional read-across studies referred to in your comments to the draft decision (source of information ii)*

In your comments to the draft decision, You propose to predict a screening for reproductive/developmental toxicity of the Substance from a new study on the analogue substances undecanal (CAS No 112-44-7; EC: CAS No 112-44-7; EC: 203-972-6). You have not provided adequate information on this study in the form of a robust study summary.

Independent on the issues identified in the Appendix on reasons common to several requests for the proposed read-across, no conclusion on the reliability of these new studies can be made.

In conclusion, it is currently not possible to conclude, based on any sources of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 422 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments to the draft decision, you also refer to a study according to OECD TG 414 that you agree to conduct. ECHA understands that you may intend to adapt this information requirement under the second column of Section 8.7.1. of Annex VIII (fourth indent). As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made. Please note that this decision does not consider 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.
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[6] administration of the Substance.

4. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

You have provided the following information:

i. An adaptation under Annex XI, Section 1.5 using a non-guideline test on the analogue substance 2-Octanone (CAS: 111-13-7; EC: 203-837-1) (Broderius et al. 1985).
ii. OECD TG 203 (non GLP) with the Substance ([redacted], 2014).

In your comments to the draft decision you have requalified the studies as sources of information of the weight of evidence adaption under section 1.2. of Annex XI. You have also provided the following studies in support of that adaption:

iii. OECD TG 203, with the analogue substance: 1-Hexadecene (CAS no. 629-73-2; EC no. 211-105-8);
iv. OECD TG 203, with the analogue substance: 1-Octadecene (CAS no. 112-88-9; EC no. 204-012-9).

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the short-term toxicity to fish.

As explained in section 4 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 documentation for your adaptation.

In spite of this critical deficiency, ECHA has nevertheless assessed the reliability and relevance of the sources of information provided.

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

To fulfil the information requirement, normally a study performed according to OECD TG 203 must be provided. OECD TG 203 requires the study to investigate the following key investigation:

- the concentration of the test material leading to the mortality of 50% of fish at the end of the test is estimated.

The sources of information (i-iv) may provide information on short-term toxicity to fish.

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

A. *Reliability of the experimental studies i and ii*

To inform on short-term toxicity to fish, normally a study according to OECD TG 203 needs to be conducted. Accordingly, the following specifications/conditions must be met:

Validity criteria

- the analytical measurement of test concentrations is conducted.

  However, no analytical measurement of test concentrations was conducted in studies i and ii.

Technical specifications impacting the sensitivity/reliability of the test

- the water temperature is adequate for the selected test species (*Danio rerio* 21-25°C).

  However, the study ii was conducted on *Danio rerio* and the test water temperature was up to 28.4°C;

- the fish are not fed during the exposure period.

  However, the fish were fed during the exposure period.

Based on the above, there are critical methodological deficiencies in the studies i and ii. More specifically, the analytical measurement of test concentrations is not conducted and the actual exposure concentration are not known and therefore, calculated effective concentrations are not reliable. In addition, the test temperature in study ii exceeds the recommended maximum temperature in the OECD TG 203 and fish were fed during the test. These deviations could have unpredictable influence on fish behaviour during the test and thereafter test results. These critical methodological deficiencies significantly affecting the reliability of study I and ii.

B. *Read-across adaptations (sources of information i, iii and iv)*

As explained in the Appendix on reasons common to several requests (Section 1 and 2), you have not demonstrated that the applied read across for the Substance currently included in your registration dossier or the newly proposed read-across proposed as part of your comments to the draft decision is adequate for the purpose of classification and labelling and/or risk assessment.

C. *Insufficient documentation of the additional read-across studies referred to in your comments to the draft decision (sources of information iii-iv)*

Under Annex XI, Section 1.5., the study to be read across must have an adequate and

reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 203. Therefore, the following specifications must be met:

Reporting of the methodology and results

- 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;
- the test procedure including e.g. fish loading and acclimation must be reported.

However, you have not provided adequate information on these studies in the form of robust study summaries including, for instance, the information listed above.

Independent on the issues identified in the Appendix on reasons common to several requests for the proposed read-across, no conclusion on the reliability of these new studies can be made. Please note that this decision does not consider 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.

As a result of these, it is not possible to conclude, based on any sources of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 203 study. Therefore, your adaptation is rejected and 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 difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.2.

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

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH (Section 8.6.2.).

To be considered compliant with the endpoint, you need to submit a study performed according to the OECD TG 408, or a valid adaptation according to either the specific rules of Column 2, Annex IX, Section 8.6.2. or the general rules of Annex XI.

In your original registration dossier, you did not submit any information for this endpoint. Hence the information requirement is not met for this endpoint.

In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of weight of evidence according to Annex XI, Section 1.2, of the REACH Regulation. In support of your adaptation you have provided the following sources of information with analogue substances:

i. TG 408 with the Substance (1998)
ii. TG 407 with the Substance (2008)

As explained in section 4 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 documentation for your adaptation.

In spite of this critical deficiency, ECHA has nevertheless assessed the reliability and relevance of the source of information provided.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system.

In-life observations

In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

The studies (i and ii) may provide information regarding in-life observations. However, based on the information provided, ECHA cannot determine whether all functional aspects and the ophthalmological aspect, as outlined in OECD TG 408, were investigated (i).

Blood chemistry

Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary)

The studies (i and ii) may provide information on blood chemistry. However, based on the information provided, ECHA cannot determine whether all haematological and biochemical parameters, as outlined in OECD TG 408, were assessed (i and ii).

Organ and tissue toxicity

Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale), and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

The studies (i and ii) may provide information on organ and tissue toxicity. However, based on the information provided, ECHA cannot determine whether all organs, as outlined in OECD TG 408, were investigated for weight, pathology and histopathology (i and ii).

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

A. *Reliability of the experimental study on the Substance (source of information ii)*

   To inform on sub-chronic toxicity, normally a study according to OECD TG 408 needs to be conducted. Accordingly, the following specifications/conditions must be met:

   a. At least 10 male and 10 female animals for each test and control group. However, only 5 rats per sex per dose were used in the study.

   b. Dosing of the Substance daily for a minimum of 90 days. However, dosing was only performed over a period of 28 days.

   As only 5 rats per sex per dose were used, instead of 10 rats per sex per dose, the study has considerably less statistical power than the OECD TG 408. Furthermore, because the dosing period is only 28 days (as compared to the 90 days needed for the OECD TG 408), exposure to the test substance was considerably less than outlined by the test guideline. These deficiencies are such that they affect significantly the reliability of the information provided by this study.

B. *Insufficient documentation of the additional read-across studies referred to in your comments to the draft decision (source of information i)*

   You have not provided adequate information on this study in the form of a robust study summary. As such, no conclusion on the reliability of this new study can be made.

In conclusion, while you have described your intentions and you have provided new scientific information addressing the information requirement, it is currently not possible to conclude, based on any sources of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 408 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Information on the design of the study to be performed (oral/rat)

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because

according to the Chemical Safety Report, risk management measures are in place to prevent exposure of humans via inhalation.

Therefore, the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

2. Pre-natal developmental toxicity study in one species

A pre-natal developmental toxicity study in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

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 analogue substances:

i. A non-guideline developmental toxicity study (2009), not according to a specific guideline, with the analogue heptanoic acid (CAS: 111-14-8; EC: 203-838-7);
ii. A non-guideline combined Repeated and Reproductive Developmental Toxicity Screening Test (2009), not according to a specific guideline, with the analogue 1-tetradecene (CAS: 1120-36-1; EC: 214-306-9);
iii. A non-guideline Reproduction and Developmental Toxicity Screening Test (2009), not according to a specific guideline, with the analogue 1-hexene (CAS: 592-41-6; EC: 209-753-1);

As explained in the Appendix on Reasons common to several requests, it would be sufficient to reject your weight-of-evidence adaptation based on the fact that you have not submitted any justification for your adaptation. In addition, endpoint specific issues are described below.

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.

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 survival (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and external malformations. However, they do not inform on structural malformations and variations (visceral and skeletal) as foreseen to be investigated in OECD TG 414.

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

A. *Read-across adaptation (information sources i, ii and iii)*

   As explained in the Appendix on reasons common to several requests, you have not demonstrated that the applied read across for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

B. *The specifications of OECD TG 414, include the following:*

- 20 female animals with implantation sites for each test and control group

  The studies (i, ii and iii) you have provided were conducted with respectively 10, 12 or an unspecified number of pregnant females for each test group. The statistical power of the information provided is either not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group set in OECD TG 414 (i and ii), or the statistical power cannot be assessed (iii).

On this basis, the sources of information (i, ii and iii) were conducted with sample sizes (i.e. pregnant females) that are too low (or not specified) and therefore do not provide reliable information to detect pre-natal developmental toxicity for the selected test materials.

Therefore, the provided studies cannot be considered as a reliable source of information that could contribute to the conclusion on the information investigated by the required study.

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.

The sources of information provide limited information on maternal survival (i), body weight (i) and clinical signs (i and ii). However, the reliability of all sources of information is significantly affected by reliability issues as explained above under sections *A.* and *B.* above. Therefore, they cannot contribute to the conclusion on this key element.

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 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.

However, the reliability of all sources of information is significantly affected by reliability issues as explained above under sections *A.* and *B.* above. Therefore, they cannot contribute to the conclusion on this key element.

Taken together, source studies (i-iii) provide information on maintenance of pregnancy and only limited information on prenatal developmental toxicity and maternal toxicity, but 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[7] administration of the Substance.

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

In the comments to the draft decision, you agree to perform the requested study.

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[8] administration of the Substance.

3. 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. (Q)SAR predicted value, long-term toxicity to aquatic invertebrates by ECOSAR version 1.10, key study;
ii. Read across, TG 211, Reliability: 2 (reliable with restrictions), supporting study, read across from docosanoic acid (CAS: 112-85-6; EC: 204-010-8).

In your comments to the draft decision you have requalified the studies as sources of information of the weight of evidence adaption under section 1.2. of Annex XI. In support of your adaptation, you have provided the following additonal sources of information:

iii. OECD TG 211, with the analogue substance: 1-Decene (CAS no. 872-05-9; EC no. 212-819-2);
iv. OECD TG 211, with the analogue substance: 1-Dodecanol (CAS no. 112-53-8; EC no. 203-982-0).

As explained in section 4 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 documentation for your adaptation.

In spite of this critical deficiency, ECHA has nevertheless assessed the reliability and relevance of the sources of information provided.

As explained under Appendix on Reasons common to several requests, Section 3, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

To fulfil the information requirement, normally a study performed according to OECD TG 211 must be provided. OECD TG 211 requires the study to investigate the following key investigations:

- The concentrations of the test material leading to no observed effect (NOECs), following an exposure time sufficient to produce three broods, the following should be estimated:
  1) the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test, and
  2) the survival of the parent animals during the test, and
  3) the time to production of the first brood

The sources of information (i-iv) may provide information on the long-term toxicity to aquatic invertebrates.

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

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

A. *Reliability of your (Q)SAR adaptation (study i)*

As explained in the Appendix on reasons common to several requests, your adaptation is not reliable.

In addition, we have identified the following endpoint specific issue:

The prediction is not adequate due to low reliability

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 condition must be met:

- the model predicts well substances that are similar to the substance of interest.

Your registration dossier provides the following information: predictions were conducted with the model for neutral organics (baseline toxicity).

The following information is also available for the Substance used as input for the prediction: the Substance is a mono aldehyde and considered as an organic chemical with excess toxicity in ECOSAR (i.e. not only as a neutral organic chemical since it possesses more specific mode of toxicity) and the applied model in ECOSAR 1.11 is not sufficiently robust for mono-aldehydes (based on 0 points of experimental data).

The prediction for the Substance used as input is not reliable because the model you used has no similar substances in training set.

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

B. *Read-across adaptations (sources of information ii-iv)*

As explained in the Appendix on reasons common to several requests (Section 1 and 2), you have not demonstrated that the applied read across for the Substance currently included in your registration dossier or the newly proposed read-across proposed as part of your comments to the draft decision is adequate for the purpose of classification and labelling and/or risk assessment.

C. *Insufficient documentation of the additional read-across studies referred to in your comments to the draft decision (sources of information iii-iv)*

Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 211. Therefore, the following specifications must be met:

Reporting of the methodology and results

- the full record of the daily production of living offspring during the test (by each parent animal/in each replicate) is provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is reported;
- the coefficient of variation for control reproductive output is reported;

- 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 adequate information on these studies in the form of robust study summaries including, for instance, the information listed above.

Independent on the issues identified in the Appendix on reasons common to several requests for the proposed read-across, no conclusion on the reliability of these new studies can be made. 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.

In conclusion, it is not possible to conclude, based on any sources of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 211 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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.2.

4. 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. (Q)SAR estimated long-term toxicity to fish by ECOSAR version 1.01

We have assessed this information and identified the following issue:

A. Assessment of your (Q)SAR adaptation

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

In addition, we have identified the following endpoint specific issue: *The prediction is not adequate due to low reliability*

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 condition must be met:

- the model predicts well substances that are similar to the substance of interest.

Your registration dossier provides the following information: predictions were conducted with the model for neutral organics (baseline toxicity).

The following information is also available for the Substance used as input for the prediction: the Substance is a mono aldehyde and considered as an organic chemical with excess toxicity in ECOSAR (i.e. not only as a neutral organic chemical since it possesses more specific mode of toxicity) and the applied model in ECOSAR 1.11 is not sufficiently robust for mono-aldehydes (based on 2 points of experimental data and point of assumption that for chronic toxicity, at log Kow = 8 all lines of models converge).

The prediction for the Substance used as input is not reliable because the model you used has no similar substances in training set.

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

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you agree to perform the requested study.

Study design

OECD TG 210 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.2.

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[9].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

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 variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - 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 and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[10].

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

Appendix E: Procedure

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

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

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

The compliance check was initiated on 04 May 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 F: List of references - ECHA Guidance[11] 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)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[13]

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[14]

[11] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[12] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[13] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[14] 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 G: 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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