EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 04 June 2021

Addressees
Registrant(s) of EC264-867-9 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
14/03/2019

Registered substance subject to this decision ("the Substance")
Substance name: Dodecenylsuccinic acid, compound with 2,2',2''-nitrilotriethanol (1:1)
EC number: 264-867-9
CAS number: 64396-12-9

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

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

3. Ready biodegradation (Annex VII, Section 9.2.2.1.; 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 gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

2. 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

3. 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)

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 to IX of REACH, as you registered the Substance at 100-1000 tpa.

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". 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 Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying read-across approaches in accordance with Annex XI, Section 1.5:

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

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

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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[2] and related documents[3, 4].

A. Predictions for (eco)toxicological properties

You have not provided a read-across justification document in either IUCLID Section 13 or the CSR document. However, we note that you provided some justification under the respective endpoints.

The selected analogue substances used for the predictions are described below.

i. Toxicological endpoints

In vitro gene mutation study in mammalian cells

- OECD TG 479 on triethanolamine (EC no. 203-049-8)

Screening for reproductive/developmental toxicity

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

[3] 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)

[4] 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

- OECD TG 422 on disodium succinate (EC no. 205-778-7)
- SEV report on triethanolamine (EC no. 203-049-8)

Sub-chronic toxicity study (90-day)
- OECD TG 422 on disodium succinate (EC no. 205-778-7)
- OECD TG 408 on triethanolamine (EC no. 203-049-8)

Pre-natal developmental toxicity study
- Non guideline developmental toxicity study via the dermal route with triethanolamine (EC no. 203-049-8)

ii. Ecotoxicological endpoints

Short-term toxicity testing on aquatic invertebrates
- OECD TG 202 on disodium succinate (EC no. 205-778-7)

Growth inhibition study aquatic plants
- OECD TG 201 on disodium succinate (EC no. 205-778-7)

Short-term toxicity testing on fish
- OECD TG 203 on disodium succinate (EC no. 205-778-7)

iii. Environmental fate endpoints

Ready biodegradability
- Non guideline study on disodium succinate (EC no. 205-778-7)
- OECD TG 301B on triethanolamine (EC no. 203-049-8)

iv. Justification for the predictions

You have provided the following reasoning for the prediction of toxicological, ecotoxicological and environmental fate properties:
- *"The substance dissociates under biological conditions and the dissociation products have been assessed"*;
- *"The triethanolamine and alkyl succinic acid have been well-evaluated* [...]";
- *"Disodium succinate may be used as an analogue for succinic acid as there is no significant difference in toxicity expected between succinic acid and disodium succinate, since both substances will dissociate into succinate ion under physiological conditions"*.

For the read-across to disodium succinate (EC no. 205-778-7) and triethanolamine (EC no. 203-049-8), ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. 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, ecotoxicological and environmental fate properties:

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*" (ECHA Guidance 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, where relevant, information on the formation of the common compound(s), supporting information on the properties of non-common compound(s) and bridging studies to compare properties of the Substance and of the source substances.

i. Missing information on the formation of common compounds

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance to common compounds. In this context, information on the rate and extent of the hydrolysis of the Substance (i.e. alkyl succinate) to release non-alkylated succinate anions is necessary to confirm the formation of the proposed common hydrolysis product and to assess the impact of the exposure to the parent compounds.

You have not provided any experimental data, or other adequate and reliable information, to support the hydrolysis of your Substance to form non-alkylated succinate anions.

The Substance is a salt and, upon dissolution, the release of triethanolamine is expected. However, with regard to the release of succinate anions, you have not provided any supporting evidence establishing that the proposed common hydrolysis product is formed as assumed in your read-across hypothesis. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

ii. Missing supporting information to compare properties of the substances

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 substances is necessary to confirm that the 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 substances.

For the toxicological endpoints listed above you have not provided any bridging studies to compare the properties of the Substance and the selected analogues Substances.
For the ecotoxicological and environmental fate endpoints listed above, you have provided information on the Substance in addition to information on the selected analogues. However, for the reasons explained under the corresponding appendices the studies provided on the Substance are not reliable.

In the absence of adequate and reliable bridging information on the properties of the Substance and of the selected analogues, you have not established that they are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

iii. Missing supporting information on the impact of non-common compounds

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

For the read-across to triethanolamine (EC no. 203-049-8), the main non-common compounds are the isomers of Dodecenylsuccinic acid (i.e. 3-[(2E)-dodec-2-enyl]dihydrofuran-2,5-dione and 3-[(2Z)-dodec-2-enyl]dihydrofuran-2,5-dione). You have not provided any information on the properties of these non-common compounds for any of the endpoints for which a read-across to triethanolamine is claimed.
For the read-across from disodium succinate (EC no. 205-778-7), the main non-common compounds are triethanolamine and isomers of unsaturated dodecanol. You have not provided any information on the properties of the C12 alcohol. Furthermore for the ecotoxicological endpoints listed above, you have not provided information on triethanolamine.

In the absence of adequate and reliable information on the properties of the non-common compounds, 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. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

B. Conclusions on the read-across approach

In your comments on the draft decision you acknowledge the above deficiencies in your read across adaptation. You indicate that it is your intention to gather more information and improve the read across approach.

ECHA has reviewed your comments and concluded that the currently available information in your dossier and your comments remains insufficient for ECHA to make an assessment as no further data has been provided addressing the issues noted above.

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

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

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

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 deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually.

In that context, we identified the following deficiency recurrent to all information requirements for which you invoked a weight of evidence adaptation:

- Reliability of the read across approach

Section 1 of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under the weight of evidence adaptations listed above. As a consequence this information is not considered reliable to support your weight of evidence.
Additional issues related to weight of evidence are addressed under the corresponding information requirements in the following Appendices.

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

1. Short-term toxicity testing on aquatic invertebrates

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

You have provided the following information in your dossier:

1) a study according to EPA OPP 72-3 (equivalent to US EPA 40 CFR 797.1930) on the Substance ([redacted], 2008);
2) an adaptation under Annex XI, Section 1.5 (Read-across). In support of your adaptation you provided a study according to OECD TG 202 with the analogue substance Disodium succinate hexahydrate (EC no. 205-778-7) ([redacted], 2003).

We have assessed this information and identified the following issues:

A. To fulfil the information requirement, a study according to US EPA 40 CFR 797.1930 is an acceptable method (Article 13(3) of REACH; ECHA Guidance R.7, Appendix R.7.8.2). For such a study, the following specifications must be met:

Validity criteria

- the percentage of immobilised mysids is ≤ 10% at the end of the test in the controls (including the solvent control, if applicable);

Technical specifications impacting the sensitivity/reliability of the test

- *Mysidopsis bahia* is used as test species;

Characterisation of exposure

- the test material concentrations are measured at least at the beginning and at the end of the test.

Your registration dossier provides an EPA OPP 72-3 study (equivalent to US EPA 40 CFR 797.1930) on the Substance which shows the following:

- the percentage immobilised mysids in the control at the end of the test is not provided;
- the test was conducted on *Acartia tonsa*;
- no analytical monitoring of exposure concentrations was conducted.

Based on the above, the study does not meet the information requirement as:

- the validity criteria of the test guideline cannot be verified;
- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically the test species does not comply with the guideline requirements and no monitoring of exposure was conducted.

In your comments on the draft decision you add in relation to characterisation of exposure that:

"Supporting analysis was not included, but in view of the very low reported toxicity (NOEC > 800 mg/l), this is not considered to detract from the low-hazard conclusions."

However, this information does not affect the fact that characterisation of exposure is a specification of the guideline that is required to demonstrate exposure to the organism throughout the test.

B. For the reasons explained under the Appendix common to several requests, your adaptation under Annex XI, Section 1.5. (grouping and read-across) is rejected.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is difficult to test as it is surface active (surface tension = 22.7 mN/m) and ionisable (pka = 6.2 and 8). OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

2. Growth inhibition study aquatic plants

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

You have provided the following information:
1) a study according to ISO 10253 with the Substance ([redacted], 2009)
2) an adaptation under Annex XI, Section 1.5 (Read-across). In support of your adaptation you provided a study according to OECD TG 201 with with the analogue substance disodium succinate (EC no. 205-778-7) ([redacted] 2003).

We have assessed this information and identified the following issues:

A. To fulfil the information requirement, a study according to ISO 10253 is an acceptable method (Article 13(3) of REACH; ECHA Guidance R.7, Appendix R.7.8.2). For such a study, the following specifications must be met:

Characterisation of exposure
- the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within 20 % of the nominal or measured initial concentration throughout the test;

Reporting of the methodology and results
- the test design is reported (*e.g.*, number of replicates, number of test concentrations and geometric progression used);
- the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);
- the methods used to prepare stock and test solutions are reported;
- the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported;
- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

Your registration dossier provides an ISO 10253 on the Substance which shows the following:

- on the test design, no information on the number of replicates, number of test concentrations and the geometric progression used is provided;
- on the test procedure, no information on the composition of the test medium, methods used to prepare stock and test solutions and the biomass density at the beginning of the test is provided;
- no information on how the biomass was determined is provided;
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

Based on the above, the study does not meet the information requirement as:

- in the absence of adequate information on the test design and test procedure, it is not possible to verify if the study was conducted in accordance with the specifications of ISO 10253;
- without the result of the analytical monitoring of exposure concentrations, it is not possible to verify that exposure was satisfactorily maintained during the exposure phase and that the results can reliably be expressed based on nominal concentrations;
- without tabulated data on the algal biomass determined daily for each treatment group and control is it not possible to verify that the reported results are reliable.

In your comments on the draft decision in relation to the characterisation of exposure you add that:
"Supporting analysis was not included, but in view of the very low reported toxicity, this is not considered to detract from the low-hazard conclusions. The substance is also biodegradable in water which may impact on a validity of any algal study where media renewal is not applicable."

However, this information does not affect the fact that characterisation of exposure is a specification of the guideline that is required to demonstrate exposure to the organism throughout the test.

B. For the reasons explained under the Appendix common to several requests, your adaptation under Annex XI, Section 1.5. (grouping and read-across) is rejected.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section A.1.

3. Ready biodegradability

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

You have provided the following information:

1) a study according to OECD TG 306 with the Substance ([redacted]

2011)

2) an adaptation under Annex XI, Section 1.2 (Read-across). In support of your adaptation you provided:
   a. a study equivalent to OECD TG 301B with the analogue substance Triethanolamine (EC no. 203-049-8) ([redacted], 1996);
   b. a non-guideline study with the analogue substance Disodium succinate (EC no. 205-778-7) listed on the NITE-CHRIP website.

We have assessed this information and identified the following issues:

A. To fulfil the information requirement, a study according to OECD TG 306 is an acceptable method (Article 13(3) of REACH; ECHA Guidance R.7, Appendix R.7.9.1). For such a study, the following specifications must be met:

Information on the test material
- the nature and relative proportions of the major constituents of the test material are provided;

Applicability domain
- the OECD TG 306 describes two methods: a shake flask method and a closed bottle method. The shake flask method is similar to the OECD TG 301E and is therefore not applicable to adsorbing test materials unless appropriate adsorption controls are included in the test design;
- the shake flask method cannot be used for test substance that significantly adsorb onto the glass surfaces;

Validity criteria
- for a closed bottle test, the blank respiration does not exceed 30% of the oxygen in the bottle at the start of the test;

Technical specifications impacting the sensitivity/reliability of the test
- for the shake-flask test, the background concentration of DOC does not exceed about 20% of the total DOC concentration after addition of test material;
- for the closed bottle test, the use of a nitrification inhibitor is not foreseen by the guideline;

Reporting of the methodology and results
- the test design is reported (e.g. type of test, type on controls, replicates);
- the test procedure is reported (e.g. DOC of the seawater, pre-treatment prior to testing);
- for the closed bottle test, the calculation of the theoretical oxygen demand (ThOD) is described and justified;
- the data described in Annex 2 of OECD TG 306 are reported.

Your registration dossier provides an OECD TG 306 on the Substance, which shows the following:
- the test material is described as a commercial grade with a purity of 43%. It is not specified if the test material is a formulation in water or if other constituents are present in the commercial product;
- you report the test as a "*28 day closed-bottle test, using natural seawater*" and that the parameter monitored was "*DOC removal*";
- you report that a nitrification inhibitor was used with no further justification;
- on the test design, you have not specified what type of control was/were included,

the number of replicate. Furthermore as explained above you provided ambiguous information on the test method;
- on the test procedure, you have not specified the DOC of the seawater or if the seawater was pre-treated prior to testing (e.g. ageing);
- the data described in Annex 2 of OECD TG 306 are not reported.

Based on the above, the study does not meet the information requirement as:
- you have not provided adequate information on the composition of the test material;
- you provided conflicting information on the study procedure and it is not possible to determine whether a shake flask or a closed bottle test was conducted. We note that the test material is surface active (surface tension = 22.7 mN/m) and therefore it has a high adsorption potential. Therefore, the shake flask is not applicable;
- You provided insufficient information on the study design, study procedure and study results to verify if the study followed the specifications of OECD TG 306 and to conduct an independent assessment of its reliability.

B. You have further 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. a study equivalent to OECD TG 301B with the analogue substance Triethanolamine (EC no. 203-049-8) ([redacted] 1996);
   ii. a non-guideline study with the analogue substance Disodium succinate (EC no. 205-778-7) listed on the NITE-CHRIP website.

As explained in Section 2 of the Appendix on General considerations, the weight of evidence 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 301/310 must be provided. These TG require the study to investigate the following key element: The percentage of ultimate aerobic biodegradation (as measured by parameters such as DOC removal, CO2 production and oxygen uptake) of the test material under low inoculum concentration in a specified timeframe.

Source of information i. and ii. may provide relevant information on the above key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on General considerations.

Taken together, even if these sources of information provide information on the above key element, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

On the basis of the information provided in the Appendix on Reasons common to several requests and above, 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 301/310.

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

In your comments, you indicate your agreement to conduct a new study on the Substance.

ECHA acknowledges your agreement.

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

1. 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 negative results for both an Ames test and an *in vitro* cytogenicity study. Therefore, the information requirement is triggered.

ii. Information provided

You have provided the following information:

1) an adaptation under Annex XI, Section 1.5 (Read-across). In support of your adaptation you provided a study according to OECD TG 479 with the analogue substance triethanolamine (EC no. 203-049-8).

We have assessed this information and identified the following issues:

A. *Grouping of substances and read-across approach (Annex XI, Section 1.5)*

For the reasons explained under the Appendix common to several requests, your adaptation under Annex XI, Section 1.5. (grouping and read-across) is rejected. In addition, the study provided on the analogue substance does not meet the information requirement as further explained under issue B. below.

B. *Adequacy of the source study on the analogue substance*

To fulfil the information requirement, a study must be an *in vitro* gene mutation study in mammalian cells and have adequate and reliable coverage of the key parameters of the OECD TG 476 or 490 (Annex XI, Section 1.5 of REACH and ECHA Guidance R.7, Table R.7.7-2).

Your dossier provides a study conducted according to OECD TG 479. This study does not provide information on gene mutations but on chromosomal aberrations and indication of induced damage to DNA via sister chromatid exchange. Therefore, it does not meet the information requirement.

On this basis, the information requirement is not fulfilled.

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.

2. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant.

i. Triggering of the study

There is no information available in your registration dossier indicating that the Substance may be a developmental toxicant. Therefore, the information requirement is triggered.

ii. Information provided

You have provided the following information:

1) An adaptation under Annex XI, Section 1.2 (Weight of evidence). In support of your adaptation, you have provided the following sources of information:
   (i.) a study according to OECD TG 422 with the analogue substance disodium succinate (EC no. 205-778-7) ([redacted], 2002)
   (ii.) a substance evaluation report for the analogue substance triethanolamine (EC no. 203-049-8) ([redacted], 2015).

As explained in Section 2 of the Appendix on General considerations, the weight of evidence 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 422 must be provided. OECD TG 422 requires the study to investigate the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity:

1) Sexual function and fertility

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

Source of information (i.) may provide relevant but limited information on sexual function and fertility. This study does not provide information on the organ weights and histopathology of reproductive organs and tissues. Source of information (ii.) does not provide information on sexual function or fertility.

2) *Toxicity to offspring*

Information on pre- and perinatal developmental toxicity reflected by litter sizes, post-implantation 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.

Source of information (i.) may provide relevant information on toxicity to offspring while source of information (ii.) provides only limited information (post-implantation loss, implants, delivered pups).

3) Systemic toxicity

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

Sources of information (i.) and (ii.) provide very limited information on systemic toxicity (body weight, clinical signs and NOAEL values).

Moreover, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on General considerations.

Taken together, the sources of information listed above provide only partial information on reproductive toxicity and essential parts of information on the hazardous property is lacking, including information on organ weights and histopathology of non/reproductive organs and tissues, survival, food consumption, haematology, clinical chemistry, organ weights and other potential aspects of systemic toxicity. In addition, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

On the basis of the above, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 421/422. Hence, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Outcome

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 administration of the Substance (ECHA Guidance R.7.6.2.3.2).

3. 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:

1) a study according to OECD TG 203 with the Substance ([redacted], 2011)
2) an adaptation under Annex XI, Section 1.5 with the following supporting information:
   i. study according to OECD TG 203 on Disodium succinate hexahydrate (CAS No.: 6106-21-4, EC no. 205-778-7) ([redacted], 2003)

We have assessed this information and identified the following issues:

A. To fulfil the information requirement, a study must comply with OECD TG 203 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must

be met:

Validity criteria
- the analytical measurement of test concentrations is conducted;

Technical specifications impacting the sensitivity/reliability of the test
- the test medium fulfils the following condition(s): particulate matter ≤ 5 mg/L, total organic carbon (TOC) ≤ 2 mg/L or carbon oxygen demand (COD) ≤ 5 mg/L,
- at least 7 fish are used at each test concentration and in the controls;

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;
- in semi-static tests, test concentrations are measured at least twice over one exposure period (before and after renewal of test solutions). If the concentrations of the test material are expected to decline by more than 20%, analytical monitoring is conducted on all test concentrations with an additional determinations on the other exposure period(s);

Reporting of the methodology and results
- for semi-static tests, dissolved oxygen, pH, salinity (if relevant) and temperature measured prior to and after each water renewal are reported. The results of hardness and TOC determinations in the dilution water are 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;
- mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) are reported. The frequency of observations includes at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4;

Your registration dossier provides an OECD TG 203 on the Substance, which shows the following:
- no analytical monitoring of exposure concentration;
- on the test design, you have not specified the number of test organisms used to conduct the study;
- on the test procedure, you have not specified the quality parameters of the dilution water, in particular particulate matter, total organic carbon (TOC) or carbon oxygen demand (COD);
- tabulated data on mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) obtained on at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4 for each treatment group and control are not reported;

Based on the above, as no analytical monitoring of exposure concentration was provided the validity criteria of OECD TG 203 are not met. Furthermore, you have not provided the mandatory information on the study design and procedure and the study results. Therefore an independent assessment of the study cannot be conducted. Accordingly, this study does not meet the information requirement.

In your comments on the draft decision in relation to characterisation of exposure you

add that *"The absence of stability confirmation does not detract from the lack of toxicity demonstrated by the existing study."*

However, this information does not affect the fact that characterisation of exposure is a specification of the guideline that is required to demonstrate exposure to the organism throughout the test.

B. For the reasons explained under the Appendix common to several requests, your adaptation under Annex XI, Section 1.5. is rejected.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section A.1.

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.).

You have provided the following information:

1) An adaptation under Annex XI, Section 1.2 (Weight of evidence). In support of your adaptation, you have provided the following sources of information:
   i. Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test ([redacted], 2003) with the analogue substance disodium succinate (EC no. 205-778-7), according to OECD TG 422
   ii. Repeated Dose 90-Day Oral Toxicity in Rodents (1995) with the analogue substance triethanolamine (EC no. 203-049-8), according to OECD TG 408

As explained in Section 2 of the Appendix on General considerations, the weight of evidence 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 408 must be provided. OECD TG 408 requires the study to investigate the following aspects: systemic toxicity with an exposure duration of at least 90 days.

Systemic toxicity for an exposure duration of at least 90 days

Information on systemic toxicity includes clinical observations, body weight, food/water consumption, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, haematology, clinical biochemistry, organ weights, pathology and full detailed gross necropsy and subsequent histopathology of tissues.

Both sources of information provide limited information on systemic toxicity for an exposure duration of at least 90 days as further explained below.

Source of information i. may provide relevant information on clinical observations, body weight, food/water consumption, haematology, clinical biochemistry, organ weights, pathology and histopathology. However, it does not provide information on ophthalmological examination and sensory reactivity to various stimuli and functional observations of the animals. In any case, the exposure duration of study i. was approximately 60 days (for females) and 52 days (for males) rather than 90 days.

Source of information ii. does not provide information on food/water consumption, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, haematology, clinical biochemistry, organ weights, pathology and full detailed gross necropsy and subsequent histopathology of tissues. The study only provides information on clinical observations and body weight for an exposure duration of at least 90 days.

Moreover, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on General considerations.

Taken together, the sources of information listed above provide only partial information on repeated dose toxicity and essential parts of information of the hazardous property is lacking, including information on systemic toxicity (such as food/water consumption, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, haematology, clinical biochemistry, organ weights, pathology and full detailed gross necropsy and subsequent histopathology of tissues) following a repeated exposure of at least 90 days. In addition, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

On the basis of the above, 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 408. Hence, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Outcome

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 the substance is likely to have a low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.

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 (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

You have provided the following information:

1) An adaptation under Annex XI, Section 1.2 (Weight of evidence). In support of your adaptation, you have provided only one source of information:
   i. Developmental Toxicity study ([redacted], 2011), dermal route, with the analogue substance triethanolamine (EC no. 203-049-8).

As explained in Section 2 of the Appendix on General considerations, the weight of evidence 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.

Annex XI, section 1.2 requires a weight of evidence to be established "*from several independent sources of information*". However, you have submitted only one source of information to substantiate your weight of evidence adaptation. As long as the information you submitted does not allow any weighing of several pieces of evidence, your adaptation does not meet an essential condition set out in Annex XI, section 1.2.

In spite of these critical deficiencies, which in themselves could lead to the rejection of the adaptation, ECHA has nevertheless assessed the reliability of your adaptation and identified the follwoign isues:

A. A study performed according to OECD TG 414 on one species must use the most appropriate route of administration (Annex IX, Section 8.7.2.). According to ECHA Guidance R.7.6.2.3.2, the oral route is the "default" route (except for gases), and

case-specific deviations from the default approach must be justified.

The source of information provided in the dossier was performed using the dermal route. However, in the dossier there are no indications that the Substance has a high dermal penetration and indications for a specific toxicity following dermal absorption. Moreover, you have not provided any specific justification to indicate why the oral route would not be relevant.

Therefore, you have not justified that the dermal route is the most appropriate route of administration of the Substance.

B. Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report.

However, for this source of information you have only reported that there was "No effect on mating or fertility or offspring growth or survival". Therefore, you have not provided adequate and reliable documentation in a form of a robust study summary, as required by Article 10(a)(vii) and Article 3(28).

C. For the reasons explained under the Appendix common to several requests, your adaptation under Annex XI, Section 1.5. is rejected.

On the basis of the information provided in the Appendix on Reasons common to several requests and above, you have provided only one source of information and, in any case, it is not possible to conclude, based on the source of information provided, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 414. Hence, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Outcome

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral administration (ECHA Guidance R.7.6.2.3.2) of the Substance.

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[5].

B. Test material

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[6].

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

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

A. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in ECHA Guidance R.11 (Section R.11.4.2.2), you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthetize its relevant constituents and/or fractions.

Appendix F: Procedure

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

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

The compliance check was initiated on 11 July 2019.

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

ECHA took into account your comments and did not amend the requests.

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

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

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

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.

[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

OECD Guidance documents[9]
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.

[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix H: Addressees of this decision and the corresponding information requirements applicable to them

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

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

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