EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 2 June 2021

Addressee
Registrant of JS_101012-97-9_DTDA as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
30/05/2018

Registered substance subject to this decision ("the Substance")
Substance name: Tridecanamine, N-tridecyl-, branched and linear
EC number: 309-798-8
CAS number: 101012-97-9

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 ***11 March 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)

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: [EU C.3./OECD TG 201 // EU C.26./OECD TG 221])

B. Information required from all the Registrants subject to Annex VIII of REACH

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

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

3. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: OECD TG 210)

4. Soil simulation testing (triggered by Annex VIII, Section 9.2.; test method: EU C.23./OECD TG 307) at a temperature of 12 °C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

5. Sediment simulation testing (triggered by Annex VIII, Section 9.2.; test method: EU C.24./OECD TG 308) at a temperature of 12 °C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

6. Identification of degradation products (triggered by Annex VIII, Section 9.2; test method: test methods: OECD TG 307/308)

7. Bioaccumulation in aquatic species (triggered by Annex I, sections 0.6.1. and 4.; Annex XIII, Section 2.1.; test method: OECD TG 305)

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 Annexes VII and VIII to REACH, for registration at 10-100 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".

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

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of 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 a read-across approach in accordance with Annex XI, Section 1.5:

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- 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.)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)

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 a read-across justification document entitled "[redacted]" in IUCLID Section 13.2.

You read-across between the tridecylamine, branched and linear (TDA), EC No. 289-185-9 (CAS No. 86089-17-0) as source substance and the Substance (DTDA) as target substance.

You have provided the following reasoning for the prediction of toxicological properties:

- *"Read-across from TDA to DTDA is based on*
  1) structural similarity of the two compounds,
  2) similarities in physico-chemical data, and
  3) the available toxicological data which are also comparable and strengthen the category approach (acute toxicity data, irritation/corrosion and mutagenicity)."
- *"[...] TDA, like other monoalkylamines, undergoes oxidative deamination by Monoamine Oxidase and is further metabolized to CO2. As both compounds have a high calculated octanol-water partitioning coefficient (log Kow) and other similar chemical properties, DTDA is assumed to undergo the same metabolic pathways even though being a secondary amine."*

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.
ECHA notes the following shortcomings with regards to predictions of toxicological properties:

[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

a) *Relevance of the supporting information*

According to the ECHA Guidance R.6.2.2.1.f, "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance have similar properties for the endpoints under consideration in the read-across approach, you refer to their acute toxicity, skin irritation, eye irritation and *in vitro* gene mutation properties.

Whilst this data set suggests that the substances may have similar properties for acute toxicity, skin and eye irritation, and *in vitro* gene mutation, these studies do not inform on the repeated dose toxicity and developmental and reproductive toxicity properties of the target and source substances. Accordingly, this information is not considered as relevant to support prediction of the endpoints under consideration.

b) *Supporting information*

Annex XI, Section 1.5 of the REACH Regulation states that "*human health effects 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).

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 substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

In support of your adaptation, you have provided information on studies showing that the source substance and the Substance are corrosive, show a similar acute toxicity profile and are negative in *in vitro* gene mutation studies in bacteria and mammalian cells. However, you have not provided bridging studies with comparable design and duration on the source substances and the Substance to inform on the repeated dose toxicity and reproductive/developmental toxicity.

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

c) *Characterisation of the source substance*

Annex XI, Section 1.5 of the REACH Regulation provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar*

or follow a regular pattern as a result of structural similarity may be considered as group."

According to the ECHA Guidance, "*the purity and impurity profiles of the substance and the structural analogue need to be assessed"*, and "*the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded*". The purity profile and composition can influence the overall toxicity/properties of the Substance and of the source substance(s) (ECHA Guidance R.6.2.3.1.). Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

Furthermore, whenever the Substance and/or the source substances are UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances, qualitative compositional information of the individual constituents of the substances needs to be provided; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable (ECHA Guidance R.6.2.5.5.).

Both the source substance and the Substance are UVCB substances. In the read-across justification document you claim that "*it is not expected that any impurities present in DTDA and TDA will significantly affect the 28-day repeated dose toxicity and the reproduction/developmental toxicity*". In your dossier, you have only provided compositional information for the Substance. You have not provided information on the presence of impurities and on the composition of individual constituents in the selected source substance.

Therefore, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the composition of the source substance.

d) Adequacy and reliability of source studies

In addition, we have identified deficiencies with the source study provided on the selected source substance. These deficiencies are addressed under the corresponding Appendix (Appendix B.2).

In your comments on the draft decision, you agreed that there are significant toxicological differences that might invalidate the current read across approach.

B. Predictions for environmental fate properties

You have provided a read-across justification document entitled "[redacted]" *in* IUCLID Section 13.2.

You read-across between the following substances:

- Diisotridecylamine, EC No. 260-598-6 (CAS No. 57157-80-9)
- 10-methyl-N-(9-methyldecyl)undecan-1-amine, No EC or CAS provided
- 15-methyl-N-(10-methylundecyl)hexadecan-1-amine, No EC or CAS provided
- Tridecylamine, branched and linear, EC No. 289-185-9 (CAS No. 86089-17-0)
- Isotridecylamine, EC No. 252-693-6 (CAS No. 35723-81-0)
- Hexadecan-1-amine, EC No. 205-596-8 (CAS No. 143-27-1)

as source substances and the Substance (DTDA) as target substance.

You have provided the following reasoning for the prediction of toxicological properties:

- *"ECOSAR lists all source chemicals as aliphatic amines within its aquatic toxicity scheme"*;
- *"according to the acute aquatic toxicity classification of OASIS for the mode of action, all source chemicals are classified as narcotic amines"*;
- *"all source substances could not be classified according to the decision rules of Verhaar (class 5), with the exception of iso-tridecylamine (CAS 35723-81-0) being classified as a less inert compound (class 2)"*;
- *"all listed substances are assumed to be of high purity and that it is not likely that they contain any impurities which might have an influence on the read-across justification presented"*. You provided information to support this claim only for the Substance and for the analogue substance Tridecylamine, branched and linear, EC No. 289-185-9 but not for any other source substances listed above;
- "[The Substance and sources substances] *contain the same functional groups and a similar chemical structure*". Structural differences relates to the presence of an amine group with a single or two alkyl chains, differences in alkyl chain length and branching of the alkyl chain(s);
- "[The Substance] *as well as the source chemicals are characterized by a low vapor pressure, a low water solubility and a rather high n-octanol/water partition coefficient (log Kow)*";
- *"The substances are considered to be hydrolytically stable as they contain no chemical groups liable to hydrolysis"*;
- *"The target and source substances are considered not readily biodegradable"*;
- With regard to bioaccumulation in aquatic species:
  - you indicate Tridecylamine, branched and linear, EC No. 289-185-9 "*was assessed to be not B/vB according to the European PBT Working Group* [(PBT list no 93, Rev 13/14, March 2006)]";
  - you consider that QSAR predictions on the selected analogues support that the Substance has a low bioaccumulation potential;
  - you consider that a pilot BCF study on Hexadecan-1-amine, EC No. 205-596-8 provides further evidence of the low bioaccumulation potential of the Substance.

On that basis, you conclude that the Substance and the selected source substances have a low potential for bioaccumulation.

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

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

a) *Relevance of the supporting information*

According to the ECHA Guidance R.6.2.2.1.f, "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance have similar

properties for the endpoints under consideration in the read-across approach, you refer to their acute aquatic toxicity classification from OASIS, Verhaar classification, hydrolysis and ready biodegradability properties.

Whilst this data set suggests that the substances may have similar acute toxicity mode of action and degradation properties, this information do not inform on the bioaccumulation properties of the target and source substances. Accordingly, this information is not considered as relevant to support prediction of the endpoints under consideration.

b) *Missing supporting information to demonstrate that structural differences will not impact the prediction*

Annex XI, Section 1.5 of the REACH Regulation states that "*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).

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 substance cause the same type of effects. Such information can be obtained, for example, from toxicokinetic studies showing that the Substance and of the source substance(s) have similar ADME properties (*i.e.* similar absorption, distribution, metabolism, and excretion).

Your read-across justification does not include any supporting information that the Substance and the selected substance have similar ADME properties.

In the absence of this information, you have not provided supporting evidence establishing that the structural differences between the Substance and the selected analogues (i.e. presence of an amine group with a single or two alkyl chains, differences in alkyl chain length and branching of the alkyl chain(s)) will not impact the prediction. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

c) *Adequacy and reliability of the provided supporting information*

In addition, we have identified deficiencies with the information included in your registration dossier to support the proposed read-across adaptation. These deficiencies are addressed under Appendix B.6.

ECHA takes note of your comments on the draft decision, in which you specified that "*you will provide an update of the IUCLID dossier for the Substance. The information requirements for the Substance will be covered using data derived for the Substance itself as well as for individual components of the Substance, but not using data from structurally similar substances. Therefore, a read-across justification addressing environmental fate and ecotoxicological properties is not needed further and will not be provided with the update*".

C. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

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 a short-term toxicity study on aquatic invertebrates (OECD TG 202) on the Substance, but no information on long-term toxicity on aquatic invertebrates for the Substance. On the information requirement for Long-term toxicity testing on aquatic invertebrates, you state the following: "*No data (not required under REACH)*".

In section 4.8 of your technical dossier you state that the Substance "*is not soluble in water*".

We understand from these statements that you consider that long-term toxicity testing on aquatic invertebrates is not required 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.7b, Section 7.8.5).

Section 4.8 of your registration dossier provides a water solubility study according to OECD TG 105 based on the column elution method. The water solubility of the Substance was determined to be < 30 µg/L.

Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided in accordance with column 2 of Section 9.1.1.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you agreed to conduct a long-term toxicity testing on aquatic invertebrates based on OECD TG 211 with the Substance.

Study design

The Substance is difficult to test due to the low water solubility (< 30 µg/L). 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:

i. a key study according to OECD TG 201 on the Substance ([redacted], 2011)
ii. a disregarded study based on a method from the Swedish Board for Technical Development on the analogue substance Diisotridecylamine, EC No. 260-598-6. The study was disregarded on the following basis: *"Poor documentation; only short abstract available; only 48-h exposure period; no analytical monitoring"*

We have assessed this information and identified the following issues:

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

Characterisation of exposure

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

Additional requirements applicable to difficult to test substances

- if the test material is poorly water soluble, the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions is determined;
- if losses of the test material are expected within the timeframe of the test, a preliminary stability study is conducted.
- a justification for, or validation of, the separation technique is provided.

Reporting of the methodology and results

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

Other considerations

- algal biomass is determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (e.g. flow cytometry, in vitro or in vivo fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test.

Your registration dossier provides an OECD TG 201 study performed on the Substance (study i.) showing the following:

Characterisation of exposure

- You report that no analytical monitoring of exposure concentrations was conducted. You explained that *"a GC analytical method was developed"* and that *"this analytical method could determine test substance in water down to 10 mg/L"*.

You have not provided any justification as to why a lower limit of quantification (LOQ) could not be reached;

Additional requirements applicable to difficult to test substances
- the maximum dissolved concentration that can be achieved in the specific test solution is not reported;
- the Substance tested has low solubility and high adsorption potential and therefore losses of the test material may be expected. The result of a preliminary stability study is not reported;
- a justification for, or validation of, the separation technique is not provided;

Reporting of the methodology and results
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported;

Other considerations
- biomass was determined based on *in vivo* fluorescence. No data to support the validity of this approach is provided.

Based on the above, there are critical methodological deficiencies resulting in the rejection of the study. In particular:
- you have not provided adequate information on the characterisation of exposure during the test. You explained that the test material concentration could not be determined. However, we note that the analytical method used in this study had low sensibility (i.e. LOQ = 10 mg/L) and you provided no information to demonstrate that an analytical method with lower sensibility cannot be developed;
- the Substance is difficult to test (poor water solubility) and the specific requirements of OECD GD 23 are not met as you have not provided the estimation of the saturation concentration of the test material in the test medium, the result of a preliminary stability study and a justification for the separation technique that was used;
- the Substance has low water solubility in pure water (< 30 µg/L) and is highly adsorptive (it is ionisable and has a log Koc predicted to be > 5), therefore significant losses may be expected through adsorption. In the absence of reliable information exposure to the test material during the test, you have not demonstrated that effect values can be based on nominal concentrations;
- as you have not provided tabulated data on the algal biomass determined daily for each treatment group and control, it is not possible to verify whether or not the validity criteria of OECD TG 201 were met;
- biomass was determined based on in vivo fluorescence. No justification is provided that this method was adequate for determination of biomass (e.g. evidence of correlation between the measured parameter and dry weight for both control and treated groups). The physiological status of algal cells is known to impact the efficiency of the non-photochemical quenching (NPQ) of fluorescence and differences in physiological status between treatments may bias the relationship between re-emitted fluorescence and biomass.

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

In your comments, you stated that additional information on this study is available and that you will provide this information in an updated of your registration dossier. The information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration

dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

B. On study ii. above, we agree with your conclusion that this study is not a reliable source of information. Therefore, the validity of any read-across adaptation from Diisotridecylamine, EC No. 260-598-6 for this endpoint was not assessed further.

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.

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

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

A Short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

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

i. a key 90-days repeated dose toxicity study according to OECD TG 408 via oral route in rats with the analogue substance, tridecylamine, branched and linear, with EC No. 289-185-9 ([redacted], 2003).

We understand from the information you submitted 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:

Under Section 8.6.1, Column 2, first indent of Annex VIII to REACH, the study may be omitted if a reliable sub-chronic (90 days) or chronic toxicity study is available.

You have submitted 90-days repeated dose toxicity study on an analogue substance. However, for the reasons explained 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 the information requirement is not fulfilled.

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 the Substance is a liquid with very low vapour pressure (< 0.0001 Pa at 20ºC) and its uses does not include spraying applications. In addition, the Substance is a corrosive liquid and you apply self-classification as Skin Corr. 1A (H314). ECHA Guidance R.7.6.2.3.2. specifies that corrosive or highly irritating substances must be tested preferably via the oral route. However, testing at concentration/dose levels causing corrosivity must be avoided. Testing of neutral salts of alkaline or acidic substances is therefore more appropriate as it allows the investigation of intrinsic properties at adequate dose levels. These specifications are valid also for testing of repeated dose toxicity.

In your comments on the draft decision, you argue against testing with the neutralised form of the Substance. ECHA agrees with your arguments supporting the use of the Substance, rather than the neutralised form, as a test material (See the request B.2 below).

Therefore, the short-term 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) (see request B.2 below), 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.).

2. 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 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. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

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

i. a key pre-natal developmental toxicity study according to OECD 414 via oral route (gavage) in rats with the analogue substance, tridecylamine, branched and linear, with EC No. 289-185-9 (BASF, 2003);
ii. a 90-days repeated dose toxicity study according to OECD TG 408 with additional examination of reproductive organs in males and females via oral route in rats with the analogue substance, tridecylamine, branched and linear, with EC No. 289-185-9 ([redacted], 2003).

In addition, you provided an adaptation under Annex VIII, Section 8.7.1., Column 2, fourth indent. In support of your adaptation, you provided the following justification: "*the study does not need to be conducted because a pre-natal developmental toxicity study is available*".

We have assessed this information and identified the following issues:

Read-across adaptation

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5, relying on both study (i.) and study (ii.), is rejected.

B. Moreover, 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 422. Therefore, the following specifications must be met:
   - Dosing of the Substance for a minimum of four weeks for males and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation.
   - Examination of parameters for sexual function and fertility such as those for mating and fertility, duration of gestation, parturition, lactation and weight and histopathology of reproductive organs and tissues.
   - Examination of offspring parameters such as 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.

However, the study (ii.) does not include mating and several key parameters have not been examined. These include:

- the dosing did not cover conception, pregnancy and at least 13 days of lactation in females.
- Investigations for parameters for sexual function and fertility such as those for mating and fertility, and duration of gestation, parturition and lactation have not been performed.
- Examination of all offspring parameters is missing.

Therefore, the study (ii.) does not have adequate and reliable coverage of the key parameters of the OECD TG 421 or 422.

Column 2 adaptation

C. Under Section 8.7.1., Column 2, fourth indent of Annex VIII to REACH, the study may be omitted if a pre-natal developmental toxicity study (OECD TG 414) is already available.

However, for the reasons explained under issue A, study (i.) is not a reliable source of information to inform on the properties of the Substance. Therefore, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

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 421/422), 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.7a, Section R.7.6.2.3.2.).

In your comments, you agreed to perform a study according to OECD TG 422.

As already explained in Appendix B.1., the Substance is a corrosive liquid and you have applied self-classification as Skin Corr. 1A (H314). ECHA Guidance R.7.6.2.3.2 specifies that corrosive or highly irritating substances must be tested preferably via the oral route. However, testing at concentration/dose levels causing corrosivity must be avoided. Testing of neutral salts of alkaline or acidic substances is therefore more appropriate as it allows the investigation of intrinsic properties at adequate dose levels.

In your comments, you deemed that the oral route is appropriate, but you argue against testing with the neutralised form of the Substance for the following reasons:

- *"The substance is insoluble in water (<0.03mg/L). No pH value could be determined. It is unknown, if and to what a degree the substance can be neutralized, nor how this can be checked, since the pH cannot be determined.*
- *Even though the substance has been classified for skin corrosion category 1A, no significant local irritation has been observed in three independent studies for acute toxicity after oral exposure. In the two most recent studies, no animals died at 2000 mg/kg (0/12), there were no gross pathological abnormalities [...]. In the older study, the LD50 was determined at 2700 mg/kg [...] Gross pathology reported*

diarrhea and atonic intestine in animals that died at and above 1600 mg/kg, but no ulceration or bloody content. These results do not indicate local corrosive effects. It is hypothesized that no water solubility in combination with a comparable low number of amine groups due to the high molecular weight are responsible for this seeming mismatch of high skin corrosivity and very limited acute oral toxicity.

- *Consequently, local irritation is not expected to be the dose limiting factor in a repeated dose study."*

ECHA accepts that the neutralisation of the Substance may not be possible in practice. Based on the acute toxicity results, ECHA also considers that local corrosivity or irritation would not likely be the dose limiting factor in a screening study.

Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral administration (ECHA Guidance R.7.6.2.3.2.) of the Substance.

3. 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 short-term toxicity to fish studies (OECD TG 203 and DIN 38412, part 15) on the Substance. You also provided supporting short-term toxicity studies on analogue substances. However, you have provided no information on long-term toxicity on aquatic invertebrates for the Substance. On the information requirement for Long-term toxicity testing on fish, you state the following: "*No data (not required under REACH)*".

In section 4.8 of your technical dossier you state that the Substance "*is not soluble in water*".

We understand from these statements that you consider that long-term toxicity testing on fish is not required 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.7b, Section 7.8.5).

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

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you acknowledge that the Substance is poorly soluble in water and long-term toxicity testing should be considered according to REACH Regulation, Annex VIII, Section 9.1.3, Column 2. However, you specify that you intend to adapt this information requirement with the following justification:

- "[...] *acute toxicity data for DTDA* [indicate that] *aquatic invertebrates are more sensitive to the Substance than fish. Even if the short-term toxicity data might not give a true measure of the toxicity of this poorly water-soluble substance, the data still reflect the relative sensitivity of the organisms to the Substance. The 96-h LL50 for fish was*

determined to be > 100 mg/L, while the effect levels for aquatic invertebrates and algae were lower (aquatic invertebrates: 48-h EL50 = 46.9 mg/L; algae: 72-h ErL50 = 12.3 mg/L)";

- *"Avoiding unnecessary testing of vertebrate animals is in line with the REACH Regulation 1907/2006, which states in §25 that testing on vertebrate animal shall be undertaken as a last resort"*.

Finally, you stated that you intend to conduct first a long-term toxicity on aquatic invertebrates in a first step and, depending on the outcome of this test, a long-term study on fish.

We have assessed the additonnal information from your comments on the draft decision and identified the following issue:

A registrant may only adapt this information requirement based on the specific rules set out in Annex VIII, Section 9.1.3., Column 2 or the general rules set out in Annex XI.

Your justification to omit this information does not refer to any legal ground for adaptation under Annex VIII, Section 9.1.3., Column 2 or Annex XI to REACH.

Therefore, you have not demonstrated that this information can be omitted. Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the specific rules of Annex VIII, Section 9.1.3., Column 2 or the general rules of Annex XI.

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 Section A.1.

4. Soil simulation testing

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

You have not provided any information on soil simulation testing. Instead your provided the following statement: *"Experimental data on the biodegradation in surface water and sediment of the* [Substance] *are not available. Based on results of two ready tests [...], it is expected that the* [Substance] *is not biodegraded through growth linked processes"*.

We have assessed this information and identified the following issue:

This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as:

- it is not readily biodegradable (*i.e.* <60 % degradation in an OECD 301F), and
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as:
  - it has a high potential to partition to lipid storage (*e.g.* log K_{ow} > 4.5);
  - for some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid;
- it meets the T criteria set in Annex XIII: NOEC or EC_{10} < 0.01 mg/L or classification as Carc. 1A or 1B, Muta. 1A or 1B, Repro. 1A, 1B or 2, or STOT RE 1 or 2.

Your registration dossier provides the following:

- the Substance is not readily biodegradable (no significant biodegradation observed after 28 days in two OECD TG 301F studies);
- you reported that the predicted log Kow of the Substance is > 4.5. In addition, the Substance is an ionisable substance. Therefore, high potential for bioaccumulation cannot be excluded based on available information;

Furthermore, the information in your dossier is currently incomplete and therefore:

- it is not possible to conclude on the bioaccumulation potential of the Substance (see Appendix B.7. of this decision), and
- it is not possible to conclude on the toxicity of the Substance see Appendices A.1 to A.2. and B.1 to B.3. of this decision).

The information above indicates that the Substance is a potential PBT/vPvB substance.

Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation. Based on the adsorptive properties of the Substance, soil represents a relevant environmental compartment.

In your comments on the draft decision, you disagree to conduct a degradation simulation study in soil as based on the results of ready biodegradability studies you consider that "*it is expected that the Substance is not biodegraded through growth linked processes*" and as you consider the Substance to be P/vP.

We have assessed this additional justification from your comments on the draft decision and identified the following issue:

> Annex XIII, Section 2.1., 2nd paragraph, explains that additional information for the assessment of PBT/vPvB properties can only be omitted if there is no indication of P or B properties following the result from the screening test or other information.
>
> However, for the reasons already explained above and also acknowledged by you, there are indications that the Substance may be P/vP. Furthermore, as already explained above and under Appendix B.7., there are indications that the Substance may be B/vB. Furthermore, the absence (or low) degradation observed in ready biodegradability studies is not definitive proof of the absence of degradation under envrionmentally relevant conditions. Therefore, you have not demonstrated that this information is not needed.

On this basis, the information requirement is not fulfilled.

Study design

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

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

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

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

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

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

5. Sediment simulation testing

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

You have not provided any information on sediment simulation testing. Instead your provided the following statement: "*Experimental data on the biodegradation in surface water and sediment of the* [Substance] *are not available. Based on results of two ready tests [...], it is expected that the* [Substance] *is not biodegraded through growth linked processes*".

We have assessed this information and identified the following issue:

As already explained under Appendix B.4. above, the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation. Based on the adsorptive properties of the Substance, sediment represents a relevant environmental compartment.

In your comments on the draft decision, you disagree to conduct a degradation simulation study in soil as based on the results of ready biodegradability studies you consider that "*it is expected that the Substance is not biodegraded through growth linked processes*" and as you consider the Substance to be P/vP.

We have assessed this additional justification from your comments on the draft decision and identified the following issue:

> Annex XIII, Section 2.1., 2nd paragraph, explains that additional information for the assessment of PBT/vPvB properties can only be omitted if there is no indication of P or B properties following the result from the screening test or other information.
>
> However, for the reasons already explained above and also acknowledged by you, there are indications that the Substance may be P/vP. Furhtermore, as already explained above and under Appendix B.7., there are indications that the Substance may be B/vB. Furthermore, the absence (or low) degradation observed in ready biodegradability studies is not definitive proof of the absence of degradation under envrionmentally relevant conditions. Therefore, you have not demonstrated that this information is not needed.

On this basis, the information requirement is not fulfilled.

Study design

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

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

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

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

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

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

6. Identification of degradation products

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

As already explained under Appendix B.4., the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

You have not provided information on the identity of transformation/degradation products for the Substance in your registration dossier.

In your comments on the draft decision, you explain that you intend to adapt this information requirement under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation, you provide the following source of information:

i. The predicted degradation products of two representative structures (a linear isomer and a branched isomer for the C26 fraction of the Substance using CATALOGIC 301C.

The additional information from your comments on the draft decision is considered relevant. However, it only provides partial coverage of the information required for the Substance as it does not cover all fractions of the Substance (in particular the fractions with longer C-chain length). Furthermore, it only partially covers the range of isomers that may be present in the C26 fraction.

On this basis, the information requirement is not fulfilled.

ECHA emphasises that as explained in ECHA Guidance R.11.4.1., following the obligation of the registrant under Article 13(3) of REACH in the situation where new degradation simulation testing is necessary, the transformation and degradation products relevant for the registrant's own PBT/vPvB assessment are those products, which must be identified in tests C.23, C.24 and C.25 carried out in accordance with Council Regulation No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation No 1907/2006 (REACH) ("Test Methods Regulation").

Study design

Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation studies requested in Appendix B.4 and B.5 or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

To determine the degradation rate of the Substance, the requested studies according to OECD TG 308 and 307 (Appendices B.4 and B.5) must be conducted at 12°C and at test material application rates reflecting realistic assumptions. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline) and at higher application rate (*e.g.* 10 times).

7. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is required for the purpose of PBT/vPvB assessment (Annex I, Sections 0.6.1 and 4 to REACH).

Although you claim in your dossier that a study is not required for this tonnage band you indicate that you have provided data to discuss the bioaccumulation potential within the PBT assessment.

As already explained under Appendix B.4., the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further investigation.

You have provided an adaptation under Annex XI, Section 1.2 ('Weight of evidence'). In support of your adaptation, you have provided the following information:

1) a QSAR prediction for the analogue substance Diisotridecylamine (EC No. 260-598-6) based on the BCF model from the VEGA platform v.1.0.8.;
2) a QSAR predictions for the analogue substance Diisotridecylamine (EC No. 260-598-6) based on the BCFBAF model from the EPI Suite v4.11.;
3) a QSAR prediction for the analogue substance Diisotridecylamine (EC No. 260-598-6) based on T.E.S.T. v4.1.;
4) a QSAR prediction for the analogue substance Diisotridecylamine (EC No. 260-598-6) based on the CAESAR v2.1.13 model from the VEGA platform v.1.0.8.;
5) QSAR predictions for the analogue substance Diisotridecylamine (EC No. 260-598-6) based on the BCF base-line model v.02.07 from Catalogic v.5.11.13.;
6) a QSAR prediction for the analogue substance Diisotridecylamine (EC No. 260-598-6) based on the Meylan v1.0.2 model from the VEGA platform v.1.0.8.;
7) QSAR predictions for the analogue substances, Isotridecylamine (EC No. 252-693-6), Diisotridecylamine (EC No. 260-598-6), 10-methyl-N-(9-methyldecyl)undecan-1-amine (No EC or CAS provided) and 15-methyl-N-(10-methylundecyl) hexadecan-1-amine (No EC or CAS provided) based on the BCFBAF model from the EPI Suite v4.11.;
8) a reference to a bioaccumulation study in aquatic species claimed to be conducted according to OECD TG 305 on the analogue substance Hexadecan-1-amine, EC No. 205-596-8. You explain that this study was assessed in the context of the RAC Opinion on amines, coco alkyl, EC No. 262-977-1;
9) a statement that the Expert Working Group of the Technical Committee of New and Existing Chemicals concluded that Tridecylamine, branched and linear, EC No. 289-185-9 should be removed from the list of potential PBT/vPvB substances (PBT list no 93, Rev 13/14, March 2006).

In your comments on the draft decision, you explain that you will update your registration dossier. You explain that you will not perform an experimental study on the bioaccumulation in fish for reasons of animal welfare. Instead, you intend to adapt the information requirement under Annex XI, Section 1.3. In support of your adaptation, you provided the following information:

10) Contrary to your earlier claim, you now consider that the Substance is well defined. You provided an analytical report (report no. [redacted] which list the relative abundance of the various fractions of the substance. For each fraction, you report the smile code of the linear isomer and of a single branched isomer, which you consider to be a worst-cases as they "*contain a maximum number of branches*";
11) QSAR predictions for a linear and a branched isomer of each of the fraction of the Substance using the BCF base-line model v04.11 from OASIS Catalogic v.5.14.1.5.

We have assessed this information and identified the following issues:

1. *On your adaptation under Annex XI, Section 1.2. ('Weight of evidence') from your registration dossier*

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.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of 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 of the information for the given regulatory information requirement. Subsequently, relevance, reliability, 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 and identified the following issues.

Relevant information that can be used to support weight of evidence adaptation for the information requirement on bioaccumulation in aquatic species includes similar information that is produced by the OECD TG 305. Therefore, at least one of following key parameters needs to be covered:

1) the uptake rate constant (k_1) and loss rate constants for the substance including the depuration rate constant (k_2), and/or
2) the steady-state bioconcentration factor (BCF_{SS}) of the substance, and/or
3) the kinetic bioconcentration factor (BCF_K) of the substance, and/or
4) the biomagnification factor (BMF) of the substance.

All sources of information 1) through 9) may provide relevant information on the above key parameters since they can provide information on the BCF.

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

A. With regard to all of the sources of information 1) through 9):

   As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. Given the critical deficiencies identified, the reliability of any information derived from these analogue substances in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

B. With regard to the QSAR predictions 1) through 7):

B.1. The structures used for the prediction are not consistent with the substance identity information given in the registration dossier

ECHA Guidance R.6.1.7.3. specifies that a prediction is considered adequate for the purpose of classification and labelling and/or risk assessment if the following conditions are met:

- the composition of the substance is clearly defined, and
- representative structure(s) for the assessment are selected, and
- different constituents of the same substance are predicted individually.

In Section 1.2 of your registration dossier, you provide a report entitled "[redacted]". In this report, you define the Substance as "*a statistical mixture of different homologues (mainly C13, but also some C12 and C14 species) and isomers, mainly branched*". You further state that the Substance "*does not have a well-defined structure. The C13/C26 chain length is predominant but it consists of many isomers*". For the predictions 1) through 6) reported in your registration dossier, you have mainly used a single chemical structure corresponding to a single constituent and assuming the minimum branching possible (i.e. "iso" branching of the alkyl chains).

Therefore, the Substance and the predictions included in your dossier do not meet the conditions listed above. The composition of the Substance is not clearly defined, you have not demonstrated that the selected structures are representative of the Substance and in particular why the chosen degree of branching would be representative of more highly branched constituents. Finally, you have not reported individual predictions for all constituents of the Substance.

Accordingly, the reliability of such information derived from single constituents in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

B.2. The selected structures are outside the applicability domain of the model

ECHA Guidance R.6.1.5.3. specifies that a prediction is reliable, i.e. within applicability domain of the model, when, among others, the following conditions are satisfied:

- the selected structures falls within descriptor, structural, mechanistic and metabolic domain;
- the model predicts well chemicals that are similar to the chemical of interest.

With regard to source of information 1), you consider that "*according to the model's application domain index, the* [predictions is] *reliable*". However, we note that the model estimates a reliability score of 1/3 for the selected structure which indicates that the prediction is outside the applicability domain of the model.

With regard to source of information 2), you state that "*the substance is entirely within the applicability domain of the submodel* [...] *but as it does appreciably ionize at physiological pH, the [prediction] may be less accurate*". We agree with your assessment that this model does not predict well the bioaccumulation potential of ionisable substances.

With regard to source of information 3), you state that "*based on the mean absolute errors of the models the confidence in the predicted results is low*". We agree with

your assessment that the prediction of this model is not reliable for the selected representative structure.

With regard to source of information 4), you state that "*the substance is possibly not within the applicability domain of the model*". We agree with your assessment that the selected representative structure is not in the applicability domain of this model.

With regard to source of information 5), you state that "*the substance is not in the applicability domain of the model*" and we agree with your assessment.

With regard to source of information 7), you state that "*all substances are within the applicability domain of the calculation method according to* [redacted] *(1997/1999)*". However, as already explained above, as the selected structures correspond to ionisable substances, this model does not predict well their bioaccumulation potential. Furthermore, we note that you have used inconsistently corrected and uncorrected log Kow estimates when assessing the parametric applicability domain. Finally, at least some of the selected structures may have surfactant properties and would therefore fall outside the mechanistic domain of the model.

Therefore, sources of information 1) to 5) and 7) do not meet the conditions listed above and their reliability in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

C. With regard to source of information 9), we emphasize that, as specified on the ECHA webpage listing the evaluation from the TC NES sub-group on identification of PBT and vPvB substances, the statements made by the TC NES sub-group on identification of PBT and vPvB substances are without prejudice to any formal regulatory activities that ECHA or the Member States may have initiated or may initiate at a later stage.

Conclusion

The sources of information 1) to 9) listed above, provide information on bioaccumulation in aquatic species. However, the reliability of these source of information is significantly affected by the deficiencies outlined above.

On the basis of the information, 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 305. Therefore, your adaptation is rejected

2. *On the proposed adaptation under Annex XI, Section 1.3. ('QSAR') from your comments on the draft decision*

With regard to the adaptation under Annex XI, Section 1.3. ('QSAR') proposed in your comments on the draft decision, we note the following issues:

A. *The substance is outside the applicability domain of the model.*

Under ECHA Guidance R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

The structures used as input for the prediction have the following properties related to the estimation of applicability domain: 3.6 to 6.7% of the fragments of the selected

representative structures are not correctly predicted.

The structures used as input for the prediction includes fragments that are concluded to be incorrectly predicted by the model. This means that the software will not predict the metabolisation of these fragments correctly for the training set chemicals, while metabolism has a significant effect on the predicted BCF values. Furthermore, the substance possibly includes other possible parent structure which may also include incorrectly predicted fragments.

Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model, and in particular with regard to prediction of fish metabolisation.

B. *The prediction is not adequate due to low reliability*

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

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used

All the structures selected for prediction must fulfil the above conditions.

The model referred to in your comments on the draft decision provides the following information:

- the training set of CATALOGIC baseline model does not include aliphatic amines with length comparable to the representative structures;
- the predictions use as input parameter log Kow calculated by the software.

The predictions for the selected structures used as input are not reliable because:

- the training set of CATALOGIC baseline model does not include aliphatic amines with length comparable to the representative structures,
- For some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms than partitioning to lipid storage may drive bioaccumulation (e.g. binding to protein/cell membranes). For this reason, the use of the logKow of the neutral form of the representative structures as inout parameter, especially in absence of justification, is not adequate as log Kow is not considered a valid descriptor of the bioaccumulation potential for such substances (ECHA Guidance R.7c, Appendix R.7.10-3).

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

On this basis, the information requirement is not fulfilled.

Study design

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

- a stable and fully dissolved concentration of the test substance in water cannot be maintained within ± 20% of the mean measured value, and/or

- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

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

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

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[4].

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 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 the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

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[5].

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

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

A. Strategy for the PBT/vPvB assessment

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

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

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

B. 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 synthesize its relevant constituents and/or fractions.

Appendix E: 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 24 March 2020.

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

ECHA took into account your comments and amended the request B.2, to change the test material, but did not amend the other requests.

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

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

Appendix F: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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[8]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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

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

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

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

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

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

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.