~~Confidential~~

Helsinki, 13 April 2022

Addressees
Registrant(s) of JS_205_460_8 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
16/12/2016

Registered substance subject to this decision ("the Substance")
Substance name: 2,6,10-trimethylundec-9-enal
EC number: 205-460-8
CAS number: 141-13-9

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 ***18 October 2024***.

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

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

1. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

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 test performed for the information requirement of 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. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

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

5. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; 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 VIII 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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 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". 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.**

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

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 properties

You have provided three read-across justification documents entitled "[redacted]" for the endpoints reproductive toxicity, repeated dose toxicity and genotoxicity, respectively.

You read-across between the structurally similar substances, 3,7-dimethyl-2,6-octadienal (Citral) EC No. 226-394-6 (CAS No. 5392-40-5) and 2,6-Dimethylhept-5-enal (Melonal) EC No. 203-447-2 (CAS 106-72-9) as source substances and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: "*This read-across is based on the hypothesis that the target and source substances have similar systemic toxicity properties as a result of similarity in structure, mode of action and physicochemical properties relevant for systemic toxicity and genotoxicty".*

To support your read-across justification, you have provided:

- Structural similarity index values generated using the OECD QSAR Toolbox to support structural similarity between the Substance and the selected source substances;
- You consider that the selected source substances are "*more reactive than the target substance*" and that "*the predicted reproductive dose toxicity, repeated dose toxicity and genotoxicity for the target substance,* [redacted]*, is based on conservative read-*

[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

across substances, Melonal and citral EC No. 226-394-6". You did not provide further justification to this claim;

- You provided mutagenicity testing (i.e. bacterial reverse mutation assay) for the Substance and the source substance citral with EC No. 226-394-6 and acute oral toxicity testing for the Substance and the source substances citral with EC No. 226-394-6 and melonal with EC No. 203-447-2;
- For the genotoxicity endpoint, you state the following: "*The OECD toolbox predicts the source substance citral EC No. 226-394-6 and the target substance to be of low safety concern according to the profiles that are general (mechanistic) and specific*";
- For the repeated dose oral toxicity, you state the following: "*The OECD toolbox predicts the source substance citral EC No. 226-394-6 and the target substance to be of low toxicity according to Cramer classification and neither is categorized based on the Hazard Evaluation Support System (HESS) database for toxicological effects";*
- for the reproductive toxicity, you state the following: "*The OECD toolbox predicts the source substance Melonal and the target substance to be of low toxicity according to Cramer classification, to not bind to the estrogen receptor, and neither is known as precedent for reproductive and developmental toxic potential based on the DART Scheme (v.1.0*)".

You referred to data obtained with the OECD QSAR Toolbox, v3.4. (2016). Moreover, predicted potential metabolites using the in vivo rat profiler within the TIMES v.2.27.19.13 software, were also provided.

Based on the above, ECHA understands that you used the QSAR Toolbox for the identification of analogues and use the information on these analogues to predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substances.

ECHA notes the following shortcomings with regards to predictions of toxicological properties:

A. 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).

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).

Experimental data are available from mutagenicity testing (i.e. bacterial reverse mutation assay) for the Substance and the source substance citral EC No. 226-394-6 and from acute oral toxicity testing for the Substance and the source substances citral EC No. 226-394-6 and melonal EC No. 203-447-2. Information on mutagenicity and acute toxicity on the Substance

and the selected source substance(s) may provide support that they have similar properties regarding those two endpoints. However, these data do not inform on *in vitro* gene mutation in mammalian cells, *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study, repeated dose toxicity and reproductive toxicity for the Substance and the selected source substances. Therefore, the experimental data provided are not relevant to support your read-across hypothesis for these endpoints.

For the endpoints listed above, you have provided no bridging studies allowing to compare the properties of the Substance and of the source substance(s).

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

B. Inadequate read-across hypothesis

A read-across hypothesis must be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. Firstly, this hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). Secondly, 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 the structural similarity between the source substance(s) and the Substance, which you consider a sufficient basis for predicting the properties of the Substance. However, your hypothesis does not explain why the structural differences between the substances do not influence the toxicological properties or do so in a regular pattern.

In particular, the structural alerts by ISS for in vitro mutagenicity (Ames test) and in vivo mutagenicity (micronucleus) are different between the Substance and the source substance citral with EC No. 226-394-6 (simple aldehyde for the Substance and alpha,beta-unsaturated carbonyls for the source substance). This is related to the structural differences between the source substance and the target substance where the source substance has an alpha-beta unsaturation, while the target substance does not. You did not discuss this dissimilarity and its impact on toxicological properties.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it 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 or ecotoxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances.

C. The provided source study(ies) for screening for reproductive/developmental toxicity are not reliable.

ECHA has identified deficiencies with regard the reliability of the provided study(ies) for the endpoint Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.). These deficiencies are addressed under the corresponding endpoint.

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 substances. 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 your weight-of-evidence adaptation under 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 cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- *In vitro* gene mutation in mammalian cells (Annex VIII, section 8.4.3)
- Screening for reproductive/developmental toxicity (Annex VIII, section 8.7.1)

Your weight of evidence adaptation raises the same decifiencies 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.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation. Your weight of evidence approach has deficiency that is common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Appendices below.

A. Your weight-of-evidence adaptations do not rely on several independent sources of information

Under Annex XI, Section 1.2., a weight of evidence must rely on several independent sources of information leading to the assumption/consumption that a substance has or has not a particular dangerous property.

In your dossier, you have provided only one source of information for:

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.), i.e. an *in vivo* bone marrow mouse micronucleus with the analogue substance Citral (EC No. 226-394-6);
- *In vitro* gene mutation in mammalian cells (Annex VIII, section 8.4.3), i.e. an *in vitro* gene mutation study in mammalian cells with the analogue substance Citral (EC No. 226-394-6);
- Screening for reproductive/developmental toxicity (Annex VIII, section 8.7.1), i.e. a screening for reproductive/developmental study with the Substance.

For each of the information requirement listed above, you have submitted a weight of evidence adaptation that rely on a single source of information. As a results your adaptation does not meet the requirements of Annex XI, Section 1.2.

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

1. Long-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.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided an OECD TG 202 study on aquatic invertebrates but no information on long-term toxicity on aquatic invertebrates for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7.8.5).

In the provided OECD TG 105 (2015), the saturation concentration of the Substance in water was determined to be 0.67 mg/L.

Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

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

Study design

The Substance is difficult to test due to the low water solubility (water solubility limit of 0.67 mg/L) and high adsorptive properties (log Koc of 3.86). OECD TG 211 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 211. 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.

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

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

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

You have provided an adaptation according to Annex XI, Section 1.2. (weight of evidence). In support of your adaptation you provided the following source of information:

i. An *in vivo* bone marrow mouse micronucleus ([redacted],2003), according to the National Toxicology Program protocols, not specified if GLP, with the source substance substance Citral with EC No. 226-394-6 (CAS RN 5392-40-5)

ECHA understands from the information you submitted that you intend to fufil the information requirement using an *in vivo* cytogenicity study, in accordance with Section 8.4.2, column 2 of Annex VIII.

We have assessed this information and identified the following issues:

A. Your weight of evidence adaptation relies on a single source of information

As explained in Section 2 of the Appendix common to several requests, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "*from several independent sources of information*".

As you have only provided one source of information, you adaptation does not meet the requirement of Annex XI, Section 1.2.

Irrespective of this deficiency, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided source of information and found the following deficiency:

B. Your read-across is rejected

The reliability of the source of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

Therefore, your adaptation under Annex XI, Section 1.2 is rejected.

On this basis, the provided study is not regarded as providing reliable information to inform on the properties of the Substance. Therefore, the condition set out in Section 8.4.2, Column 2, first indent of Annex VIII to REACH is not met and the information requirement is not fulfilled.

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

Study design

To fulfil the information requirement for the Substance, either *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) 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 under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

i. Triggering of the study

Your dossier contains:
(i) a negative result for *in vitro* gene mutation study in bacteria, and
(ii) inadequate data for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier is rejected for the reasons provided in section B.1.

The result of the request for information in section B.1 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.

ii. Assessment of information provided

You have provided an adaptation according to Annex XI, Section 1.2. (weight of evidence). In support of your adaptation you provided the following source of information:

i. An *in vitro* gene mutation study in mammalian cells ([redacted], 2008), according to OECD TG 476, GLP, with the analogue substance Citral with EC No. 226-394-6 (CAS RN 5392-40-5)

We have assessed this information and identified the following issues:

A. Your weight of evidence adaptation relies on a single source of information

As explained in Section 2 of the Appendix common to several requests, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "*from several independent sources of information*".

As you have only provided one source of information, you adaptation does not meet the requirement of Annex XI, Section 1.2.

Irrespective of this deficiency, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided source of information and found the following deficiency:

B. Your read-across is rejected

The reliability of the source of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

Therefore, your adaptation under Annex XI, Section 1.2 is rejected and the information requirement is not fulfilled.

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

Study design

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

3. Short-term repeated dose toxicity (28 days)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH.

You have provided an adaptation according to Annex XI, Section 1.5. in your dossier.
In support of your adaptation, you have provided:

i. a 90-days repeated dose toxicity study according to the National Toxicology Program Protocols (not GLP), via oral route in rats with a source substance citral with EC No. 226-394-6 (CAS RN 5392-40-5) ([redacted], 2003)

In addition, you stated that *"Short-term toxicity study does not need to be conducted because a reliable sub-chronic (90 days) or chronic toxicity study is available, conducted with an appropriate species, dosage, solvent and route of administration. In additi[on]l a suitable 14 day oral toxicity study was submitted as supporting information".*

ECHA understands that you intend to fulfil the information requirement using a 90-days repeated dose toxicity study, in accordance with Section 8.6.1, Column 2 of Annex VIII to REACH.

We have assessed this information and identified the following issue:

> As provided in Annex VIII, Section 8.6.1, Column 2, you may adapt the information requirement, provided that a reliable sub-chronic toxicity study (90-day) is available.
>
> You have provided a 90-days repeated dose toxicity study on a source substance. However, for the reasons explained under section 1 in the Appendix on Reasons common to several requests your read-across adaptation is rejected.
>
> On this basis, the provided study is not regarded as providing reliable information to inform on the properties of the Substance. Therefore, the condition set out in Section 8.6.1, Column 2, first indent of Annex VIII to REACH is not met and your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

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

Study design

Referring to the criteria in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because it is a liquid with a low vapour pressure (0.3112 at 20°C) and although the information indicate that human exposure to the Substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation, local effects.

Therefore the sub-acute toxicity study must be performed according to the OECD TG 407, in rats and with oral administration of the Substance.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (OECD TG 407) nor for the screening study for reproductive/developmental toxicity (OECD TG 421), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to avoid unnecessary animal testing and because it fulfils the information requirement in both Annex VIII, Section 8.6.1. and 8.7.1. of REACH (ECHA Guidance R.7.6.2.3.2.).

4. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have provided an adaptation according to Annex XI, Section 1.2. (weight of evidence). In support of your adaptation you provided the following source of information:

i. A key study screening for reproductive/developmental toxicity according to Guidelines for Reproduction studies for Safety Evaluation of Drugs for Human use (not GLP specified) in female rats by oral route with the source substance Melonal with EC No. 203-427-2 (CAS RN 106-72-9) ([redacted], 1990).

We have assessed this information and identified the following issues:

A. Your weight of evidence adaptation relies on a single source of information

As explained in Section 2 of the Appendix common to several requests, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "*from several independent sources of information*".

As you have only provided one source of information, you adaptation does not meet the requirement of Annex XI, Section 1.2.

Irrespective of this deficiency, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided source of information and found the following deficiency:

B. Your read-across is rejected

The reliability of the source of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

C. The provided study is not reliable

Under Annex XI, Section 1.5., the results to be read across must provide 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 421 or EU B.64/OECD TG 422. The key parameters of this test guideline include:

- At least 10 male and 12-13 female animals for each test and control group

  However, the study you have provided was conducted only with 10 female animals for each test group. In addition, the study reported the death of 8 rats at the highest dose during the premating period. Therefore, it does not fulfil the criterion

of at least 10 male animals and 12-13 female animals for each test group.

- 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

  However, in the study you have provided the animals were exposed *"for seven days prior to and then through cohabitation (maximum of seven days), gestation, delivery and a four-day lactation/postparturition period (dams that delivered litters)."* The study does not have a required exposure duration according to OECD TG 421 because the exposure does not cover two weeks of premating and at least 13 days of lactation. Therefore it does not fulfil the criteria set in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

- Examination of parameters for sexual function and fertility such as those for, parturition, lactation and weight and histopathology of reproductive organs and tissues

  However, in the study you have provided investigations for parameters for sexual function and fertility such as, parturition, lactation and weight and histopathology of reproductive organs and tissues have not been performed as required in EU B.63/OECD TG 421.

- Monitoring of oestrus cycles

  However, in the study you have provided oestrus cycles have not been monitored as required in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

- Examination of offspring parameters such as number and sex of pups, litter weight, anogenital distance, number of nipples, areolae in male pups

  However, in the study you have provided, investigations for number and sex of pups, /stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/number of nipples/areolae in male pups have not been performed as required in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

Therefore, this study does not provide equivalent information to an EU B.63/OECD TG 421 or an EU B.64/OECD TG 422 study.

Therefore, your adaptation under Annex XI, Section 1.2 is rejected and the information requirement is not fulfilled.

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

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[4] administration of the Substance.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (OECD TG 407) nor for the screening study for reproductive/developmental toxicity (OECD TG 421), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to avoid

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

unnecessary animal testing and because it fulfils the information requirement in both Annex VIII, Section 8.6.1. and 8.7.1. of REACH (ECHA Guidance R.7.6.2.3.2.).

5. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have provided an OECD TG 203 study on fish but no information on long-term toxicity on fish for the Substance.

As already explained under Section A.1, the Substance is poorly water soluble and therefore information on long-term toxicity on fish must be provided.

On this basis, the information requirement is not fulfilled.

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

Study design

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

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

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

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[5].

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[6].

[5] https://echa.europa.eu/practical-guides
[6] https://echa.europa.eu/manuals

Appendix D: Procedure

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

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

The compliance check was initiated on 04 May 2021.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the requests.

In your comments on the draft decision, you requested an extension of the deadline to provide information from 9 to 27 months (best case) or up to 40 months (worst case) from the date of adoption of the decision. You justify the extension by referring to lab capacities of main Contract Research Organisations (CROs) and also to the fact that the substance is difficult to test. You further justify the need to extent the deadline to 40 months by referring to the ECHA Guidance on Registration, Section 7.2.. You consider that "*an additional deadline of 12 month (after the final testing reports are received) should be applied as the requested data would trigger the rework of the current CSR*". However, the above section of the ECHA Guidance on Registration refers to relevant maximum deadlines for spontaneous update in relation to the conditions set out under Article 22(1) of REACH. Under Article 22(2) of REACH, an update of the registration dossier to provide the information required by the decision made in accordance with Artcile 40 must be provided within the deadline specified in that decision. Therefore, your request for an additional extension of 12 months is irrelevant.

ECHA has assessed the information provided as part of your justification and has granted the request and extended the deadline to 27 months.

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

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

Appendix E: List of references - ECHA Guidance[7] 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)[8]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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[10]

[7] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[8] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[9] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[10] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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

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

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

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

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

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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.