~~Confidential~~

Helsinki, 08 February 2022

Addressees
Registrants of triethylamine as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
12/03/2014

Registered substance subject to this decision ("the Substance")
Substance name: Triethylamine
EC number: 204-469-4
CAS number: 121-44-8

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 ***16 May 2025***.

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

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. /OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102

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

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

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

3. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study requested below (Annex VIII, Section 8.7.1.)

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

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit). Due to reasons explained in Appendix C.1., the test sample must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutral salt of the Substance.

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

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

D. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat/rabbit). Due to reasons explained in Appendix D.1., the test sample must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutral salt of the Substance.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:

   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

   Due to reasons explained in Appendix D.2., the test sample must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutral salt of the Substance.

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 X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

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

Failure to comply

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

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

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

Appendix on Reasons common to several requests

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

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

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

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

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

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

You have not provided any read-across justification document in your registration dossier.

You read-across between the following substances:

- Trimethylamine, EC number 200-875-0 (CAS RN 75-50-3)
- Tripropylamine, EC number 203-047-7 (CAS RN 102-69-2)
- Tributylamine, EC number 203-058-7 (CAS RN 102-82-9)

as source substances and the Substance as target substance.

You have not provided any reasoning for the prediction of toxicological, ecotoxicological and fate properties.

In your comments on the draft decision, you indicate your intention to further explore the read-across adaptation.

ECHA acknowledges your intention to investigate hypotheses for a potential read-across adaptation and provide a read-across justification, if possible. However, we also note that currently you have not provided any new information in the registration dossier to further support your read-across adaptation. The information provided in your comments does change the assessment.

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

[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

ECHA notes the following shortcomings with regards to predictions of toxicological, ecotoxicological and fate properties.

A. *Absence of read-across documentation*

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

You have provided studies conducted with other substances than your 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.

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.

B. *Adequacy and reliability of source study*

In addition to issue A. above, we have identified deficiencies with the source studies for some endpoints. These are addressed under the corresponding appendices.

Conclusions on the read-across approach

As explained above, you have not established in your registration dossier or in your comments on the draft decision 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. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

You have provided the following information:

i. a study similar to OECD 471 on the Substance and with the following *S. typhimurium* strains TA 97, TA 98, TA 100, TA 1535 and TA 1537, which all gave negative results (Zeiger et al. 1987).
ii. a non-TG study on the Substance and with the following *S. typhimurium* strains T98 and 100, which both gave negative results ([redacted] 1982).
iii. a study non-TG study on the Substance in *S.typhimurium* (strains not specified) with negative result (no author 1985).

We have assessed this information and identified the following issue:

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997) (ECHA Guidance R.7a, Table R.7.7–2). Therefore, the following specifications must be met:

- The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

However, the reported data for the study (i.) you have provided did not include the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The reported data for the study (ii.) did not include 3 of the strains including the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The reported data for the study (iii.) do not include any information on the strains.

The information provided does not cover one of the key investigations required by OECD TG 471.

On this basis, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

In your comments on the draft decision, you agree to perform the requested study and to revise the registration dossier accordingly.

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 study according to OECD TG 201 on the Substance ([redacted], 1999);
ii. a non-guideline study on the Substance (Bringman and Kuhn, 1959);

iii. a study according to DIN 38412, Part 9 on the analogue substance tripropylamine (EC number 203-047-7) ([redacted], 1989);
iv. an adaptation under Annex XI, Section 1.3. ('QSAR'), including predictions from ECOSAR v1.00 (EPIWIN software).

We have assessed this information and identified the following issues:

A. *The studies provided on the Substance and the selected analogue substances are not reliable*

To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH) and the requirements of 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.

  For study ii., you report effect values based on yield (i.e. cell number). You have not reported effect values based on inhibition of growth rate. Further, you have not specified whether the reported effect value corresponds to a NOEC or ECx.

  Therefore, independent of other deficiencies described below, study ii. does not provide an adequate coverage of the key parameters to be measured in the OECD TG 201.

Characterisation of exposure

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

  For study iii., you specify that no analytical verification of exposure concentrations was conducted.

  In the absence of this information, you have not demonstrated that exposure was satisfactorily maintained during the test and that effect values can reliably be expressed based on nominal concentrations.

Reporting of the methodology and results

- the test design is reported (*e.g.*, number of replicates, number of test concentrations and geometric progression used);
- the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);
- the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported;

- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

For study ii., you have not provided any of the information listed above.

For study i., the robust study currently provided in your dossier does not provide any of the information listed above. However, in your comments on the draft decision, you provided an updated robust study summary for that study with the following additional information:

- On the test design: the study was conducted in triplicates. You specify that the test concentrations were [redacted] mg/L (corresponding to a spacing factor of 2.2);
- On the test procedure: the OECD medium was used. The test temperature was 23 ± 2°C. The test species was *Selenastrum capricornutum*. The biomass at the beginning and end of the test was $1x10^4$ and $51x10^4$ cells/mL, respectively;
- On the method for determination of biomass: you specify that "*cell concentrations were measured by a particle counter (CDA-500) after mixing 1.0 mL of the test solution from each test vessel with 9.0 mL of electrolyte for the particle counter (Cell-Pak)*". However, you have not provided evidence of correlation between the measured parameter and dry weight are reported;
- You have provided effects values recalculated using ToxRat Pro v3.2.1. In a table, you provide mean inhibition percentage for each test concentration. The table indicates that these values do not cover the entire exposure period but were calculated over the 24-72h exposure phase. You have not provided the results of algal biomass determined in each flask at least daily during the test period in a tabular form nor an justification as to why the 0-24h exposure phase was excluded from the calculation;
- You have provided some description of the analytical method. With regard performance parameters of the method, you only specified a limit of detection (i.e. LOD) of 0.006 mg/L. You have not provided an estimate of the limit of quantification (i.e. LOQ) not any information on other performance parameters (e.g. precision, linearity, application range, specificity). You provided the results of the analytical monitoring of exposure concentrations at each test concentrations (based on mixed samples from replicate test vessels) at t=0h and t=72h. You used gemotric mean measured concentrations to calculate effect values.

  ECHA acknowledges that the updated robust study summary regarding study i. attached to your comments on the draft addresses some of the missing information identified above.

  However, ECHA notes that some information is still missing on the performance of the method for determination of algal biomass and of the analytical method. Most importantly, the robust study summary still lacks the results of algal biomass determined in each flask at least daily during the test period in a tabular form. ECHA further notes that the effect values recalculated using ToxRat Pro v3.2.1. only cover the exposure phase ranging from 24h to 72h. In the absence of adequate biomass data, ECHA cannot assess to what extent this deviation from the specifications of OECD TG 201 may have impacted the effect values reported in your updated robust study summary.

Therefore, none of these studies meet the requirements of OECD TG 201.

B. *The proposed read-across adaptation is rejected*

For the reasons explained in the Appendix of reasons common to several requests, your read-across adaptation relating to study iii. is rejected. The issues related to the reliability of the source study are covered under issue A. above.

C. *The provided QSAR predictions are not acceptable*

1. The prediction is not adequate due to low reliability

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

- the prediction is consistent with information available for other related endpoint(s).

For study iv., your registration dossier provides the following information:

- you report a predicted EC50 at 1.167 mg/L and ChV at 12.822 mg/L

The predictions for the Substance used as input are not reliable because it predicts an acute effect value (EC50) which is lower to the chronic effect value (ChV).

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

2. Inadequate documentation of the model (QMRF)

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

For study iv., you have not provided a QMRF and, in particular, the information listed above.

In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

3. Lack of or ina*dequate documentation of the prediction (QPRF)*

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

For study iv., you have not provided a QPRF and, in particular, the information listed above.

In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

In your comments on the draft decision, you agree that an independent assessment on the reliability of the studies i., ii.and iii., as currently reported in your dossier, is not possible due to insufficient reporting of the methodology and results. You specify that study ii. and iii. "*will be graded as* "other information"" in the next update of the registration dossier as no further information is available. You also specify that study iv. will be removed from your registration dossier due to low reliability, as specified above. However, on study i., you consider that the additional information provided in an updated robust study summary attached to your comments addresses the issues identified in the draft decision. Therefore, you disagree to conduct the requested study. However, as explained above under issue A., your robust study summary still lacks critical information to conduct an independent assessment of the reliability of this study.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to its adsorptive properties (predicted log Koc of 2.57 at pH 5 to 9) and potential for volatilisation (vapour pressure of 72 hPa at 20°C and a predicted HLC of 8.65 Pa m³/mol). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

3. Ready biodegradability

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

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

i. a reference the Commission Working Group on the Classification and Labelling of dangerous substances which agreed to conclude the Substance as readily biodegradable ([redacted], 1995);
ii. a non-guideline study on the Substance (NITE, 2010);
iii. a study according to OECD TG 301A on the Substance ([redacted], 2001).
iv. a non-guideline study on the Substance ([redacted], 1977);
v. a study according to ISO 7827 on the Substance ([redacted], 1992);
vi. a reference to a study on the Substance listed in a handbook (Verschueren, 1983);
vii. a non-guideline study on the Substance ([redacted], date not specified, report no. [redacted]);
viii. a BOD-test on the Substance (Chuodba et al., 1969);
ix. a reference to a publication on the Substance (Thom and Agg, 1975).
x. an inherent biodegradability test according to OECD TG 302C on the Substance ([redacted], 1992);

xi. a study according to OECD TG 301E on the analogue substance tripropylamine (EC number 203-047-7) ([redacted], 1990);
xii. a study according to OECD TG 301B on the analogue substance tributylamine (EC number 203-058-7) ([redacted], 2010);

We have assessed this information and identified the following issue:

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, 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.

To fulfil the information requirement, normally a study performed according to OECD TG 301 or 310 must be provided. These test guidelines require the study to investigate the following key parameter:

- the ultimate aerobic biodegradation (as measured by parameters such as DOC removal, CO_2 production and oxygen uptake) of the test material under low inoculum concentration is measured at sufficiently frequent intervals to allow the identification of the beginning and end of biodegradation.

Ready biodegradability studies are conducted under stringent conditions and positive results in such studies are indicative of rapid and ultimate degradation in most environments (ECHA Guidance R.7.9.1.1.). For substances that fail the pass level for the ready biodegradability, results from other screening tests (enhanced ready tests or tests on inherent biodegradation) may be used for the determination of persistence in vPvB/PBT assessment but are not to be used for Classification and Labelling and quantitative exposure and risk assessment (ECHA Guidance R.7.9.4.1.). This is because the optimised conditions in inherent biodegradability tests stimulate adaptation of the micro-organisms thus increasing the biodegradation potential, compared to natural environments.

Based on the above, we have assessed whether the sources of information i - xii listed above provide information on the key parameters investigated by the study normally required, i.e. a OECD TG 301 or 310 study.

Source of information i. corresponds to an opinion from the European Commission Working Group on the Classification and Labelling of Dangerous Substances. Source of information ix.

is limited to a statement that the Substance should be degradable by biological sewage treatment. Both sources of information do not provide any information normally investigated by a study performed according to OECD TG 301 or 310.

Source of information x. corresponds to an inherent biodegradability test conducted at high inoculum concentration (100 mg/L). For source of information ii. (study with no test guideline specified), you report that the initial inoculum concentration was high (i.e. 100 mg/L) and the study is therefore concluded to be similar to an inherent biodegradability test. As explained above, such information do not inform on rapid and ultimate degradation in most environments. As a consequence, these studies do not provide the information normally investigated by a study performed according to OECD TG 301 or 310.

The sources of information iii. to viii. and xi. may provide relevant information on ready biodegradability.

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

A. *Inadequate information is provided on the identity of the test materials used in the studies on the Substance (sources of information iii. to viii.)*

   To provide reliable information, the test material in a study must be representative for the Substance (Article 10 and Recital 19 of REACH; ECHA Guidance R.4.1).

   For studies ii. to viii. , you have identified the test material as "*N,N-diethylethanamine / 121-44-8 / 204-469-4*". without further information, including composition.

   In the absence of composition information on the test material, the identity of the test material and its impurities cannot be assessed, and you have not demonstrated that the test material is representative for the Substance. As a result, these source of information are concluded to have a low weight in support of your adaptation.

B. *Critical methodological and reporting deficiencies for sources of information iii. to vi.*

   For a study according to OECD TG 301, the following requirements must be met to ensure the reliability of the results:

   Applicability domain
   - The test material falls into the applicability domain of the selected test method. In this regard, OECD TG 301 specifies that:

     1) The OECD 301 A is not applicable to adsorbing test materials unless appropriate adsorption controls are included in the test design;
     2) The OECD 301 A is/are not applicable to volatile substances. Moderately volatile test materials may still be tested using OECD TG 301A if:
        - there is sufficient gas space in the test vessels, and
        - an abiotic control is included to estimate any physical loss;

   Sources of information iii. and v. correspond to studies conducted according to ISO 7827 (which you state is similar to OECD TG 301A). The Substance is ionised at environmentally relevant pH and you report a predicted log Koc of 2.57 at pH 5 to 9 based on the method from [redacted] (2008). Furthermore, in the publication by [redacted] (1991), cited in [redacted] (2008) as a source for the training set of the model, an experimental log Koc (sediment) of

2.83 is reported for the Substance. This information indicates that the Substance has significant adsorption potential. Then, there is currently no fully reliable estimate of the Henry's Law constant (HLC) for the Substance. However, you report a vapour pressure for the Substance at 72 hPa at 20°C and a predicted HLC of 8.65 Pa m^3/mol using SRC HENRYWIN v3.10. This indicates that the Substance may show significant volatilisation from the test system. For the source of information iii., you state that an abiotic control was included without any further information. For the source of information v. you have not specified if an abiotic control was included.

The intrinsic properties of the Substance indicate it has significant adsorption and volatilisation potential. As, you have not provided adequate information on abiotic control for studies iii. and v., you have not demonstrated that the test method used to conduct these studies provides a reliable basis to estimate the mineralisation potential for the Substance.

Technical specifications impacting the sensitivity/reliability of the test

- The inoculum is not be pre-adapted to the test material and must originate from a treatment plant or laboratory-scale unit receiving predominantly domestic sewage;

  For study iv, you describe the inoculum as that "activated sludge, industrial, adapted". Therefore, this inoculum does not correspond to a non-adapted inoculum from a unit receiving predominantly domestic sewage.
  For study iii. and v., you have provided no information on the source of the inoculum and whether or not it was adapted to the test material prior to conducting the test.
  For study vi., you report that the study was conducted with *Aerobacter* as an inoculum. Therefore, such inoculum is not equivalent to a mixed inoculum as expected from a unit receiving predominantly domestic sewage.

  Therefore, for source of information iv. and vi., the inoculum used to conduct these test is not representative of what is normally expected in a ready biodegradability study. For source of information iii. and v., the adequacy of the inoculum cannot be verified.

Reporting of the methodology and results

- The source of the inoculum, its concentration in the test and any pre-conditioning treatment are reported;
- The test temperature is reported;
- The methods of preparation of test solutions/suspensions is reported, including the test material concentration;
- The results of measurements at each sampling point in each replicate is reported in a tabular form.

  For study iii., iv. and vi., you have not reported any of the information listed above. For study v., you have only reported the test material concentration.

  In the absence of this information, the reporting of these studies lacks essential elements to assess their reliability.

As a results of the deficiencies identified above, there a critical methodological and reporting deficiencies that severely affect the reliability of source of information iii. to

vi. As a result, these source of information are concluded to have a low weight in support of your adaptation.

C. *The reported BOD5/COD tests on the Substance (sources of information vii. and viii.) are not reliable and does not support the conclusion on ready biodegradability*

ECHA Guidance R.7.9.5.1. specifies that information on the 5-day biochemical oxygen demand (BOD5) can be used for classification purposes when no other measured degradability data are available. Adequate reporting must be provided to allow an independent assessment of such studies (Article 10(a) to REACH).

Studies vii. and viii. correspond to BOD test on a test material identified as the Substance. For these studies you have provided no other information than the BOD/COD at the end of the test. The reported value indicates low biodegradation potential.

In the absence of adequate reporting, it is not possible to assess the reliability of sources of information vii. and viii. Furthermore, the reported results contradict your conclusion that the Substance is not be regarded as readily biodegradable. As a result, these source of information are concluded to have a low weight in support of your adaptation.

D. *The proposed read-across using information on the analogue substances tripropylamine and tributylamine is rejected (sources of information xi. and xii).*

For the reasons explained in the Appendix of reasons common to several requests, your read-across adaptation regarding source sof information xi. and xii. is rejected.

E. *Inconsistency of the results provided by sources of information xi. and xii.*

In addition, the study on tripropylamine (study xi.) indicates a negative ready biodegradability result (0-10% biodegradation after 28 days) while the study on tributylamine (study xii.) indicates a positive result. Therefore, these studies do no support consistent results among the selected source substances. As a result, the sources of information xi. and xii. are concluded to have a low weight in support of your adaptation.

As a conclusion, sources of information iii. to viii. and xi. to xii. provide information on ready biodegradability but the reliability of these sources of information is severely affected by the issues identified above.

Accordingly, 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 301 or 310 study. Therefore, your adaptation is rejected, and the information requirements is not fulfilled.

In your comments on the draft decision, you specify that you agree to conduct new testing with the Substance. You specify that a study according to OECD TG 301F is currently ongoing.

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

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

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

We understand that you have adapted this information requirement under Annex VIII, Section 8.4.2., Column 2. In support of your adaptation, you provided the following information:

i. a non-guideline *in vivo* chromosome aberration assay via inhalation with the Substance in rats ([redacted] 1971)

We have assessed this information and identified the following issue:

Under Section 8.4.2., Column 2, first indent, Annex VIII to REACH, the study may be omitted "if *adequate data from an in vivo cytogenicity test are available*". ECHA Guidance (R.7a, R.7.7.6.3) clarifies that the *in vivo* study must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474 or 475, respectively (ECHA Guidance R.7a, Table R.7.7–3).

For the data from an *in vivo* cytogenicity test to be considered adequate, the *in vivo* study you submitted has to meet the requirements of OECD TG 475, and the specifications/conditions of this test guideline include:

- The study must include a minimum of three doses/groups of treated animals, as well as a negative control group and a positive control group.
- Each group must have a minimum of 5 analysable animals (the test can be performed in either sex).
- The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow.
- The mitotic index must be determined as a measure of cytotoxicity in at least 1000 cells per animal for all treated animals (including positive controls), untreated or vehicle/solvent negative control animals.
- At least 200 metaphases must be analysed for each animal for structural chromosomal aberrations including and excluding gaps.
- The mitotic index and the mean number of cells with aberrations per group must be reported for each group of animals.

However, the reported data for the *in vivo* study (i.) you submitted did not include:

- the appropriate number of doses as only 2 dose levels were used
- data on how many animals per group were used
- a maximum studied dose that is a MTD or induces toxicity as toxicity is not specified
- the analysis of the adequate number of cells
- a negative control with a response inside the historical control range of the laboratory as you did not provide any information on historical control.
- a positive control group (or scoring control).
- data on the mitotic index and the mean number of cells with aberrations per group for each group of animals.

The information provided does not cover specifications/conditions required by OECD TG 475.

Therefore, the requirements of Section 8.4.2., Column 2, first indent, Annex VIII to REACH are not met.

On this basis, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

In your comments on the draft decision, you agree to perform the requested study and to revise the registration dossier accordingly.

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

i. Triggering of the study

Your dossier contains data for an *in vitro* gene mutation study in bacteria, and an adaptation for an in vitro cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in Appendices A.1. and B.1.

The result of the requests for information in Appendices A.1. and B.1. will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

ii. Assessment of information provided

Your dossier does not contain any study or adaptation in accordance with column 2 of Annex VIII, Section 8.4.3. or with the general rules of Annex XI for this standard information requirement.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

Study design

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

In your comments on the draft decision, you agree to perform the requested study, if negative results are obtained in the studies requested under Appendix A.1. and B.1., and to revise the registration dossier accordingly.

3. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study

Screening for reproductive/developmental toxicity is an information requirement under Annex VIII to REACH (Section 8.7.1.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

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

i. a study according to OECD TG 422 via oral route in rats (Sprague-Dawley) with an analogue substance, Trimethylamine (EC 200-875-0) (Takashima et al. 2001).

We have assessed this information and identified the following issue:

As explained in the Appendix on Reasons common to several requests you read-across adaptation under Annex XI, Section 1.5. is rejected.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you disagree to submit the requested justification. You indicate your intention to consolidate your read-across and "*to perform in the first place a Screening for reproductive/developmental toxicity study (OECD TG 421 or OECD 422) with the registered substance*". Note that compliant information must in any case be submitted for this information requirement by the deadline set out in the present decision.

The present decision requests the registrants concerned to generate and submit an extended one-generation reproductive toxicity study (EOGRTS) (see Section D.2). Once an EOGRTS is available, according to Column 2 of Annex VIII, Section 8.7.1. and in order to prevent unnecessary animal testing, a screening for reproductive/developmental toxicity does not therefore need to be conducted. While you still have to comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation based on Column 2 of that provision.

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

1. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

You have 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 key studies for this endpoint:

i. A study according to OECD TG 414 via oral route in rats (Sprague-Dawley) with an analogue substance, Tributylamine (EC 203-058-7) ([redacted] 1991).

ii. A study according to OECD TG 422 via oral route in rats (Sprague-Dawley) with an analogue substance, Trimethylamine (EC 200-875-0) (Takashima et al. 2001).

We have assessed this information and identified the following issue(s):

A. As explained in the Appendix on Reasons common to several requests you read-across adaptation under Annex XI, Section 1.5. is rejected.

B. 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 414. Therefore, the following specifications must be met:

- External, skeletal and visceral malformations and variations have to be investigated

However, the study (ii.) does not inform on skeletal and visceral malformations and variations. Therefore, the study (ii.) does not provide an adequate and reliable coverage of the key parameters of the OECD TG 414.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you disagree to conduct an OECD TG 414 study in a first species. Instead you state your intention to follow a tiered testing approach "*in order to be able to evaluate potential read-across possibilities*". Note that compliant information must in any case be submitted for this information requirement by the deadline set out in the present decision.

Study design

The Substance is a corrosive liquid and it has harmonized 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 on the draft decision you also state "*If the results of the above mentioned bridging study show that read-across is not an option, the Registrants agree to perform an OECD 414 in rodents to fulfill the information requirements.*"

However, you disagree to use a neutralised form of the Substance due to following reasons:

- *"[…] a realistic toxicity profile of the substance can only be reflected when the registered substance itself is used in toxicological studies."*
- *"The neutralised form of the substance had not been subject to registration by the Registrants. Triethylamine hydrochloride is a separate registration and this substance is only registered as an intermediate."*
- *"Furthermore, the registered substance triethylamine is not marketed in the neutralised form. Triethylamine is only used in industrial and professional settings and is never neutralised in these applications."*
- *"These facts also imply that any user would never (voluntarily or involuntarily) touch, inhale or swallow the corrosive substance in amounts that could be reached by using the neutralized substance for testing. Such quantities just can not be reached under realistic conditions."*
- *"[…] it is nowhere indicated in Regulation EC No 1907/2006 (REACH) and the respective Guidance documents that new studies need to be performed with a neutralised form of substances."*
- *"[…] the neutralised form (i.e. Triethylamine hydrochloride) would be a read-across source substance for the registered substance in accordance with REACH Annex XI point 1.5."*
- *"[…] if the generation of new study data is considered necessary, the Registrants want to assess their registered substance with its substance-specific characteristics as it is (Triethylamine) and not a different substance (Triethylamine hydrochloride)."*

In addition, you provided the following statement "*If – despite of the arguments presented by the Registrants above, that the representative compound is the one put on the market and should therefore be the one to be tested - it is considered that the requested OECD TG 414 (first species), […] should be conducted with a neutralised form of the registered substance, the Registrants wish an additional time period of 6 months to search for suppliers, to evaluate analytical methods and to organize testing.*"

According to ECHA guidance R.7.6.2.3.2. "*[…] in vivo testing with corrosive substances at concentration/dose levels causing corrosivity must be avoided (see REACH Annex VII-X preamble). The vehicle should be chosen to minimise gastrointestinal irritation. […] In certain cases, testing of neutral salts of alkaline or acidic substances may be appropriate and allows investigation of intrinsic properties at adequate dose levels*".

Therefore, ECHA considers that investigating intrinsic properties related to reproductive toxicity at adequate dose levels would only be possible by testing a neutralised form of the Substance, even though it is not marketed as such. Otherwise, the already known corrosivity of the Substance may not allow investigation in relation to systemic toxicity. Also, the corrosivity/irritation of the Substance may affect the behaviour of the animals confounding the interpretation of reproductive toxicity-related parameters. In addition, local effects might induce unnecessary stress to the animals with consequences to the outcome of the study.

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 10.75 at 25 °C. Therefore, the Substance will exist as a protonated form (NH_2^+) under physiological conditions as will the neutralised form of the Substance. Thus, read-across for systemic effects between the Substance and its neutralised form would be plausible as such.

Therefore, a PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species by oral route (ECHA Guidance R.7.6.2.3.2). The test sample

must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutralised salt of the Substance. Your request for a deadline extension is addressed under Appendix F (Procedure).

If the PNDT study submitted in response of this decision does not deliver reliable results because of gastrointestinal irritation, further testing may be considered necessary in order to investigate the intrinsic properties at adequate dose levels. Therefore, if the competent Member State authorities consider that a concern must be clarified in that respect, they may decide to require further information under Substance Evaluation.

2. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided the following information:

i. a study according to OECD TG 211 on the Substance ([redacted], 1999);
ii. a study according to Method 1002.0 ([redacted], 1989) on the Substance ([redacted] and also reported as [redacted] 1995 in your dossier);

We have assessed this information and identified the following issues:

A. Inadequate information is provided on the identity of the test materials used in study i.

To comply with this information requirement, the test material in a study must be representative for the Substance (Article 10 and Recital 19 of REACH; ECHA Guidance R.4.1).

For studies i., you have identified the test material as "*N,N-diethylethanamine / 121-44-8 / 204-469-4*". without further information, including composition.

In the absence of composition information on the test material, the identity of the test material and its impurities cannot be assessed, and you have not demonstrated that the test material is representative for the Substance. As a result, this study is rejected.

In your comments on the draft decision, you provided an updated robust study as an attachment. On the composition / purity of the test material you specified "*analytical grade*". However, you have not provided an estimate of the purity of the test material nor information on the presence of impurities. Furthermore, the information you provided is not supported by any documentary evidence, such as for instance an analytical certificate. Therefore, the issue identified above remains.

B. The studies i. and ii. do not meet the requirements of OECD TG 211

To fulfil the information requirement, a study must comply with the OECD TG 211 [and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Reporting of the methodology and results

- the test design is reported (*e.g.* semi-static or flow-through, number of replicates, number of parents per replicate);
- the test procedure is reported (*e.g.* loading in number of *Daphnia* per litre, test medium composition);

- detailed information on feeding, including amount (in mgC/daphnia/day) and schedule is reported;
- the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels are reported;
- water quality monitoring within the test vessels (*i.e.* pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) is reported;
- the full record of the daily production of living offspring during the test by each parent animal or, if appropriate, in each replicate is provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is reported;
- the coefficient of variation for control reproductive output is reported.

For study i. you have not provided any of the information listed above. For study ii, you have not provided adequate reporting of the study results including among others, detailed information on feeding, the nature and concentration of the vehicle used to prepare the test solutions, the results of all analyses to determine the concentration of the test substance in the test vessels, the full record of the daily production of living offspring during the test, the number of deaths among the parent animals, the coefficient of variation for control reproductive output. As a consequence, ECHA cannot make an independent assessment of the reliability of these studies.

In your comments on the draft decision, you provided an updated robust study summary for study i. with the following additional information:

- On the test design: you specify that the test was conducted under semi-static conditions (daily renewal). You specify that 10 replicates were used for the control and each test concentrations. One parental animal was held individually in each replicate;
- On the test procedure: you provided information allowing to determine loading. You specify that the test medium was Elendt M4 as specified in OECD TG 211;
- You specify that parental animal were fed daily at 0.15 mgC per Daphnia per day;
- You specify that nominal concentrations were [redacted] mg/L (corresponding to a spacing factor of 2.2). You provided the results of the analytical monitoring of exposure concentrations at each test concentrations once a week. You used time-weighted average of measured concentrations to calculate effect values;
- You provide information on water quality parameters, including temperature, pH, dissolved oxygen and hardness measured for three renewal periods. You did not provide information on TOC and/or DOC but considering that a mineral medium was used and that the test was conducted with daily renewal, this deviation is considered secondary;
- You provide reporting of total offspring production per parental animal at the end of the test, information on death of parental animals and on mean cumulative offspring production determined daily and information on time to first brood. The information shows that 30% parental mortality was observed at the highest nominal concentration of 50 mg/L.

ECHA acknowledges that the updated robust study summary attached to your comments on the draft addresses most of the missing information identified above. However, this information indicates that dose-dependent mortality of parental animals was observed. The OECD TG 211 states that if parental mortality follows a concentration-response pattern, the parental mortality should be assigned as an effect of the test substance and the replicates should not be excluded from the analysis.

Therefore, the effects values as currently presented in the updated robust study summary is erroneous. Furthermore, as the information is currently not available in your registration dossier, the issue remains.

Therefore, none of these studies meet the requirements of OECD TG 211.

In your comments on the draft decision, you agree that an independent assessment on the reliability of the studies i. and ii. is not possible due to insufficient reporting of the methodology and results. You specify that study ii. "*will be graded as* "other information"" in the next update of the registration dossier. However, on study i., you consider that the additional information provided in an updated robust study summary attached to your comments addresses the issues identified in the draft decision. Therefore, you disagree to conduct the requested study. However, as explained under issue A., you have not provided adequate information to confirm the identity of the test material used in that study. In addition, as explained under issue B., the interpretation of the study results is currently erroneous.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.2.

3. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided the following information:

i. a non-guideline 60d study on *Oncorhynchus mykiss* with the Substance (van Leeuwen *et al.* 1990);
ii. a study claimed similar to OECD TG 210 on Danio rerio with the Substance (van Leeuwen *et al.* 1990).

We have assessed this information and identified the following issues:

A. Inadequate information is provided on the identity of the test materials used in study i. and ii.

To comply with this information requirement, the test material in a study must be representative for the Substance (Article 10 and Recital 19 of REACH; ECHA Guidance R.4.1).

For studies i. and ii., you have identified the test material as "*N,N-diethylethanamine / 121-44-8 / 204-469-4*". without further information, including composition.

In the absence of composition information on the test material, the identity of the test material and its impurities cannot be assessed, and you have not demonstrated that the test material is representative for the Substance. As a result, this study is rejected.

B. The studies i. and ii. do not meet the specifications of OECD TG 210

To fulfil the information requirement, a study must comply with the OECD TG 210 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria

- the analytical measure of the test concentrations is conducted.

  However, for studies i. and. ii., no analytical verification of exposure concentrations was conducted. Therefore, these studies do not meet the validity criteria of OECD TG 210.

- overall survival of fertilised eggs and post-hatch success in the controls and, where relevant, in the solvent controls is ≥ to the limits specified for the test species.

  However, for studies i. and. ii., this information is not reported and therefore this validity criteria cannot be verified.

Technical specifications impacting the sensitivity/reliability of the test

- at least 80 eggs, divided equally between at least four replicate test chambers, are used per concentration;

  For study i., 100 eggs were used per concentrations. However, these were only divided in duplicates. For study ii., only 60 eggs were used and these were not divided in replicates. These deficiencies in both study may have impacted the sensitivity of the tests.

- For a test conducted on *Danio rerio*, the duration of the test is at least 30 days.

  For study ii., you report that the test duration was only 7 days. This indicates that the test has likely lower sensitivity than an OECD TG 210 study.

- five concentrations are tested (or a justification must be provided if fewer than five concentrations are used);

  For study i., the number of test concentrations is not specified.

Reporting of the methodology and results

- data on mortality at each stage (embryo, larval and juvenile) measured daily and cumulative mortality are reported;
- days to hatch, numbers of larvae hatched each day, and end of hatching are reported;
- the number of healthy fish at end of test is reported;
- data for length (specify either standard or total) and weight of surviving animals at the end of the test are reported;
- the incidence, description and number of morphological abnormalities, if any, are reported;

  For study i. and ii. the above information is not reported. In the absence of this information, an independent assessment of the results of these studies is not possible.

Therefore, none of these studies meet the requirements of OECD TG 210.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you agree that studies i., ii. do not provide adequate information on the identity of the test materials used and do not meet the specifications of OECD TG 210. Therefore, you agree to conduct the requested study.

Study design

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

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.2.

Appendix D: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X to REACH (Section 8.7.2.).

You have provided a PNDT study only in one species (See Appendix C.1.)

As you have not provided any information on a second species or any adaptation under column 2 of Section 8.7.2 or under Annex XI, the information requirement is not fulfilled.

In your comments on the draft decision, you disagree to conduct an OECD TG 414 study in a second species. Instead you indicate your intention to follow a tiered testing approach to evaluate potential read-across possibilities and conduct an OECD 421/422 bridging study as described under C.1. You also state "*If the evaluation of potential read-across after conduct of an OECD 421/422 bridging study with the registered substance and consideration of the currently generated and the already available OECD 414 studies in rabbits performed with structural analogues, revealed that read-across is an option, the Registrants intend to perform read-across to address the endpoint Prenatal developmental toxicity (second species).*"

Due to the reasons explained in Appendix on Reasons common to several requests, the information provided in your comments does not change the assessment and your read-across adaptation is rejected.

You also indicated in your comments on the draft decision "*If the results of the above mentioned bridging study show that read-across is not an option, the Registrants agree to perform an OECD 414 in rabbits to fulfill the information requirements.*" In either case, note that compliant information must in any case be submitted for this information requirement by the deadline set out in the present decision.

However, you disagree to use a neutralised form of the Substance due to following reasons:

- "*[…] a realistic toxicity profile of the registered substance can only be reflected when the substance itself is used in toxicological studies.*"
- "*[…] if the generation of new study data is considered necessary-the Registrants want to assess their registered substance with its substance-specific characteristics as it is (Triethylamine) and not a different substance (Triethylamine hydrochloride).*"

In addition you provided the following statement "*If – despite of the arguments presented by the Registrants above, that the representative compound is the one put on the market and should therefore be the one to be tested - it is considered that the requested […] OECD TG 414 (second species), […] should be conducted with a neutralised form of the registered substance, the Registrants wish an additional time period of 6 months to search for suppliers, to evaluate analytical methods and to organize testing.*".

For the reasons explained under Appendix C.1., ECHA considers that investigating intrinsic properties related to reproductive toxicity at adequate dose levels would only be possible by testing a neutralised form of the Substance

Study design

A PNDT study according to the OECD TG 414 study must be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request C.1. in this decision). The study must be performed by oral route (ECHA Guidance R.7.6.2.3.2). The test sample must be chosen to minimise gastrointestinal irritation and to

allow investigation of intrinsic properties at adequate dose levels due to the reasons explained under the request C.1. This could be achieved by testing a neutralised salt of the Substance. Your request for a deadline extension is addressed under Appendix F (Procedure).

If the PNDT study submitted in response of this decision does not deliver reliable results because of gastrointestinal irritation, further testing may be considered necessary in order to investigate the intrinsic properties at adequate dose levels. Therefore, if the competent Member State authorities consider that a concern must be clarified in that respect, they may decide to require further information under Substance Evaluation.

2. Extended one-generation reproductive toxicity study

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X to REACH (Section 8.7.3.). Furthermore, Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

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 key study for this endpoint:

i. A study according to OECD TG 422 via oral route in rats with an analogue substance Trimethylamine (EC No 200-875-0) ([redacted] 2003)

In addition, you have provided the following study records as other supporting information:

ii. A non-TG study on fertility via oral route in female rabbits with the Substance (Chang 1964).
iii. A study similar to OECD 416 via oral route in rats with the Substance ([redacted] 1965).
iv. A non-TG two-generation study via oral route in rats with the Substance ([redacted] 1965/[redacted] 1989).

You have also included a statement in which you refer to a chronic inhalation toxicity study on the Substance, a screening study (OECD TG 422, study i.) on an analogue substance (Trimethylamine, EC 200-875-0) and a PNDT study (OECD TG 414) on an analogue substance (Tributylamine, EC 203-058-7). You state that no effects were observed in reproductive organs in the chronic study. In addition, you consider that the data on the analogue substances indicate a low concern for reproductive toxicity. Therefore, you conclude that further testing for reproductive toxicity is not needed. However, you have not specified in relation to which adaptation under the REACH Regulation you provided this statement. As far as ECHA cannot relate this statement to any possible adaptation, it must be considered irrelevant.

We have assessed this information and identified the following issues:

A. As explained in the Appendix on Reasons common to several requests you read-across adaptation under Annex XI, Section 1.5. is rejected.

B. 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 443. Therefore, the following specifications must be met

- at least 20 pregnant females per dose group in parental P0 generation

- dosing of the substance should cover full spermatogenesis and folliculogenesis, mating, gestation, lactation, and exposure of the F1 generation up to the adulthood

However, the study (i.) you provided does not cover all relevant life stages required in OECD TG 443, as the extensive postnatal investigations of the fully exposed F1 generation up to the adulthood are not included. Furthermore, the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group as required in OECD TG 443. Therefore, the study (i.) does not conform with the key parameters of the OECD TG 443.

C. To be considered compliant, the study has to meet the requirements of OECD TG 443 as specified in REACH. The following criteria of this test guideline include
   - testing of at least three dose levels and a concurrent control
   - each test and control group must contain a sufficient number of mating pairs to yield at least 20 pregnant females per dose group.
   - dosing of the substance to sexually-mature males and females with examinations on both sexes
   - dosing of the Substance should cover full spermatogenesis and folliculogenesis, mating, gestation, lactation, and exposure of the F1 generation up to the adulthood
   - examination of relevant life stages
   - examination of key parameters for sexual function and fertility
   - examination of key parameters for pre/peri/postnatal developmental toxicity
   - examination of key parameters for endocrine modes of action
   - examination of key parameters for systemic toxicity

   However, in the study (ii.), artificially inseminated female rabbits were exposed only for 1 to 3 days. You have not provided any information how many doses were used. In addition, only the development of ova into normal blastocyst was examined. Therefore, the study (ii.) does not fulfil any of the criteria specified in the OECD TG 443.

   In the study (iii.), only 2 dose levels and 10 animals/sex/dose were used. Furthermore, you have not provided any information on the examinations and results on sexual function and fertility, developmental toxicity and endocrine modes of action. Examination of systemic toxicity excluded clinical biochemistry and haematology, organ weights and histopathology in P and F1 animals. Therefore, the study (iii.) does not fulfil the criteria set in OECD TG 443.

   For the study (iv.) you only conclude "*A two generation reproduction study in rats administered up 200 ppm in the drinking water did not cause toxic or reproductive effects.*" without providing any further information on the test method, examinations performed and results. Therefore, the study (iv.) does not fulfil the requirements of OECD TG 443.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you agree that "*limited information on sexual function and fertility has been provided by each piece of evidence submitted for this endpoint.*". However, you disagree to conduct an OECD TG 443 study with a neutralised form of the Substance. Instead you proposed to follow a tiered testing approach to evaluate potential read-across possibilities and conduct an OECD 421/422 bridging study as described under

C.1. Due to the reasons explained in Appendix on Reasons common to several requests, your read-across adaptation is rejected.

You also indicated in your comments on the draft decision "*If the results of the above mentioned bridging study show that read-across is not an option, the OECD 421/422 study can still serve as a range finder for the requested OECD 443 study in rodents, which – in this case - the Registrants agree to perform to fulfil the information requirements.*" In any case, note that compliant information must in any case be submitted for this information requirement by the deadline set out in the present decision.

However, you disagree to use a neutralised form of the Substance due to following reasons:

- "*[…] a realistic toxicity profile of the registered substance can only be reflected when the substance itself is used in toxicological studies.*"
- "*[…] if the generation of new study data is considered necessary - the Registrants want to assess their registered substance with its substance-specific characteristics as it is (Triethylamine) and not a different substance (Triethylamine hydrochloride).*"

In addition, you provided the following statement "*If – despite of the arguments presented by the Registrants above, that the representative compound is the one put on the market and should therefore be the one to be tested - it is considered that the requested […] and the OECD 443 should be conducted with a neutralised form of the registered substance, the Registrants wish an additional time period of 6 months to search for suppliers, to evaluate analytical methods and to organize testing.*".

For the reasons explained under Appendix C.1., ECHA considers that only testing of a neutralised form of the Substance will enable to investigate intrinsic properties related to reproductive toxicity by allowing to use adequate dose level.

Study design:

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration (ECHA Guidance R.7.6.).

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Species and route selection

The study must be performed in rats by oral route (ECHA Guidance R.7.6.2.3.2.). The test sample must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels due to the reasons explained under the request C.1. This could be achieved by testing a neutralised salt of the Substance. Your request for a deadline extension is addressed under Appendix F (Procedure).

If the EOGRTS submitted in response of this decision does not deliver reliable results because of gastrointestinal irritation, further testing may be considered necessary in order to investigate the intrinsic properties at adequate dose levels. Therefore, if the competent Member State authorities consider that a concern must be clarified in that respect, they may decide to require further information under Substance Evaluation.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Annex X, Section 8.7.3., Column 2. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance R.7.6.

Appendix E: 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

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

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity,
   - as explained under Appendix C.1., D.1 and D.2. the test sample must be chosen to minimise gastrointestinal irritation andto allow the investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutralised salt of the Substance. 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 and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

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

Appendix F: Procedure

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

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

The compliance check was initiated on 18 November 2020.

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

ECHA took into account your comments and amended the requests for PNDT and EOGRT studies by giving further advice on the test material, but did not amend the other requests.

In your comments on the draft decision, you requested an extension of the deadline from 30 to 36 months, if the requested PNDT studies (1st and 2nd species) according to OECD TG 414 and EOGRTS according to OECD TG 443 should be conducted with a neutralised form of the Substance. You consider that an additional time period of 6 months is needed to "*[…] search for suppliers, to evaluate analytical methods and to organize testing.*"

ECHA acknowledges that additional time is needed either to find a supplier for the neutralised form of the Substance or to evaluate options to manufacture it. On this basis, ECHA has agreed with the request and extended the deadline to 36 months.

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

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

Appendix G: 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)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[9]

[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] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[9] 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 H: Addressees of this decision and their corresponding information requirements

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

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