~~Confidential~~

Helsinki, 09 February 2022

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

Date of submission of the dossier subject to this decision
28/08/2015

Registered substance subject to this decision ("the Substance")
Substance name: Tripropylamine
EC number: 203-047-7
CAS number: 102-69-2

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 ***14 November 2024***.

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

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

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

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

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats. Due to reasons explained in Appendix B.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.

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit). Due to reasons explained in Appendix C.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.

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

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

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to IX of REACH", respectively.

Information required depends on your tonnage band

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 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.

(i) Assessment of the Grouping of substances and 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:

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

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.

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.

You read-across between the structurally similar substances,

- Trimethylamine (TMA), EC No. 200-875-0 (CAS No. 75-50-3),
- Triethylamine (TEA), EC No. 204-469-4 (CAS No. 121-44-8) and
- Tributylamine (TBA), EC No. 203-058-7 (CAS No. 102-82-9)

as source substances and the Substance as target substance.

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

- *"The hypothesis for the analogue approach is based on this common structure which determines the similarity in a lot of physico-chemical and toxicity properties (OECD SIDS tertiary amines, 2012)*
- *"Since the nitrogen in an amine bears an unshared pair of electrons, and since the tendency to share these electrons underlies the chemical behaviour of amines as a group, the tertiary functional amine group was considered as main/basic parameter allowing to group substances, suitable for read across purpose within an analogue approach."*
- *"From a toxicological point of view, the analogue approach justification regarding the series of tertiary amines considered above is mostly based on a common metabolism pathway".*

[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 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 substances.

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

A. Relevance of the supporting information

According to the ECHA Guidance (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 substances have similar properties for the endpoints under consideration in the read-across approach, you refer to their acute toxicity, skin irritation, eye irritation, skin sensitisation and mutagenicity properties.

Whilst this data set suggests that the substances may have similar properties for acute toxicity, skin and eye irritation, skin sensitisation and mutagenicity, these studies do not inform on the repeated dose toxicity, and reproductive and developmental toxicity of the target and source substances. Accordingly, these information are not considered as relevant to support prediction of all the endpoints under consideration, including sub-chronic toxicity study (90-d), screening for reproductive/developmental toxicity and pre-natal developmental toxicity study.

B. Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*" (ECHA Guidance R.6.2.2.1.f). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substances.

Supporting information must include bridging studies to compare properties of the Substance and source substances.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substances is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substances.

In the registration dossier, you have not provided any repeated dose toxicity, reproductive and developmental toxicity studies performed with the Substance that could be used as a bridging information in order to compare the properties of the Substance with the proposed analogues for the endpoints under consideration.

In your read-across justification, you also refer to the OECD SIDS on 5 tertiary amines (2012) and provided also the document in your registration dossier. However, the Substance was not included in the OECD SIDS assessment.

Therefore, the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and of the source substances to support your read-across hypothesis.

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

In your comments on the draft decision, you indicate your intention to provide supporting information. While ECHA acknowledges your intention, we also note that currently you have not provided any new information in your comments or in the registration dossier to further support you read-across adaptation.

C. *Adequacy and reliability of source study*

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

B. Conclusions on the read-across approach

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

2. Assessment of your QSAR adaptations under Annex XI, Section 1.3.

You seek to adapt the following standard information requirements based on QSAR predictions in accordance with Annex XI, Section 1.3:

- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex VIII, Section 9.1.3, column 2)

We have assessed this information and identified the following issues which are common to all adaptations submitted for the endpoints listed above:

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

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

You have not provided an assessment of the applicability domain of the selected models. However, for all models used to cover the information requirements listed above you state that the predications are "*based on the neutral organics SAR (Baseline Toxicity)*".

The Substance has the following properties related to the estimation of applicability domain: the Substance corresponds to an aliphatic amine.

The Substance is an aliphatic amine and you have not justified why you have not used

the corresponding model available in ECOSAR. Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model.

B. *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 unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

You have not provided information about the model, an 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.

C. 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 model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

You have not provided information about the prediction, an 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.

On this basis your adaptations are rejected.

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 provided the following information:

i. a study according to DIN 38412, Part 9 on the Substance ([redacted] 1989);
ii. an adaptation under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation you provided predictions from ECOSAR v1.00 (EPIWIN software).

We have assessed this information and identified the following issues:

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

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 i. above, you specify that no analytical monitoring of exposure concentration was conducted. The substance is ionisable and therefore potentially strongly adsorbing. As you have not provided an analytical verification of exposure you have not demonstrated that the results can reliably be based on nominal concentrations.

In your comments on the draft decision, you provide an updated robust study summary for study i. You acknowledge that "*the test concentrations of the substance were not monitored*" but you consider that the study results are still considered to be reliable as "*the test item is well soluble in water it can be assumed, that the nominal concentrations could be achieved initially and a loss of test material due to the adsorptive potential can be expected in the course of the study only. However, an adaption of the test design including water renewal is not feasible for algae. Therefore, the nominal concentrations can be considered as loading rate following the recommendations in OECD 23 if a test substance is not stable*".

ECHA notes that you have not provided any justification as to why the substance should be regarded as unstable and that the OECD GD 23 does not specify that results can be based on loading rate for test substances that are not stable. The OECD GD 23 specifies that for "*tests with chemicals that cannot be quantified by the most sensitive analytical methods at relevant concentrations, the effect concentration can be expressed based on the nominal concentrations or loading rate (for mixtures)*". However, your have not provided any justification as to why conducting an analytical monitoring of exposure concentration for the substance is not feasible. Therefore, you have not justified that such information can be omitted.

Technical specifications impacting the sensitivity/reliability of the test

- 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.

For study i. above, you specify that algal biomass was monitored using a fluorimeter. However, you have not provided any supporting information that the method provide an satisfactory correlation with biomass under the conditions of this test.

In your comments on the draft decision, you provide an updated robust study summary for study i. However, the missing information listed above is not provided.

Reporting of the methodology and results

- the test design is reported (including the number of replicates);
- the test conditions are reported (including the composition of the test medium);
- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;

For study i., you have not provided adequate information on the test design and test conditions, and in particular the information listed above. Furthermore, you have provided information on mean biomass in the control and test concentrations but no information on replicates. In the absence of this information the validity criteria of OECD TG 201 cannot be verified and the interpretation of the results cannot be assessed.

Therefore, study i. does not meet the requirements of OECD TG 201.

In your comments on the draft decision, you provide an updated robust study summary for study i. You specified the following:

a) 4 replicates were used per test concentration and in the control;
b) the composition of the test medium is not provided;
c) biomass data are provided in a tabular form only as an average value in the control and test concentrations.

ECHA acknowledges that the additonal information provided indicates that an adequate number of replicates was used. However, your updated robust study summary still lack key information on the composition of the test medium and adequate reporting of biomass data.

B. Concerning point ii. (ECOSAR v1.00), for the reasons explained in the Appendix of reasons common to several requests, you QSAR adaptation under Annex XI, Section 1.3. is rejected.

In your comments on the draft decision, you agree with ECHA's assessment and specify that you will remove this information from your dossier.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you specify that you disagree with conducting a new study and you intend to submit the updated robust study summary attached to your

comments on the draft decision. However, as explained above this information is still incompliant with the information requirement.

Study design

The Substance is difficult to test as it is ionisbale under environmentally relevant pH and therefore potentially highly adsorptive. OECD TG 210 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 210. 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.

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

1. 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 information:

i. A study according to OECD TG 422 via oral route in rats with an analogue substance Trimethylamine (EC 200-875-0) (Takashima 2003).

Under Annex XI, Section 1.2. a weight of evidence adaptation requires necessarily the submission of "several independent sources of information" that would lead to the conclusion that a substance has or has not a particular dangerous property. As you have only submitted one source of information, this cannot refer to a weight of evidence adaptation.

We have assessed this unique source of information and identified the following issue:

As explained in the Appendix on Reasons common to several requests your 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 agreed that the current registration dossier does not contain sufficient data to cover this endpoint.

Study design

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

In your comments, you disagree to conduct an OECD TG 421 or 422 study with a neutralised form of the Substance but indicate your intention to conduct the study with the Substance due to the 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."*
- *"Tripropylamine hydrochloride aka Tripropylammonium chloride would bea separate registration but has not been registered under REACH."*
- *"Furthermore,the registered substance tripropylamine is not marketed in the neutralized form. Itis only used in industrial and professional settings and is never neutralized 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."

- "*Additionally, 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 neutralized form of substances."*
- "*[…] the neutralized form (i.e. TPA-HCl) 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 (TPA) and not a different substance (TPA-HCl)."*

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 421/421 […] should be conducted with a neutralised form of the registered substance, the Registrants want to point out, that there seems to be no supplier providing tripropylammonium chloride. Therefore, the Registrants wish an additional time period of 12 months to try again to search for suppliers, to evaluate manufacturing options, to establish an analytical method and to organize testing with the neutralized form."*

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 only the testing of a neutralised form of the Substance will enable to investigate intrinsic properties related to reproductive toxicity by allowing to use adequate dose levels. Otherwise, the already known corrosivity of the Substance may not allow investigation of 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 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 10.65. 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 study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 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. This could be achieved by testing a neutralised salt of the Substance. Your request for a deadline extension is addressed under Appendix E (Procedure). If the Screening for reproductive/developmental toxicity 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 testing under Substance Evaluation.

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

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH (Section 8.6.2.).

You have 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 information:

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).
ii. A study according to OECD TG 414 via oral route in rats with an analogue substance Tri-n-butylamine (EC No. 203-058-7) ([redacted], 1991).
iii. A study similar to OECD TG 413 via inhalation route in rats with an analogue substance Triethylamine (EC No. 204-469-4) (Lynch, 1990).
iv. A study, no TG followed, via inhalation route in rats with an analogue substance Triethylamine (EC No. 204-469-4) ([redacted], 1984).
v. A study, no TG followed, via inhalation route in rats with an analogue substance Tributylamine (EC No. 203-058-7) ([redacted], 1970).
vi. A study, no TG followed, via inhalation route, in rats with an analogue substance Trimethylamine (EC No. 200-875-0) (Rotenberg and Mashbits , 1967).
vii. A study similar to OECD TG 412 via inhalation route in rats with an analogue substance Trimethylamine (EC No. 200-875-0) ([redacted], 1983).

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.

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 408 or 413. Therefore, the following specifications must be met:

- testing of at least three dose levels and a concurrent control
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study

The studies (i., ii., iv., v., vii.) you have provided do not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 42 days at maximum. In addition, the studies (iii. and vi.) were conducted with less than three dose levels.

Therefore, the studies (i.-vii.) do not provide an adequate and reliable coverage of the key parameters of the OECD TG 408 or 413.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you disagree to conduct the requested OECD TG 408 study by oral route in rats. Instead you proposed to follow a tiered testing approach "*In order to be able to evaluate potential read-across possibilities, the Registrants intend to conduct an OECD 421/422 with the registered substance as a bridging study […] If read-across has been found to be an option, the Registrants intend to perform read across to address the endpoint Sub-chronic toxicity.*"

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 408 study and the Registrants agree in this case to perform an OECD 408 in rats to fulfil the information requirements.*"

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 liquid of low vapour pressure (4.3 hPa at 20°C) and no uses with spraying applications are reported that could potentially lead to aerosols of inhalable size.

In your comments on the draft decision, you disagree to use a neutralised form of the Substance as you consider that "*[…] a realistic toxicity profile of the registered substance can only be reflected when the substance itself is used in toxicological studies.*". ECHA agrees that in the investigation of repeated dose toxicity, the use of a neutralised form of the Substance could partially hamper the investigation of potential local effects. ECHA notes that currently there are no data available in the dossier on the potential local effects of the Substance after repeated exposure.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

2. Pre-natal developmental toxicity study in one species

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

You have 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 information:

i. A key study according to OECD TG 414 via oral route in rats with an analogue substance Tri-n-butylamine (EC 203-058-7) ([redacted], 1991).
ii. A supporting study according to OECD TG 422 via oral route in rats with an analogue substance Trimethylamine (EC 200-875-0) ([redacted] 2003).

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. invoked with the studies (i. and ii.) 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
- dosing of the Substance from implantation until the day prior to scheduled caesarean section

The study (ii.) does not inform on skeletal and visceral malformations and variations. In the study (i.), the animals were exposed during GD 6-15. The study does not have a required exposure duration because the exposure duration is not from implantation until the day prior to scheduled caesarean section as required in OECD TG 414. Therefore, the studies (i. and ii.) do 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 propose to follow a tiered testing approach "*In order to be able to evaluate potential read-across possibilities, the Registrants intend to conduct an OECD 421/422 with the registered substance as a bridging study.*" Due to the reasons explained in Appendix on Reasons common to several requests, your read-across adaptation is rejected.

You also indicate in your comments on the draft decision "*If the results of the above mentioned bridging study show that read-acrossis 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 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 (Tripropylamine) and not a different substance (Tripropylamine 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 OECD TG 414 (first species) should be conducted with a neutralised form of the registered substance, the Registrants want to point out, that there seems to be no supplier providing tripropylammonium chloride. Therefore, the Registrants wish an additional time period of 12 months to try again to search for suppliers, to evaluate manufacturing options, to establish an analytical method and to organize testingwith the neutralized form*."

Due to reasons explained under Appendix B.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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species via oral route (ECHA Guidance R.7.6.2.3.2) due to the reasons explained under the request B.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 neutralised salt of the Substance. Your request for a deadline extension is addressed under Appendix E (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 testing under Substance Evaluation.

3. 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 justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: "*In accordance with Regulation (EC) No.1907/2006, Annex 1, Section 6.4, the chemical safety assessment for the chemical demonstrates that 1) the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC, and 2) the likelihood and severity of an event occurring due to the physicochemical properties of the substance in the aquatic environment are negligible; therefore, the criteria for adaptation are met. Specifically, all risk characterization ratios are under 1.0; and there are no physicochemical hazards identified for this substance in the aquatic environment. Therefore, long-term aquatic toxicity testing on invertebrates is not indicated*".

ii. an adaptation under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation you provided predictions from ECOSAR v1.00 (EPIWIN software).

We have assessed this information and identified the following issues:

A. Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

   Your adaptation is therefore rejected.

B. Concerning point ii. (ECOSAR v1.00), for the reasons explained in the Appendix of reasons common to several requests, you QSAR adaptation under Annex XI, Section 1.3. is rejected.

In your comments on the draft decision, you disagree to conduct the study as you consider that fish is a more sensitive trophic level.

You further consider that this information can be omitted based on a weight of evidence (Annex XI, Section 1.2). In support of such adaptation you state:

- short-term toxicity tests do not indicate the need to classify the Substance for aquatic acute toxicity;
- the substance is currently classified as Aquatic chronic 3;
- a chronic hazard is highly expected for the proposed long-term study on fish according to OECD 210, representing the more sensitive species.

ECHA has assessed the information provided in your comments on the draft decision and identified the following issues:

A. The observation of sensitivity difference between trophic level is not on its own an adaptation possibility for this information requirement

   ECHA Guidance R.7.8.5.3. explains that, in the context of the derivation of an aquatic PNEC, if there is compelling evidence to suggest that the invertebrate value is likely to be at least a factor of about 10 less sensitive than algae or fish there are no further requirements for invertebrate testing.

In your comment on the draft decision, you state that "*short-term toxicity testing on aquatic invertebrates indicated that Daphnia magna is the least sensitive species of all three trophic levels. The OECD TG 203 study with Leuciscus idus revealed a 96-h LC50 of 38.3 mg/L and an EC50 (72h) of 22.4 mg/L was determined for the freshwater green algal species Desmodesmus subspicatus, while an EC50 (48h) of 99 mg/L was obtained by the acute study with Daphnia magna*".

However, the information from your dossier does not support sensitivity difference of at least a factor of about 10 between fish an invertebrates as the fifference is less than a factor of 3. Furthermore, the derivation of a PNEC is not on its own an adaptation under Annex XI, to REACH. Therefore, your adaptation is rejected.

B. *Your justification cannot be regarded as a weight of evidence*

Under Annex XI, Section 1.2. a weight of evidence adaptation requires necessarily the submission of "several independent sources of information" that would lead to the conclusion that a substance has or has not a particular dangerous property.

You have provided a single source of information on long-term toxicity on aquatic invertebrates (i.e. ECOSAR v1.00 QSAR prediction listed under point ii. above). Further, as already explained above this information is not reliable. As your dossier does not contain any valid source of information on long-term toxicity on aquatic invertebrates, your justification cannot refer to a weight of evidence adaptation.

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.1.

4. 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 justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: "*Taking into consideration results from short-term toxicity tests on fish, Daphnia and algae, there is a high probability that the most sensitive species (algae) has already been examined and that a further long-term result from fish would not be lower than the data already available. Moreover, the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC (all risk characterization ratios are under 1.0), and the likelihood and severity of an event occurring due to the physicochemical properties of the substance in the aquatic environment are negligible. Therefore, and for reasons of animal welfare, a chronic test on fish is not provided. In conclusion: In accordance with column 2 of REACH Annex IX, the long term testing on fish does not need to be conducted as the chemical safety assessment according to Annex I has not indicated a need to investigate further the effects on aquatic organisms".*
ii. an adaptation under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation you provided predictions from ECOSAR v1.00 (EPIWIN software).

We have assessed this information and identified the following issues:

A. Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

   Your adaptation is therefore rejected.

B. Concerning study ii. (ECOSAR v1.00), for the reasons explained in the Appendix of reasons common to several requests, you QSAR adaptation under Annex XI, Section 1.3. is rejected.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you agreed to conduct a study according to OECD TG 210.

Study design

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

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

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[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 B.1, and C.2., the test sample must be chosen to minimise gastrointestinal irritation and to 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 E: Procedure

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

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

The compliance check was initiated on 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 the screening study and PNDT study by giving further advice on the test material, and also amended the sub-chronic toxicity by removing the request that the study must be conducted with a neutralised form of the Substance, but did not amend the other requests.

In your comments on the draft decision, you requested an extension of the deadline from 24 to 36 months, if the requested screening study (OECD TG 421 or 422), sub-chronic toxicity study (OECD TG 408) and PNDT study in one species (OECD TG 414) should be conducted with a neutralised form of the Substance as there seem to be no supplier providing a neutralised form of the Substance. Therefore, you consider that an additional time period of 12 months is needed to "*[…] to try again to search for suppliers, to evaluate manufacturing options, to establish an analytical method and to organize testing with the neutralized form*."

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 partially agreed with the request and extended the deadline to 30 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 F: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[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 G: Addressees of this decision and their corresponding information requirements

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

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