~~Confidential~~

Helsinki, 25 October 2021

Addressees
Registrants of JS_109-89-7_Diethylamine as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
23 June 2020

Registered substance subject to this decision ("the Substance")
Substance name: Diethylamine
EC number: 203-716-3
CAS number: 109-89-7

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

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

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

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.*

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 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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

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

Failure to comply

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

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix on Reasons common to several requests

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

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

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, 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 (addressed under 'Predictions for toxicological properties').

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 read-across justification document in IUCLID Section 7.8.2 "[redacted]".

You read-across between the following:
- Dimethylamine hydrochloride, DMA-HCl, EC No. 208-046-5, and
- Dimethylamine, DMA, EC No. 204-697-4

as source substances and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties:
- "*Diethylamine […] and the source substance Dimethylamine […] have similar toxicological properties because the chemical structure, physico-chemical properties and available toxicological data of these substances are comparable*"
- "*The target and source substance […] belong to the chemical group of aliphatic secondary amines*"
- "*DMA-HCl will instantaneously dissociate to yield the diammonium ion also present in aqueous solutions of DMA and Cl- , so that within biological systems, DMA and DMA-HCl can be considered identical*"
- *"Long term inhalation studies are available for both substances that confirm that the leading toxicological effect is local irritation at relatively low concentrations. Systemic effects that occur at higher concentrations are also similar (reduced food consumption*

[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

and/ or reduced body weight).”

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

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

A. Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substances within the group (read-across approach).
A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substances and your Substance (ECHA Guidance R.6). It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical and toxicological properties between the source substances and your Substance is a sufficient basis for predicting the properties of your Substance for developmental toxicity endpoint.

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

B. Relevance of the supporting information

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

In order to support your claim that your Substance and source substances have similar properties for the endpoints under consideration in the read-across approach, you refer to their acute toxicity, respiratory irritation, skin and eye irritation/corrosion, and repeated dose toxicity properties.

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

support prediction of the endpoint under consideration, i.e. prenatal developmental toxicity.

In addition, repeated dose toxicity studies with the Substance indicate sperm effects (reduced motility) in rats and mice. Similar effects are not reported with the source substances. Therefore, differences between the Substance and source substances in some of the toxicological properties cannot be excluded.

In your comments on the draft decision, your stated your intention to strengthen the read-across justification:

- *"The registrant agrees to perform a study according to OECD 414 in the rat as a first step. This study addresses the shortcoming of missing endpoint specific information in the read across justification. Assuming there are no significant differences in the results compared to the read across substance DMA, data on the second species can be adopted from the source substance. For DMA, no hints for developmental toxicity have been observed in rats or rabbits in recent OECD 414 guideline studies."*

- *"The second observation was a questionable difference between source and target substance. Other than the source substance, the target substance caused a small decrease in sperm motility after repeated exposure. The difference was significant but not large and could be incidental especially in the absence of any histopathological findings. As requested in a separate ECHA Draft decision on a testing proposal, we also need to close the data gap for the endpoint toxicity to reproduction. Consequently, we will perform an OECD 422 study as a first step. In agreement with the 3R's, this study will be slightly modified (longer exposure time for males) to additionally address the issue of reduced sperm motility, so that no additional animals will be required to clarify the potential difference between source and target substance."*

While ECHA acknowledges your intention to strengthen the read-across justification, we also note that currently you have not provided any new information in your comments or in the registration dossier to further support your read-across adaptation.

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.

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

1. Ready biodegradability

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

You have provided the following information:

i. an OECD TG 301C key study on the Substance ([redacted], 1992). In your comments on the draft decision, you explain that you have now received the study report from the Japanese authorities and that the study should be referred to as [redacted] (1988);

ii. an OECD TG 301F supporting study on the Substance ([redacted], 2010) In your comments on the draft decision, you explain that the study was conducted in 1990 but a statistical recalculation of the study results was performed in 2010. Thus, the study should be referred to as [redacted] (1990).

We have assessed this information and identified the following issues:

A. 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 study i. and ii. above, as reported in your dossier, you have identified the test material as "N-ethylethanamine / 109-89-7 / 203-716-3" (*i.e.* the Substance) without further information, including composition, impurity profile and presence of impurities. In your comments on the draft decision, you clarified that the study report of study i. indicate a test material purity of [redacted]%. For study ii. you stated that the purity of the test material was determined to be ≥ [redacted]% based on the determination of the carbon content.

While you have provided clarifications on the composition of the test material used the above studies, you will have to add this information to your dossier in order to remove the incompliance.

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

Validity criteria

- The oxygen uptake of the inoculum blank does normally not exceed 20-30 mg O_2/L;

- For study i. and ii., the oxygen uptake in the incolum blank at the test is not reported in your dossier. However, in your comments on the draft decision, you specify that this value was 6 mg/L and 29 mg/L for study i. and ii., respectively. This information must be added to your dossier in order to remove the incompliance.

Technical specifications impacting the sensitivity/reliability of the test

- The concentration of the inoculum is set to reach a bacterial cell density of 10^7 to 10^8 cells/L in the test vessel. The suspended solid concentration is 30 mg/L;

However, for study i. and ii., the suspended solid concentration is reported in your dossier as 30 mg/L. However, no information is provided on the cell density of the inoculum.

In your comments on the draft decision, you consider that for both OECD TG 301C and 301F "*it is sufficient to state only the suspended solids concentration (mg/L) as no further information on the concentration of the inoculum is requested in the data sheet*".

ECHA disagrees with this statement. The limit values for the inoculum density in mg/L (e.g. for sludge or soil) or mL/L (e.g. for surface water or effluent) are set to ensure that the introduction of exogeneous organic matter in the test system is within an acceptable range. However, such parameter does not provide a direct estimate of bacterial biomass (as the density of bacteria in, for e.g., a sludge sample or a secondary effluent may vary by orders of magnitude). Accordingly, Appendix R.7.9-1 of ECHA Guidance R.7c specifies inoculum conditions as cell density (cells/mL) present in a relevant media (e.g. surface waters, unchlorinated sewage treatment works, activated sludge).

In the absence of supporting information to demonstrate that the inoculum concentrations used in study i. an ii. allowed reaching an adequate bacterial density, you have not demonstrated that the inoculum density was consistent with the specifications of the corresponding test method.

- The concentration of the test material is 100 mg /L;

  However, for study ii., the test material concentration reported in your dossier was 71 mg/L. As the test material was below the required concentration, the inoculum to test material ratio was too favourable.

  In your comments on the draft decision, you specify that in OECD TG 301F "*it is stated that 100 mg test substance/L giving at least 50-100 mg ThOD/L should be used*". You further explain that the applied test concentration correspond to "*187 mg $ThOD_{NH3}$/L and 249 mg $ThOD_{NH3}$/L*" and therefore "*sufficient test material was applied with regard to the theoretical oxygen demand*".

ECHA agrees that the test material concentration was sufficient to allow an adequate *measurement* of oxygen demand. However, ECHA maintains that by using a test material concentration below the required specifications of OECD TG 301F, the inoculum to test material ratio did not comply with the test method requirements and is deemed to be too favourable.

Reporting of the methodology and results

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

  However, this information is not reported in your dossier for study i. In the absence of this information, it is not possible to verify if the validity criteria of the corresponding test method were met (i.e., difference of extremes of replicate values of the removal of the test material at the plateau, at the end of the test or, if appropriate, at the end of the 10-d window is ≤ 20%. Furthermore, it is not possible to verify whether the 10d-window criteria was met.

In your comments on the draft decision, you specify that the study report of study i. does not contain this information. However, the report does include a graph from which you intend to extract the necessary information. You state that "*this information should allow the verification of the validity criteria and the degradation criteria*".

However, as you have not provided this information as part of your comments, ECHA is not in a position to assess the corresponding information.

- The calculation of the ThOD is described and justified;

  This information is not reported in your dossier for study i. and ii.

  In your comments on the draft decision:
  - on study i. you state that "*The ThOD is noted as TOD in the report*" and that "*based on analysis of nitrogen, most of the nitrogen from the test substance remained as ammonia nitrogen indicating that nitrification did not take place during the incubation. Therefore, the $ThOD_{NH3}$ is relevant for the evaluation of the degradability of the Substance in this study*".

    However, you have neither provided the ThOD value reported nor any of the supporting information indicating that nitrification did not take place. Therefore, ECHA is not in a position to assess the corresponding information.

  - on study ii., you acknowledge that "*ThOD were not unambiguously documented in the study report*". You explain that as a result the degradability of the Substance in this study was recalculated. This information is addressed further below.

- For nitrogen-containing test materials, correction for nitrification is applied on the theoretical oxygen demand (*i.e.* $ThOD_{NO3}$) unless it can be demonstrated that nitrification did not occur (*e.g.* by monitoring changes in concentrations in nitrite and nitrate);

  However, for study ii., it is not specified in your dossier if nitrification was taken into account in the calculation of the reported % biodegradation.

Therefore, none of these studies meet the specifications of OECD TG 301.

In your comments on the draft decision, you also state that "*the conclusion on the ready biodegradability of the Substance are supported by two QSAR calculations: - CATALOGIC v5.14.5 BOD 28 days MITI (OECD 301C) v11.16 - CATALOGIC v5.14.1.5, CATALOGIC Kinetic 301F v14.17*". You have not provided a QSAR Prediction Reporting Format (QPRF) for each of these two models.

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

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

available (either experimentally derived or estimated), (Q)SAR predictions can be used as supporting evidence of that the substance is not rapidly degradable.

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

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

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

On this basis, the information requirement is not fulfilled.

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

1. Adsorption/ desorption screening

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

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

i. an adaptation under Annex VIII, Section 9.3.1., column 2, first indent with the following justification: "*Diethylamine (CAS 109-89-7) has a log Kow of 0.58 (weight of evidence, IUCLID Ch. 4.7)*"
ii. an adaptation under Annex VIII, Section 9.3.1., column 2, second indent with the following justification: "*Diethylamine (CAS 109-89-7)* […] *is readily biodegradable according to OECD criteria ([redacted], 1992; [redacted], 1990)*"
iii. log Koc values predicted using KOCWIN fro EPI Suite v.4.11;
iv. a correction of the log Koc value using a method described in a publication by Franco & Trapp (2008).

We have assessed this information and identified the following issues:

A. Under Annex VIII, Section 9.3.1., Column 2, first indent, a study may be omitted if, based on the physicochemical properties, the substance can be expected to have a low potential for adsorption (e.g. a low log Kow).). To adapt this information requirement based on low Log Kow, lipophilicity must be the sole characteristic driving the adsorption potential of a substance. However, for some groups of substances (e.g. ionisable substances, surfactants) other mechanisms than lipophilicity may drive adsorption.

   You have justified the low potential for adsorption because the partition coefficient value (log Kow) of the substance is considered to be 0.58. You have provided dissociation constant data indicating that the Substance is ionized under environmentally relevant pH.

   The substance is a cationic substance that is ionised under all environmentally relevant pH. Therefore, Log Kow is not a valid descriptor of the adsorption potential of the Substance and your adaptation is rejected.

   In your comments on the draft decision, you agree with the above and state that you will remove this adaptation from the IUCLID dossier.

B. Under Annex VIII, Section 9.3.1., Column 2, first indent, a study may be omitted if the substance and its degradation products decompose rapidly.

   For the reasons explained under Appendix A.3., the information requirement on ready biodegradability is not met. Therefore, you have not demonstrated that the Substance decomposes rapidly and your adaptation is rejected.

   In your comments on the draft decision, you refer to the additional information provided on ready biodegradability and consider that this adaptation is valid. However, as explained under Appendix A.3. your dossier remains incompliant for the information requirement on ready biodegradability.

C. Annex XI, Section 1.3. states that (Q)SAR results must be adequate for the purpose

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

The log Koc values predicted using KOCWIN (v2.00) (see iii. above) do not provide information on pH-dependence of the adsorption potential of the Substance. Therefore, this predicted value is not adequate for the purpose of risk assessment, including the PBT assessment.

In your comments on the draft decision, you agree with the above and state that you will remove this adaptation from the IUCLID dossier.

D. Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when, among others cumulative conditions, adequate and reliable documentation of the applied method is provided.

According to Section 3.4 of ECHA's Practical guide "How to use and report (Q)SARs", a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have not provided sufficient documentation for the QSAR prediction ii. listed above. In particular, you have not included a QMRF and a QPRF in your technical dossier. Therefore, ECHA cannot establish whether the model is scientifically valid and whether the Substance falls within the applicability domain of the model. Therefore, your adaptation is rejected.

In your comments on the draft decision, you state that you intend to improve robust study summary by providing more details on the method and the requested information on the applicability domain by means of the QMRF and QPRF.

However, as you have not provided this information as part of your comments, ECHA is not in a position to assess the corresponding information.

On this basis, the information requirement is not fulfilled.

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 study for this endpoint:

i. A study according to OECD TG 414 via oral route (gavage) in rats (Wistar) with an analogue substance, dimethylamine hydrochloride (EC No. 208-046-5) ([redacted] 2009).

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 is rejected.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you agreed to perform the requested study according to OECD TG 414 in the rat.

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.

You disagree to testing a neutralised form of the Substance via the oral route due to following reasons:

- *"Considering the high vapour pressure of 316 hPa and purely industrial uses, the relevant route for human exposure is via inhalation."*
- *"According to REACH Annex IX, 8.7.2, the "most appropriate route of administration, having regard to the likely route of human exposure" should be chosen. Considering the high vapour pressure of 316 hPa and purely industrial uses, the relevant route for human exposure is via inhalation."*
- *"We understand that there are some concerns that concentrations are limited due to corrosive effects in the respiratory tract while oral dosing would allow for higher doses to assess intrinsic properties of the test substance. In the 90-day [redacted] study, concentrations up to 125 ppm have been used, which correspond to ca. 100mg/kg per day. This in turn approximately equals the oral LD50 value and, consequently, is at least two times above the MTD after oral exposure. This means that higher daily doses can be reached via inhalation."*
- *"Testing of the "neutral salt" as stated in the draft decision is not considered appropriate, since it masks the most important intrinsic property with regard to risk assessment."*
- *"Additionally, according to REACH Annex V and the corresponding guidance, attachment 1 (3), "deliberate neutralization of acids or bases to form the corresponding salts [...] is not covered by this exemption." Consequently, the "neutral*

salt" is not covered by the registration. Instead, for Diethylammonium chloride, a separate registration dossier exists under the CAS No. 660-68-4."

ECHA agrees that based on the vapor pressure of the Substance, the inhalation route is relevant. According to ECHA guidance R.7.6.2.3.2. *"[…] the test methods for reproductive toxicity which focus on the detection of reproductive hazards, the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases."*. Therefore, and despite your arguments, ECHA considers that in this case, also taking into account the corrosivity of the Substance as explained above, the oral route is the most appropriate administration route for a PNDT study.

You raised a concern that testing a neutralised form of the Substance masks the most important intrinsic property, i.e. corrosivity, and is therefore considered inappropriate. 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 testing of a neutralised form of the Substance will enable to investigate intrinsic properties related to reproductive toxicity in a pre-natal developmental toxicity study (OECD TG 414) by allowing to use adequate dose levels. Otherwise, the already known corrosivity of the Substance may not allow investigation of developmental toxicity in relation to systemic toxicity. Also, the corrosivity/irritation of the Substance may affect the behaviour of the animals confounding the interpretation of developmental 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 11. Therefore, the Substance will exist as a protonated form (NH_2^+) under physiological conditions as will the neutralised form of the Substance.

Therefore, 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). 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.

If the PNDT study submitted in response to this decision does not deliver reliable results because of gastrointestinal irritation, further information may be considered necessary in order to investigate the intrinsic properties at adequate dose levels. 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. an OECD TG 211 key study on the Substance ([redacted], 1999);
ii. a supporting study according to an unspecified test method by ASTM (1993) on the Substance ([redacted], 1994).

We have assessed this information and identified the following issues:

A. 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 study i. above, you have identified the test material as "N-ethylethanamine / 109-89-7 / 203-716-3" (*i.e.* the Substance) without further information, including composition, impurity profile and presence of impurities.

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

B. 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:

Key parameter to be measured

- the concentrations of the test material leading to no observed effect (NOECs) on the following parameters are estimated:
  1) the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test, and
  2) the survival of the parent animals during the test, and
  3) the time to production of the first brood.

  However, for study i., no information is provided in the dossier on the time to production of the first brood.
  For study ii., the basis for the effect values is "mortality". No information si provided on reproductive output or the time to production of the first brood. In your comments, you confirm that this study did not investigate reproduction. You state that you will no longer use this study as supporting information in your dossier.

  Therefore, these studies do no provide a comprehensive coverage of the key parameters of OECD TG 211

Validity criteria

- the mean number of living offspring produced per parent animal surviving is ≥ 60 at the end of the test;

  However, in the absence of appropriate reporting of the study results in your dossier, this validity criteria cannot be verified for studies i. and ii.

Technical specifications impacting the sensitivity/reliability of the test

- the test duration is 21 days or sufficient to produce at least three broods;

  However, for study ii., it is not specified in your dossier if the test duration (7 days) was sufficient for the parental animals to produce three broods.

Reporting of the methodology and results

- the full record of the daily production of living offspring during the test by each parent animal/in each replicate is provided;
- the coefficient of variation for control reproductive output is reported;

However, this information is not provided in your dossier for study i. and ii. Therefore, an independent assessment of the results from these studies cannot be conducted.

Therefore, none of these studies meets the specifications of OECD TG 211 in conjunction with OECD GD 23.

In your comments on the draft decision for study i., you state that you have gained access to the full study report and that you intend to improve the robust study summary (especially regarding reporting of methodology and results, but also with regard to the test material). You state that you will provide this information in an updated of your registration dossier However, as you have not provided this information as part of your comments, ECHA is not in a position to assess the corresponding information. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

On this basis, the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to the its adsorption potential (as it is ionisable) and potential for volatilisation. 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. 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: "*The hazard assessment of the substance reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment*"
ii. an adaptation under Annex XI, Section 3 ('Substance-tailored exposure-driven testing'). In support of your adaptation, you provided the following justification: "*In accordance with Annex XI Section 3, it can be demonstrated in the risk assessment*

that the manufacture and the use of the substance do not pose an unacceptable risk for all environmental compartments as the risk characterization ratios (RCRs) of the chemical safety assessment are below 1 for all compartments (see Chemical Safety Report Ch. 10)".

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 listed under i. above is therefore rejected.

B. Under Annex XI, Section 3, this information may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report. The justification must be based on a rigorous exposure assessment in accordance with Annex I, Section 5 and must meet the following criteria:
   (a) It can be demonstrated that all the following conditions are met:
      i. the absence or no significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI, Section 3.5., and
      ii. a PNEC can be derived from available data, which:
         - must be relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes and therefore must be based on reliable information on the hazardous properties of the substance on at least three trophic levels;
         - must take into account the increased uncertainty resulting from the omission of the information requirement, in this case by selecting an appropriate assessment factor (AF) as described in ECHA Guidance R.10.3.
      iii. the ratio between the results of the exposure assessment (PECs) and the PNEC (i.e the RCRs) are always well below 1.

   You have derive a $PNEC_{freshwater}$ for the Substance using an EC10 of 4.07 mg/L (from the OECD TG 211 study by NITE (1999) listed under Appendix C.2). You applied an assessment factor (AF) of 50 as aquatic invertberates were found to be more sensitive in short-term toxicity studies. Based on the proposed $PNEC_{freshwater}$ (i.e., 0.081 mg/L), you report RCR up to c.a. 0.2 for the freshwater compartment (scenario ES 1.1).

   However, for the reasons explained under Appendix C.2., the information requirement on long-term toxicity to aqsuatic invertebrates is not fulfilled. Therefore, the available data from your dossier does not provide a reliable basis to derive a PNEC for the freshwater compartment. Based on the lowest reliable acute L/EC50 from your dossier and an assessment factor of 1000, the $PNEC_{freshwater}$ is determined to be 0.0046 mg/L leading to a highest RCR of 3.49.

   Therefore, the information from your dossier does not demonstrate that the ratio between the results of the exposure assessment (PECs) and the PNEC (i.e the RCRs) are always well below 1 your adaptation is rejected.

In your comments on the draft decision, while you recognize the rejection of the proposed adaptations of the information requirement, you also specify that you intend to adapt this information requirement under Annex XI, Section 1.2. ('Weight of evidence'). You intend to

provide the following justification:

i. The structure as well as the physico-chemical properties of the Substance are clearly identified. The Substance is readily biodegradable; therefore, relevant metabolites do not need to be considered;
ii. The substance does not produce an alert for protein binding in the schemes by OECD and OASIS (OECD QSAR Toolbox v4.3; see Chapter 2.5 of the updated Read-Across Justification). According to the modified classification scheme of Verhaar, the mode of action of the Substance is narcosis of baseline toxicity. Therefore, it can be concluded that the Substance has no specific mode of action and critical long-term effects are not to be expected;
iii. You specify that no information on long-term toxicity to fish is available for the Substance and that no reliable QSAR predictions or in-vitro results for long-term toxicity to fish are not available;
iv. Fish are not the most sensitive aquatic trophic level;
v. The Substance is neither acutely nor chronically hazardous to the aquatic environment according to the CLP-Regulation (EC) No 1272/2008. You based you reasoning on aquatic chronic classification on the result of the data currently available on short-term toxicity to fish and the concept of acute-to-chronic ratio;
vi. You further consider that this information is not needed for the PBT assessment of the Substance as it is concluded no P/vP based on ready biodegradability;
vii. You refer to Article 25 to REACH to specify that vertebrate animal testing should be undertaken as a last resort.

We take note of your intention to submit an adaptation. However, we emphasize that the justification above does not seem to rely on any source of information that could be used to conclude on long-term fish toxicity.

Relevant information that can be used to support weight of evidence adaptation for long-term toxicity to fish includes similar information nroamlly obtained from an OECD TG 210 study. The sources of information must therefore cover: Parameters related to the survival and development of fish in early life stages from the stage of fertilized egg until the juvenile life-stage following exposure to the test substance are measured, including:

1) the stage of embryonic development at the start of the test, and
2) hatching of fertilized eggs and survival of embryos, larvae and juvenile fish, and
3) the appearance and behaviour of larvae and juvenile fish, and
4) the weight and length of fish at the end of the test.

Furthermore, your argument that no significant long-term toxicity on fish is expected based on available information on short-term toxicity to fish is not valid as, for the reasons explained under Appendix B.2, the information requirement for that endpoint is not fulfilled. Finally, the use of the acute-to chronic ratio concept on its own is not regarded as providing sufficient weight of evidence to conclude on chronic toxicity (ECHA Guidance R.7.8.5.).

On this basis, the information requirement is not fulfilled.

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 C.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 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 414 via inhalation in rabbits (New Zealand White) with an analogue substance, dimethylamine (EC No. 2204-697-4) ([redacted] 2016).

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 is rejected.

In your comments on the draft decision, you agreed to perform a study according to OECD TG 414 in the rat as a first step. Furthermore, you state "*This study addresses the shortcoming of missing endpoint specific information in the read across justification. Assuming there are no significant differences in the results compared to the read across substance DMA, data on the second species can be adopted from the source substance.*"

ECHA notes that currently you have not provided any new information in your comments or in the registration dossier to support your read-across adaptation.

On this basis, the information requirement is not fulfilled.

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 via 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.

If the PNDT study submitted in response of this decision does not deliver reliable results because of gastrointestinal irritation, further information may be considered necessary in order to investigate the intrinsic properties at adequate dose levels. 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.

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. and 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 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

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. EOGRTS is addressed in the related Testing proposal decision. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

As the PNDT studies requested in this decision have to be performed sequentially, and the EOGRTS requested in the related Testing proposal decision can be performed in parallel with the PNDT study in the second species, a deadline of 30 months is granted in both compliance check and testing proposal decisions.

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

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

The compliance check was initiated on 24 March 2020.

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

ECHA took into account your comments and removed the request for "In vitro cytogenicity study in mammalian cells or In vitro micronucleus study", and amended the requests for PNDT studies by giving further advice on the test material, but did not amend the other requests.

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

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

Appendix 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)[7]

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

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

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

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

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

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

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

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

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

OECD Guidance documents[8]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

Guidance document on 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]

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.