

Helsinki, 25 October 2021

Addressees

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

Date of submission of the dossier subject of a decision

23/06/2020

Registered substance subject to this decision, hereafter '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 TPE-D-XXXXXXXXXX-XX-XX/F)**DECISION ON TESTING PROPOSAL(S)**

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by **31 July 2024**.

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

1. Extended one-generation reproductive toxicity study (triggered by Annex IX, Section 8.7.3., column 1; test method: EU B.56./OECD TG 443) by oral route, in rats, as specified in request B.1.

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) by oral route, in rats, specified as follows:
 - Ten weeks pre-mating exposure duration for the parental (P0) generation;
 - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
 - Cohort 1A (Reproductive toxicity);
 - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

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*.

Your originally proposed test using an analogue substance dimethylamine (EC No. 204-697-4) is rejected, according to Article 40(3)(d):

Extended one-generation reproductive toxicity study in rats, (EU B.56./OECD TG 443)

According to Article 40(3)(c), the decision also requires registrants subject to Annex IX to also carry out that test based on Annex IX, Section 8.7.3., column 1.

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

- Appendices entitled "Reasons to request information required under Annexes IX 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.

ECHA requests the same study from registrants at different tonnages. In such case, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

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 can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: <http://echa.europa.eu/regulations/appeals>.

Approved¹ 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 A: Reasons to request information required under Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted.

1. Extended one-generation reproductive toxicity study

An extended one-generation reproductive toxicity (EOGRT) study (OECD 443) is an information requirement under Annex IX to REACH (Section 8.7.3.) if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.

ECHA considers that concerns in relation with reproductive toxicity are observed in available repeated dose toxicity studies with the Substance:

- Sub-chronic toxicity studies similar to OECD 413 via inhalation in rats and mice show a dose-related decrease in sperm motility in the absence of systemic toxicity (█ 2003). According to ECHA Guidance R.7a, "Effects on sperm parameters analysis" are considered triggers for EOGRTS at Annex IX.

Accordingly, an EOGRT study according to OECD TG 443 as specified in this decision is an information requirement for your registration, because Column 1 criteria at Annex IX, Section 8.7.3 are met.

For the specifications of the study design, see B.1 below.

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

This decision is based on the examination of the testing proposals you submitted.

1. Extended one-generation reproductive toxicity study

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the analogue substance dimethylamine (EC No. 204-697-4).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA agrees that an EOGRTS is necessary.

1.2. Grouping of substances and read-across approach

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}.

You have provided read-across justification document in IUCLID Section 7.8.2 "".

You read-across between Dimethylamine, EC No. 204-697-4, as source substance 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"*
- *"Long term inhalation studies are available for both substances that confirm that the*

² Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: [Read-Across Assessment Framework \(https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across\)](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>

leading toxicological effect is local irritation at relatively low concentrations. Systemic effects that occur at higher concentrations are also similar (reduced food consumption 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 prediction of toxicological properties.

A. Read-across hypothesis

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

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

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical and toxicological properties between the source substance 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 substance and your Substance. In addition, your hypothesis covers only the prediction of developmental toxicity.

B. Relevance of the supporting information

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

In order to support your claim that your Substance and source substance(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to their acute toxicity, 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 reproductive and 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. 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 substance. Therefore, differences between the Substance and source substance in some of the toxicological properties including reproductive toxicity cannot be excluded.

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

- *"The current read across approach was rejected by ECHA for the endpoint of toxicity to reproduction mainly because no study on reproductive / developmental toxicity was provided for the target substance and potential effects on sperm motility were observed after repeated exposure with the target but not the source substance."*
- *"Though significant, the differences in sperm motility in the repeated dose study were not large and could be incidental especially in the absence of any histopathological findings."*
- *"Aside from these points, ECHA agreed that effects after repeated exposure are quantitatively and qualitatively similar between the target and the source substance."*
- *"So, we aim to address both shortcomings by performing a study according to OECD 422 with slight modifications."*
- *"Additionally, the OECD 422 will be modified by an elongated treatment period for the males. It should cover at least one full spermatogenesis cycle but will be extended to 90 days for better comparison with the available repeated dose toxicity data."*
- *"If effects on sperm motility can be ruled out and no other effects on reproduction or developmental toxicity occur, this study can be used to justify read across to DMA. If effects on sperm motility are confirmed or any other significant differences between target and source substance are detected the RA approach is invalid and REACH Annex X must be fulfilled solely with information on the registered 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.

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

1.3. Specification of the study design

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. Therefore, the study must be conducted in the rat.

ECHA considers that the oral route is the most appropriate route of administration, since the Substance is a corrosive liquid. It has a harmonised classification as Skin Corr. 1A (H314). ECHA Guidance R.7.6.2.3.2 specifies that corrosive or highly irritating substances must be tested preferentially via the oral route. However, testing at concentration/dose levels causing corrosivity must be avoided. Testing of neutral salts of alkaline or acidic substances is therefore more appropriate as it allows the investigation of intrinsic properties at adequate dose levels.

In your comments on the draft decision, you consider inhalation route as the most appropriate route of administration for the reproductive toxicity study based on the following:

- *Effects on sperm motility were observed in an inhalation study. To clarify relevance of these effects, the follow-up reproductive toxicity study should also be performed via inhalation to exclude that potential differences (e.g. lack of effects) are caused by first-pass effects or differences in distribution.*
- *Due to the very high vapour pressure of 316 hPa, inhalation is the relevant exposure route, which should anyhow be chosen according to REACH Annex X, 8.7.3.*

ECHA agrees that based on the vapour pressure of the Substance and the effects observed in sperm motility, the inhalation route is relevant. However, according to ECHA guidance R.7.6.2.3.2. "[...] the test methods for reproductive toxicity which focus on the detection of reproductive hazards, the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases.". Therefore, ECHA considers that in this case, also taking into account the corrosivity of the Substance as explained above, the oral route is the most appropriate administration route. The corrosivity of the Substance may affect the behaviour of the animals confounding the interpretation of reproductive toxicity-related parameters. Local effects might induce unnecessary stress to the animals with consequences to the outcome of the study. 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 via the oral route is more appropriate in this case, instead of testing of the Substance via the inhalation route. Furthermore, 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.

On this basis, testing of a neutralised form of the Substance will enable investigation of intrinsic properties related to reproductive toxicity in EOGRTS (OECD TG 443) by allowing the use of adequate dose levels. Otherwise, the known corrosivity of the Substance may prevent investigation of reproductive toxicity in relation to systemic toxicity.

Pre-mating exposure duration and dose-level setting

Ten weeks pre-mating exposure duration is required because there is no substance specific information in the dossier supporting shorter pre-mating exposure duration (ECHA Guidance R.7a, Appendix R.7.6-3).

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects, with the other cohorts being tested at the same

dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

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

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

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

1.4. Outcome

Your testing proposal is rejected under Article 40(3) (d) of REACH. Under Article 40(3)(c) you are requested to carry out the additional test as specified above. 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 EOGRTS 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.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance R.7a, Section R.7.6.

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries⁴.

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 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. When selecting a neutral salt, the potential impact of the counterion must be considered. The counterion must not have 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 dossiers⁵.

⁴ <https://echa.europa.eu/practical-guides>

⁵ <https://echa.europa.eu/manuals>

Appendix D: Procedure

As the Pre-natal developmental toxicity (PNDT) studies requested in the related compliance check decision have to be performed sequentially, and the Extended one generation reproductive toxicity requested in the this decision can be performed in parallel with the PNDT study in the second species a deadline of 30 months is granted in both testing proposal and compliance check decisions.

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 24 June 2020.

ECHA held a third party consultation for the testing proposal(s) from 21 September 2020 until 5 November 2020. ECHA did not receive information from third parties.

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

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

ECHA took into account your comments and amended requests by giving further advice on the test material in the requests.

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

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

Appendix E: List of references - ECHA Guidance⁶ and other supporting documentsEvaluation 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 multi-constituent substances and UVCBs (RAAF UVCB, March 2017)⁸**Error! Bookmark not defined.**

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 documents⁸

⁶ <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

⁷ <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

⁸ <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

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

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

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

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

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

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
██████████	██████████████████	██████
██████████████████	██████████████████	██████

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.