EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 2 June 2021

Addressee
Registrant of JS_20193-20-8 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
26 November 2013

Registered substance subject to this decision ("the Substance")
Substance name: N-ethylpropylamine
EC number: 243-573-4
CAS number: 20193-20-8

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***9 June 2022***.

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

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

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 with a neutralised form of the Substance

3. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.; test method: OECD TG 106)

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".

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.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

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

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

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

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.2. for human health endpoints entitled "*Rationale and justification for the analogue read-across approach used in the registration dossier of N-ethylpropylamine CAS 20193-20-8*".

You read-across between the following:

- Diethylamine, EC No. 203-716-3 (CAS No. 109-89-7)
- Dibutylamine, EC No. 203-921-8 (CAS No. 111-92-2)
- Trimethylamine, EC No. 200-875-0 (CAS No. 75-50-3)

as source substances and the Substance as target substance.

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

- "[the read-across is] based *on structural similarity and/or similar physico-chemical and toxicological properties.*"
- "*[...] the amino group (especially of secondary and tertiary amines) was considered as main / basic parameter regrouping sources substances, suitable for read-across purpose within an analogue approach.*"
- "*Further common features which were considered for regrouping secondary and tertiary amines within the analogue group were the following:*
    - *A structure that contains only aliphatic organic substituents;*
    - *An elemental compositions of carbon, hydrogen and nitrogen;*
    - *A consistent incremental change across the group consisting of increasing*

[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

number of carbon atoms [...], *and*
  - *Molecular weights of < 500 Daltons, classifying these secondary and tertiary amines as low molecular weight aliphatic amines.*
- *"[...] absorption, distribution, metabolism and excretion [...] are quite similar"*;
- *"[...] the acute toxicity profiles [...] are quite similar";*
- *"[...] skin and eye irritation [...] are quite similar".*

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) *Read-across hypothesis*

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 (read-across approach). A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance (ECHA Guidance R.6). It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical and toxicological properties between the source substance(s) and your Substance is a sufficient basis for predicting the properties of your Substance for other endpoints.

However, similarity in chemical structure and similarity of some of the physicochemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints. As described above, a well-founded hypothesis is needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

b) *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(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to their acute toxicity, skin irritation and eye irritation properties.

Whilst this data set suggests that the substances may have similar properties for acute toxicity, skin (corrosivity) and eye irritation (serious eye damage), these studies do not inform on the repeated dose toxicity, and developmental and reproductive toxicity properties of the target and source substances. Accordingly, these information are not considered as relevant to support prediction of all the endpoints under consideration.

c) *Adequacy and reliability of the source studies*

In addition, we have identified deficiencies with the source studies on provided on the selected source substances. These deficiencies are addressed under the corresponding Appendix (Appendix B.1).

B. Predictions for ecotoxicological properties

You have provided a read-across justification document in IUCLID Section 13.2. for ecotoxicological endpoints entitled *"Justification of the analogue approach: N-ethylpropylamine (CAS 20193-20-8)"*.

You read-across between the following structurally similar substances:
- Diethylamine, EC No. 203-716-3 (CAS No. 109-89-7)
- Dibutylamine, EC No. 203-921-8 (CAS No. 111-92-2)

as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties:
- *"The three chemical substances share a common molecule skeleton. They have the same functional groups: two alkyl groups (here: -methyl and –propyl) which are bound to the nitrogen atom"*;
- "[the target and source substance] *are of high purity and that it is not likely that they contain any impurities which might have an influence on* [the prediction]";
- The target and source substances are expected to have similar environmental fate properties;
- *"A common mode of action* [for the target and source substances] *can be hypothesized for ecotoxicity endpoints"*;
- "[...] *the most critical physico-chemical properties for this assessment are comparable for these substances"*;
- You consider that available evidence support that the target and source substance show similar ecotoxicity.

In addition, in your comments on the draft decision, you provide an updated read-across justification for the analogue approach with Diethylamine, EC No. 203-716-3 (CAS No. 109-89-7). You provided the following additional justification for this analogue approach:
- the target and sources substances have no impuritites relevant for classification or the PBT/vPvB assessment;
- according to the QSAR Toolbox v4.3.1, the calculated structure similarity between the two substances is 72.7%;
- you justify the expected common mode of action based on similar mechanistic similarity as illustrated by several mechanistic profilers from the QSAR Toolbox v4.3.1 and, the USEPA New Chemical Categories and the Aquatic Toxicity Classification by ECOSAR and the Acute Aquatic Toxicity Mode of Action (MOA) of OASIS;
- the target and souce substance share similaritires in metabioolites as eight metabolites of the target substance were identified to be identical to those of the source substance using the CATABOL simulator of microbial metabolism and as these metabolites mostly belong to the classes aldehydes (mono) and aliphatic amines . You also state that "*The*

microbial metabolism estimated 18 metabolites for the target substance and 10 metabolites for the source substance":

- you consider that the target and sources substances show similar fate and ecotoxicological properties based on experimental data on the target and source substance, where available, or EPI Suite v4.11 and other (Q)SAR models predictions.

ECHA notes the following shortcomings with regards to predictions of growth inhibition on aquatic plants:

a) *Read-across hypothesis*

As already explained above, in support of your adaptation, a read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance (ECHA Guidance R.6). It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical, fate and ecotoxicological properties between the source substance(s) and your Substance is a sufficient basis for predicting the properties of your Substance for other endpoints.

Similarity in chemical structure and similarity of some of the physicochemical and ecotoxicological properties does not necessarily lead to predictable or similar ecotoxicological properties in other endpoints. As described above, a well-founded hypothesis is needed to establish a reliable prediction for an ecotoxicological property, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

b) *Adequacy and reliability of source studies*

In addition, we have identified deficiencies with the source studies provided on the selected source substances. These deficiencies are addressed under the corresponding Appendix (Appendix A.1).

C. Conclusions on the read-across approach

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

2. Assessment of your weight of evidence adaptation under Annex XI, Section 1.2. for human health endpoints

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

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

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

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

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

You have not submitted a justification for your weight of evidence adaptation for any of the endpoints indicated above, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information and identified systematic issues for all the information requirements relying on 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 all information requirements covered by the proposed weight of evidence adaptations listed above.

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. 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 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 study according to an unspecified method by US EPA 1971 with the analogue substance Diethylamine, EC No. 203-716-3 ([redacted] 1980);
ii. a supporting study according to OECD TG 201 with the analogue substance Diethylamine, EC No. 203-716-3 ([redacted] 1999);
iii. a supporting study according to DIN 38412, part 9 with the analogue substance Dipropylamine, EC No. 205-565-9 ([redacted] 1988).

We have assessed this information and identified the following issues:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. In addition, as further explained under issues B. and C. below, deficiencies were identified on the studies included in your registration dossier.

B. To inform on the properties of a substance, a test material in a study must be representative for that substance (Article 10 and Recital 19 of REACH; ECHA Guidance R.4.1).

For study ii. and iii. above, you have identified the test material as "*N-ethylethanamine / 109-89-7 / 203-716-3*" and "*N-propylpropan-1-amine / 142-84-7 / 205-565-9*" respectively, without further information, including composition, impurity profile and presence of impurities.

In the absence of composition information on the test material, the identity of the test material and its impurities cannot be assessed. Therefore, the information provided is rejected.

C. According to Annex XI, Section 1.5., the results to be read across should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 201 and OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test. Therefore, the following specifications must be met:

Key parameter to be measured

- the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated. Growth must be expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period;

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;
- the test media prepared specifically for analysis of exposure concentrations during the test is treated identically to those used for testing (*i.e.* inoculated with algae and incubated under identical conditions);
- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.

  For volatile, unstable or strongly adsorbing test substances, additional samplings for analysis at 24 hour intervals is required.
- if the concentration of the test material has not been maintained within 20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material.

Reporting of the methodology and results
- the test design is reported (*e.g.*, number of replicates);
- the test conditions are reported (*e.g.*, composition of the test medium, biomass density at the beginning of the test);
- 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.

However, your registration dossier provides a key study by [redacted]. 1980 (studies i. above) showing the following:
- you report that an analytical monitoring of exposure concentration was conducted using GC-FID. You have not reported the performance parameters of the analytical method nor the results obtained;
- you have not reported key elements of the study design and procedure, including the number of replicates, the algal biomass at the beginning of the test and the composition of the test medium;
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported.
- biomass was measured using *in vivo* fluorescence. No justification is provided that the method was adequate.

Based on the above, the reporting of this study is not sufficient to conduct an independent assessment of its reliability. More specifically:
- as you have not provided adequate information on the analytical method and the results of the analytical determination of exposure concentrations, you have not demonstrated that exposure was satisfactorily maintained over the duration of the test;
- as you have not reported the key information on the study design and procedure listed above, you have not demonstrated that the test was conducted under conditions that are consistent with the specifications of OECD TG 201;
- as you have not provided tabulated data on the algal biomass determined during

the test, it is not possible to verify if validity criteria consistent with the specifications of OECD TG 201 were met;
- as you have not provided any supporting information to demonstrate that *in vivo* fluorescence provides an adequate determination of algal biomass, it is not possible to verify that the study is reliable. 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. You have not addressed this uncertainty.

Your registration dossier also provides a supporting study by [redacted] 1999 (studies ii. above) showing the following:
- you report that an analytical monitoring of exposure concentrations was conducted. However, you have not reported any information on the analytical method (including the performance parameters of the method) or on the results of the analytical determination of exposure concentrations;
- you report some of the technical specifications of OECD TG 201 in the study summary record. However, you have not reported any information on the study design and procedure actually used to conduct this study;
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

Based on the above, the reporting of this study is not sufficient to conduct an independent assessment of its reliability. More specifically:
- as you have not provided adequate information on the analytical method and the results of the analytical determination of exposure concentrations, you have not demonstrated that exposure was satisfactorily maintained over the duration of the test;
- as you have not reported the key information on the study design and procedure listed above, you have not demonstrated that the test was conducted under conditions that are consistent with the specifications of OECD TG 201;
- as you have not provided tabulated data on the algal biomass determined during the test, it is not possible to verify if validity criteria consistent with the specifications of OECD TG 201 were met.

Finally, your registration provides a supporting study by [redacted], 1988 (studies iii. above) showing the following:
- no analytical monitoring of exposure concentrations was included. You specify that an evaluation of losses via evaporation was conducted by monitoring the TOC content of a stock solution at 100 mg/L nominal over 48 hours. Measured values were stable and the mean measured value was determined to be 79.0 mg/L and 79.3 mg/L, without or with shaking, respectively. You consider that losses will not impact exposure concentrations over the duration of the test;
- biomass was measured using *in vivo* fluorescence. No justification is provided that *in vivo* fluorescence was adequate for the determination of biomass (*e.g.* evidence of correlation between the measured parameter and dry weight for both control and treated groups).

Based on the above,
- there are critical methodological deficiencies resulting in the rejection of the results of these studies. More specifically, you have not demonstrated that exposure was satisfactorily maintained during the experiment as:
  - it is unclear if this estimate was obtained under conditions that are consistent

with the test conditions;
- a non-specific analytical method (i.e. TOC measurement) was used;
- this estimate was obtained at 100 mg/L nominal and do not inform on potential losses of the test material at lower concentrations;
- you have not assessed losses that could originate from adsorption of the test material under the test conditions. The test material is ionisable and therefore potentially highly adsorptive.

Furthermore, we note that measured values differed by over 20% of nominal concentration and that this additional experiment indicate significant losses at some stage of the process. Therefore, this information does not provide reliable evidence that exposure was satisfactorily maintained during the test.

- the reporting of the studies is not sufficient to conduct an independent assessment of their reliability. More specifically, as you have provided, no information on the relationship between measured *in vivo* fluorescence and biomass, for the reasons already explained above, you have not demonstrated that *in vivo* fluorescence was adequate for the determination of biomass.

Therefore, this study does not meet the specifications of OECD TG 201 in conjunction with OECD GD 23.

In your comments on the draft decision, you explain that the publication by [redacted] 1980 (study i.) does not contain the information listed above. Therefore, you will assign this study a reliability score of 4 and will no longer use this information as key study to cover the information requirement for the Substance. Furthermore, you explain that the study by [redacted], 1988 (study iii.) will be removed from the dossier. Finally, you explained that you have now access to the full study report for the study by [redacted] 1999 (study ii.) and that you intend to provide an improved robust study summary in an updated registration dossier.

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).

Finally, in your comments on the draft decision, you explain that the available experimental result for the source substance diethylamine (i.e. study ii.) will be supported by a predicted 72-h EC50 derived from the OECD QSAR Toolbox v4.4 for the Substance. You have provided information derived from experimental data from a group of substancesusing the OECD QSAR Toolbox and flagged the information as QSAR.

As the group of substances are used as source substances to predict the property of the Substance, we understand that you have adapted the standard information requirements under Annex XI, Section 1.5 of REACH (grouping and read-across).

We have assessed this information accordingly and identified the following issue:

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies) (ECHA Guidance R.6.2.6.2).

You specify that you used the arithmetic mean value from the 5 nearest neighbours selected by the OECD QSAR Toolbox to estimate the 72-h EC50 for the Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance, including among other appropriate characterisation of the group members, a definition of the applicability domain of the grouping, a read-across hypothesis and adequate supporting information on the source studies. Your justification should take due account for structural differences between the target and sources substances.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substances and your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to its adsorption potential (as it is ionisable) and potential for volatilisation. OECD TG 201 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 201. 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. Ready biodegradability

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

You have provided the following information:

i. A ready biodegradability study according to OECD TG 301B on the Substance ([redacted] 2005).

We have assessed this information and identified the following issue:

To fulfil the information requirement, a study must comply with the OECD TG 301 or 310 (Article 13(3) of REACH). Therefore, for a study according to OECD TG 301B, the following requirements must be met:

Validity criteria

- The total CO_2 evolution in the inoculum blank at the end of the test does not normally exceed 40 mg CO_2/L;

Applicability domain

- The test material falls into the applicability domain of the selected test method. In this regard, OECD TG 301 specifies that the OECD 301 B is not applicable to volatile

substances;

Technical specifications impacting the sensitivity/reliability of the test

- The concentration of the inoculum is set to reach a bacterial cell density of 10^7 to 10^8 cells/L in the test vessel. The suspended solid concentration is ≤ 30 mg/L;
- Biodegradation is followed by monitoring the amount of carbon dioxide produced from the test material (corrected for that derived from the blank inoculum). DOC analysis is only an optional additional parameter;

Reporting of the methodology and results

- The results of measurements at each sampling point in each replicate is reported in a tabular form;

Your registration dossier provides a key study showing the following:

- the OECD TG 301B was used. In Section 4.6 of your technical dossier you report vapour presure estimates for the Substance ranging from 77 hPa to 86 hPa at 20°C. You consider that the Substance will not significantly partition from the water to the atmosphere as the pH-corrected Henry's Law constant (based on a method described in Appendix R.7.1-2 of ECHA Guidance R.7a (version 1.0, 2008)) at pH 7 is 3.94E-04 Pa.m³/mol. We acknowledge that substances that dissociate in water have a lower tendency to partition to air;
- you have only reported results referring to DOC removal;
- you have provided only information on inoculum density in mg/L suspended solids but no information on inoculum density in cells/mL
- you have not reported the results of measurements of CO_2 production at each sampling point in each replicate (including controls).

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the results of this study. More specifically:
  - you have not demonstrated that the test material falls in the applicability domain of OECD TG 301B. We acknowledge that substances that dissociate in water have a lower tendency to partition to air. However, we note that the method you used to derive the pH-corrected Henry's Law constant for the Substance was removed from ECHA Guidance R.7a in version 2.0 (2012) as it is no longer considered scientifically valid. Therefore, considering that the Henry's Law constant (HLC) of the undissociated form is high (3.94 Pa m³/mol at 25°C) and that no reliable estimate is available for the value of the dissociated form, the Substance is regarded as volatile and therefore outside the applicability domain of this test method.

    In your comments on the draft decision, you acknowledge that the pH-corrected Henry's Law constant method was withdrawn in more recent versions of the guidance and that no HLC can be derived for the charged molecule in the environmentally relevant pH range. However, you consider that the HLC for the uncharged molecule is rather low and will be even lower for the charged molecule, reducing the potential of the loss of the substance during the test via loss from the water phase to the air. Therefore, you disagree that the Substance falls outside the applicability domain of the test method. You consider that the difference between the biodegradation percentage determined based on DOC removal and CO_2 production indicates that the loss by volatilisation is c.a. 10%. You further state that "*as the degradation was followed by the evolved CO2, the potential loss of the substance via volatilization did not impact the result of the study*".

ECHA agrees that there is currently no valid estimate of the HLC of the Substance in your registration dossier. However, ECHA disagrees with your statement that, as the percentage degradation was determined based on CO_2 production, loss by volatilization did not impact the reported results. As you have not specified how CO_2 production was measured, ECHA cannot verify whether measured values may have been biased by the presence of the test material in the volatile trap. For the same reason, your estimate of losses of the test material via volatilisation is not considered reliable. Therefore, ECHA maintains that you have not demonstrated that the test material falls in the applicability domain of OECD TG 301B.

- DOC measurements is only an optional additonnal parameters in OECD TG 301B and cannot be used to estimate ultimate bodegradation for substances were significant losses from the test system may be expected. As explained above, the test material is considered volatile and as it is ionisable it may also adsorb to particulate matter. Therefore, DOC removal is not a reliable parameter to monitor ultimate biodegradation.

  In your comments on the draft decision, you explain that the robust study summary already contains data on the degradation based on CO_2 evolution for the end of the 10-day window and for the end of the test phase (day 28). However, you intend to add the CO_2 data for all replicates and all sampling time in a tabular form in an update of your registration dossier. ECHA emphasizes that the values measured in the inoculum blank are also required to verify the validity of the test, as further explained below.

- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically:
  - you have not reported information on inoculum density in cells/L.

    In your comments on the draft decision, you state that "*the inoculum for a study according to OECD TG 301B can be derived from a variety of sources* [and therefore the inoculum density] *cannot be described using the same parameter*". You consider that Table 2 of OECD TG 301 provides several alternative parameters to characterize the inoculum density. In the study by [redacted] (2005), sludge was used as an inoculum. As the sludge was introduced at a concentration of 30 mg/L, you consider that the inoculum density was adequate.

    ECHA disagrees with this statement. The limit values for the inoculum density in mg/L (e.g. for sludge or soil) or mL/L (e.g. for surface water or effluent) are set to ensure that the introduction of exogeneous organic matter in the test system is within an acceptable range. However, such parameter does not provide a direct estimate of bacterial biomass (as the density of bacteria in, for e.g., a sludge sample or a secondary effluent may vary by orders of magnitude). In the absence of supporting information to demonstrate that the sludge concentration used in this study allowed reaching an adequate bacterial density, you have not demonstrated that the inoculum density was consistent with the specifications of OECD TG 301B.

  - as you have not provided adequate reporting of the study results, it is not possible to verify if validity criteria consistent with the specifications of OECD TG 301B were met.

In your comments on the draft decision, you quote the following requirement form the OECD TG 301B: "*the total CO_2 evolution in the inoculum blank at the end of the test should not normally exceed 40 mg/l medium. If values greater than 70 mg CO2/L are obtained, the data and experimental technique should be examined critically*". You then state that "*the values of the blank controls were below the critical value of 70 mg/L*" and conclude that "*the study fulfils this validity criterion*".

However, you have not provided information on CO_2 production in the inoculum blank over the course of the experiment or even the value reached at the end of the experiment. Therefore, ECHA cannot verify the validity of your statement or the consistency of the results obtained from replicate inoculum blanks, if any. In the absence of this information, ECHA maintains that you have not demonstrated that this study meets the validity criteria of OECD TG 301B.

Therefore, this study does not meet the specifications of OECD TG 301B.

In your comments on the draft decision, you also state that "*the conclusion on the ready biodegradability of the Substance are supported by two QSAR calculations: - CATALOGIC v5.14.5 BOD 28 days MITI (OECD 301C) v11.16 - CATALOGIC v5.14.1.5, CATALOGIC Kinetic 301F v14.17*". As an annex to your comments on the draft decision, you have provided a QSAR Prediction Reporting Format (QPRF) for each of these two models.

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

Under Section 1.3., first paragraph, third indent of Annex XI to REACH, a study may be omitted if QSAR results are adequate for the purpose of classification and labelling and/or risk assessment, including PBT assessment. ECHA Guidance R.7.9.5.1. specifies that (Q)SARs for predicting ready biodegradation are not yet sufficiently accurate to predict rapid degradation. However, when no useful information on degradability is available (either experimentally derived or estimated), (Q)SAR predictions can be used as supporting evidence of that the substance is not rapidly degradable.

You have provided the following results from the CATALOGIC v5.14.5. software:

- OECD 301C model: 70 ± 5% biodegradation based on theoretical BOD removal after 28 days;
- OECD 301F model: 80 ± 5% biodegradation based on theoretical BOD removal after 28 days but failing the 10d-window criteria.

As explained above, you registration dossier currently does not include adequate experimental or estimated information on rapid biodegradation for the Substance. In addition, as explained in ECHA Guidance R.7.9.5.1., (Q)SAR predictions are, on their own, not adequate to conclude on rapid biodegradation. Furthermore, we note that these results provide limited support to conclude that the Substance is readily biodegradable because the OECD 301C does not inform on the 10d-window criteria and the 10d-window criteria was not met according to the results of the OECD 301F model. Therefore, you have not demonstrated that the Substance is to be regarded as readily biodegradable.

On this basis, the information requirement is not fulfilled.

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 1.2 of REACH (Weight of evidence). In support of your adaptation, you provided the following sources of information on analogue substances:

i. a study similar to OECD 413 via inhalation in rats with an analogue substance, diethylamine (EC No. 203-716-3) ([redacted] 2003);
ii. a study similar to OECD 413 via inhalation in mice with an analogue substance, diethylamine (EC No. 203-716-3) ([redacted] 2003);
iii. a study similar to OECD TG 413 via inhalation in rats with an analogue substance, dibutylamine (EC No. 203-921-8) ([redacted] 2003).

We have assessed this information and identified the following issues:

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

Relevant information that can be used to support weight of evidence adaptation for Short-term repeated dose toxicity (28 days) includes similar information that is produced by the OECD TG 412. The following aspects must be covered: 1) Clinical observations, 2) body weight and food/water consumption, 3) haematology and clinical biochemistry, and 4) gross necropsy and histopathology.

The sources of information (i) to (iii) provide partial information on the aspects covered by the OECD TG 412.

Indeed, the studies (i) to (iii) you have provided did not include ophthalmological examination. In addition, only heart, right kidney, liver, lung, right testis and thymus were weighed in studies (i) and (ii). In study (iii), haematology and clinical chemistry parameters were not examined and only lung was weighed.

Therefore, the studies (i) to (iii) do not have adequate an reliable coverage of the key parameters of the OECD TG 412 study.

In any case, studies (i) to (iii) are performed with analogue substances and the reliability of these studies to inform on the properties of the Substance is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

On that basis, not only these studies provide partial coverage of the key parameters the of the OECD TG 412 study, but the information provided is in any case affected by significant deficiencies affect its reliability. Consequently, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 412 study. Therefore, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

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 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.

Therefore, the sub-acute toxicity study must be performed according to the OECD TG 407, in rats and with oral administration of a neutralised form 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 Appendix B.2.), 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.).

In your comments on the draft decision, you proposed to perform a screening study according to OECD TG 422 via inhalation with the Substance (See the request B.2 below).

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 1.2 (Weight of evidence). In support of your adaptation, you provided the following sources of information on an analogue substance:

i. a study according to OECD 422 via oral route (gavage) in rats with an analogue substance, trimethylamine (EC No. 200-875-0), weight of evidence, ([redacted] 2003).

In addition, you have provided the following statement: "*Read-across data of Trimethylamine (CAS 75-50-3, [redacted] 2003) is available. In a combined repeated dose and reproductive / developmental toxicity screening test no effects on reproductive and developmental toxicity were observed. Additionally, subchronic repeated dose toxicity studies with Diethylamine (CAS 109-89-7, [redacted] 2003) and Dibutylamine (CAS 111-92-2, [redacted] 2003) are available. Effects on sperm motility of male rats and mice and on estrous cyclicity in female mice in the repeated dose toxicity studies with Diethylamine were the only findings. No other adverse effects were observed on reproduction toxicity. Thus, it is concluded that further tests on reproduction toxicity are not necessary.*"

In your statement your refer to the following additional sources of information on analogue substances:

ii. a study similar to OECD 413 via inhalation in rats with an analogue substance, diethylamine (EC No. 203-716-3) ([redacted] 2003);
iii. a study similar to OECD 413 via inhalation in mice with an analogue substance, diethylamine (EC No. 203-716-3) ([redacted] 2003);
iv. A toxicity study similar to OECD TG 413 via inhalation in rats with an analogue substance, dibutylamine (EC No. 203-921-8) ([redacted] 2003).

We have assessed this information and identified the following issue:

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

   Relevant information that can be used to support weight of evidence adaptation for Screening for reproductive/developmental toxicity includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. The following aspects are covered: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

   The source of information (i) provides relevant information on sexual function and fertility, toxicity to offspring and systemic toxicity. The sources of information (ii) to (iv) provide relevant information on systemic toxicity and but only limited information on fertility and no information on sexual function and toxicity to offspring.

   Studies (i) to (iv) are performed with analogue substances. The reliability of these studies to inform on the properties of the Substance is significantly affected by the deficiencies identified in read-across adaptation as explained in the Appendix on Reasons common to several requests.

   Due to the significant deficiencies affect the reliability of these studies, 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 property foreseen to be investigated in an OECD TG 421 or 422 study.

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.7.6.2.3.2.).

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 appropriate and allows investigation of intrinsic properties at adequate dose levels.

In your comments on the draft decision, you proposed to perform the requested screening study according to OECD TG 422 via inhalation with the Substance due to following reasons:

- *"Ethylpropylamine is a liquid with a high vapour pressure of 86 hPa that is only used in industrial and professional applications [...] ECHA Guidance R.7 more explicitly defines that ECHA Guidance R.7 more explicitly defines that "Testing by the inhalation route is the [..] preferred route for liquids of high to very high vapour pressure at ambient temperature (>25 kPa or boiling point below 50°C) for which inhalation is usually the predominant route of human exposure."(R.7.5.6.3.4). As stated above, the vapour pressure of ethylpropylamine is far above 25kPa."*
- *"In the same section in the ECHA Guidance it is stated that testing via inhalation shall be performed, "if there is some concern for local effects in the respiratory tract for which a qualitative assessment might not be sufficiently robust to demonstrate safe handling and use of the substance (A concern for local effects in the respiratory tract might be assumed inter alia for substances that are corrosive or irritating for the skin and/or eye)." Ethylpropylamine is corrosive, and local effects are expected to be the leading health hazard for workers. In combination with the high vapour pressure, assessment of the local effects after repeated inhalation and derivation of an appropriate DNEL will be an essential part of the exposure assessment."*
- *"Testing of the neutral salt is considered inappropriate, since it masks the most important intrinsic property with regard to risk assessment."*
- *"[...] according to REACH Annex V and the corresponding guidance, [...] "deliberate neutralization of acids or bases to form the corresponding salts [...] is not covered by this exemption." Consequently, the "neutral salt" as stated in the draft decision would not be covered by the registration but would require a read across justification. We generally reject to use a read across substance, which is only manufactured for this purpose."*

ECHA notes that the vapor pressure of the Substance, i.e. 86 hPa, equals to 8.6 kPa and is therefore not far above 25 kPa as you have argued in your comments. According to ECHA guidance R.7.6.2.3.2. *"[...] the test methods for reproductive toxicity which focus on the detection of reproductive hazards, the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases."* Therefore, ECHA considers that in this case, also taking into account the corrosivity of the Substance, oral route is the most appropriate administration route as the vapor pressure of the Substance does not indicate that inhalation route would be the preferred on by default.

You raised a concern that testing a neutralised form of the Substance masks the most important intrinsic property, i.e. corrosivity, and is therefore considered inappropriate. However, ECHA considers that testing of the neutralised form of the Substance will enable to investigate intrinsic properties related to reproductive toxicity in a screening study (OECD TG 422) by allowing to use adequate dose levels as the already known corrosivity of the Substance may not allow investigating the reproductive toxicity in relation to systemic toxicity. Also, the corrosivity/irritation of the Substance may affect the behaviour of the animals confounding the interpretation of a reproductive toxicity related parameters. In addition, local effects might mask other systemic toxicity effects investigated in an OECD TG 422 study or induce unnecessary stress to the animals with consequences to the outcome of the study.

In your comments, you also argued that testing the Substance via inhalation is justified as a derivation of an appropriate DNEL is needed. ECHA notes that you have already derived DNELs for inhalation local effects (acute and long-term) based on a worst-case assumption. Regarding derivation of a specific DNEL for local effects, ECHA considers that the current approach presented in the dossier appears to be protective for the local effects.

ECHA notes that similar absorption and systemic effects are expected for the Substance and its neutralised form under physiological conditions. The dissociation constant (pKa) of the Substance is 11. Therefore, the Substance will as a protonated form (NH_2^+) under physiological conditions as will the neutralised form of the Substance. Therefore, read-across for systemic effects between the Substance and its neutralised form is plausible as such.

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 a neutralised form the Substance.

3. Adsorption/ desorption screening

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

You have adapted this information requirement under Annex XI, Section 1.3 ('(Q)SAR'). In support of your adaptation, you provided the following information:

i. a log Koc value estimated using log Kow from SRC KOCWIN (v2.00) for the uncharged molecule;
ii. a log Koc value estimated using the first-order Molecular Connectivity Index (MCI) method from SRC KOCWIN (v2.00) for the uncharged molecule;
iii. a correction of the log Koc value using a method described in a publication by Franco & Trapp (2008).

We have assessed this information and identified the following issue:

A. Annex XI, Section 1.3. states that (Q)SAR results must be adequate for the purpose of risk assessment, including PBT assessment. ECHA Guidance R.7.1.15.4 specifies that a measured adsorption coefficient is usually needed for ionising substances, since it is important to have information on pH-dependence. The guidance further clarifies that, if estimation methods are not appropriate (e.g. because the substance is a surfactant or ionisable at environmentally-relevant pH), then a batch equilibrium test is essential under Annex VIII.

   The log Koc values predicted using the MCI index or log Kow (see i. and ii. above) do not provide information on pH-dependence of the adsorption potential of the Substance. Therefore, this predicted value is not adequate for the purpose of risk assessment, including PBT assessment.

   In your comments on the draft decision, you agree with ECHA's assessment and state that this information will be removed for your registration dossier.

B. 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,

- reliable input parameters are used.

As an attachment to your comments on the draft decision, you have provided a QMRF and QPRF for the QSAR prediction ii. listed above, including references to literature. The R2 obtained on the training set (available as supplement data in the paper of Franco & Trapp, 2008) is 0.76, while R2 obtained on the validation set (i.e. the overall predictivity of the model) was determined to be 0.55. The model predicts a log Koc of 2.43 at pH 5-8 for the Substance (as retrieved from your registration dossier).

Supporting information on the original publication describing the model is publicly available (Franco & Trapp, 2008). This information indicates that:

- the training set includes only one secondary aliphatic amine (i.e. dimethylamine). It also includes one tertiary aliphatic amine (i.e. trimethylamine);
- the validation set does not include any secondary aliphatic amine and includes a single primary aliphatic amine (i.e. n-butyl amine);
- for these substance, the input parameter (i.e. measured log Koc) were retrieved from a publication by van Oepen, Körder and Klein, 1991 (Chemosphere, vol 22(3-4):285-304). In this publication, log Koc was determined using a modified OECD TG 106 on podzol, alfisol and sediment. For dimethylamine, trimethylamine and n-butyilamine, log Koc values ranging from 0.60 to 2.70, 0.78 to 2.83 and 0.70 to 2.03, respectively, are reported. For the same substances, input values of 2.04, 1.99 and 1.74 were used.

However, the prediction for the Substance used as input is not reliable because:

- the training and validation sets include only a very limited number of substances with some structural similarity with the Substance. In particular, the training set includes only methylated aliphatic amines and no aliphatic amines with C-chain length similar to the Substance. Also the validated set does not include any secondary aliphatic amine;
- It is unclear how the experimental values on aliphatic amines were selected in the paper of Franco & Trapp (2008) and why they differ from the experimental values retrieved from the source publication by van Oepen, Körder and Klein (1991);
- The publication van Oepen, Körder and Klein (1991) indicates significant variation in log Koc depending on the nature of the soil/sediment matrix. This information can only be obtained from testing the substance in different matrices (as required by the OECD TG 106) and is not reflected by the model prediction.

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.

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.
   - as explained under Appendix B.1. and B.2., the use of a neutral salts of the Substance (*e.g.* hydrochloride salt of the Substance) is more appropriate for conducting the tests requested under Appendix B.1. and B.2. as it allows the investigation of intrinsic properties at adequate dose levels. When selecting a neutral salt, the potential impact of the counterion must be considered. The counterion must have no known systemic toxicity.

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[5].

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

Appendix D: Procedure

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

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

The compliance check was initiated on 24 March 2020.

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

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

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

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.