~~Confidential~~

Helsinki, 01 March 2024

Addressee(s)
Registrant(s) of Ethylenediamine, propoxylated as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
08 December 2022

Registered substance subject to this decision ("the Substance")
Substance name: Ethylenediamine, propoxylated
EC/List number: 500-035-6

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)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***9 September 2024***.

Requested information must be generated using the analogue substance 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol (EC No. 203-041-4)

Information required from all 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 premating exposure duration for the parental (P0) generation;
- The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
- Cohort 1A and 1B (Reproductive toxicity);
- Cohorts 2A and 2B (Developmental neurotoxicity);

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressee(s) of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

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

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 1: Reasons for the decision

Contents

Reasons related to the information under Annex X of REACH

1. Extended one-generation reproductive toxicity study

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

1.1. Information provided to fulfil the information requirement

2 You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the analogue substance 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol (EC No. 203-041-4).

3 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.

4 ECHA agrees that an EOGRTS is necessary.

1.2. Evaluation of the read-across approach

5 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used.

6 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.

7 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.

8 In IUCLID section 7.8.1, you propose to fulfil the information requirement by means of an ongoing EOGRT study with the analogue substance 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol (EC No. 203-041-4).

9 You have provided a read-across justification document in IUCLID Section 13.2., grouping three ethylenediamine-initiated NLP Alkoxylates:

- Ethylenediamine, propoxylated (EC No. 500-035-6), the Substance;
- 1,1',1'',1'''-(ethane-1,2-diyldinitrilo)tetrapropan-2-ol (EC No. 203-041-4), source substance (1); and
- ethylenediamine, ethoxylated and propoxylated (EC No. 500-047-1), source substance (2).

10 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects and that the properties of the Substance, in terms of reproductive toxicity, may be predicted from data that is being generated with source substance (1), 1,1',1'',1'''-(ethane-1,2-diyldinitrilo)tetrapropan-2-ol (EC No. 203-041-4). In addition, according to the read-across justification document, you consider that source substance (2) ethylenediamine, ethoxylated and propoxylated (EC No. 500-047-1) provides relevant information on repeated-dose toxicity properties of the Substance.

11 The Substance and the source substances (1) and (2) show structural similarities. The structures are based on an ethylenediamine core that has been alkoxylated with either propylene oxide monomers (the Substance and source substance (1)), or with propylene

oxide and ethylene oxide monomers (source substance (2)). Hence, all three substances contain common constituents.

12 You justify the read-across based on the structural similarities, uniform physicochemical properties, and similarities in the low toxicological profiles of the substances. In the justification document, you provide studies (OECD TG 422 with the Substance and source substance (1), OECD TG 421 and OECD TG 407 with source substance (2), OECD TG 414 in rats with the Substance and source substance (2), and 90-day RDT studies with source substances (1) and (2)), whose comparison currently supports your hypothesis. Furthermore, the reproductive toxicity properties of the Substance are predicted based on a conservative approach due to observed effects (vacuolation of epithelial cells in brain ventricles) in the OECD TG 422 study with source substance (1), 1,1',1'',1'''-(ethane-1,2-diyldinitrilo)tetrapropan-2-ol (EC No. 203-041-4).

13 ECHA agrees that based on the read-across justification provided and the information available in the dossier there is a basis for considering the read across plausible. Therefore, you have plausibly demonstrated that relevant properties of the Substance may be predicted from data on the source substance.

14 However, ECHA emphasises that any final determination on the validity of your read-across adaptation will only be possible when the information on requested studies will be available in the dossier after assessing whether it confirms or undermines the read-across hypothesis.

1.3. Specification of the study design

1.3.1. Species and route selection

15 You proposed testing in the rat. ECHA agrees with your proposal because the rat is the species preferred by OECD TG 443.

16 You proposed testing by oral route. ECHA agrees with your proposal.

1.3.2. Pre-mating exposure duration

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

18 You proposed ten weeks pre-mating exposure duration. ECHA agrees with your proposal.

19 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter pre-mating exposure duration (Guidance on IRs & CSA, Appendix R.7.6-3).

1.3.3. Dose-level setting

20 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, para. 22; OECD GD 151, para. 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

21 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and

fertility, but no deaths (i.e., no more than 10% mortality; Annex I, Section 3.7.2.4.4. to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, para. 18) in the P0 animals.

22 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

23 In summary: Unless limited by the physical/chemical nature of the test substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or
(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(4) the highest dose level in P0 animals must follow the limit dose concept.

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

25 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

1.3.4. Cohorts 1A and 1B

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

1.3.4.1. Histopathological investigations in Cohorts 1A and 1B

27 In addition to histopathological investigations of cohorts 1A, organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, para. 67 and 72) if

- the results from Cohort 1A are equivocal,
- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

1.3.4.2. Splenic lymphocyte subpopulation analysis

28 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, para. 66; OECD GD 151, Annex Table 1.3).

1.3.4.3. Investigations of sexual maturation

29 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, para. 12 in conjunction with OECD TG 443, para. 47). For statistical analyses, data on

sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

1.3.5. Cohorts 2A and 2B

30 Annex IX/X, Section 8.7.3., Column 2 provides that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

31 The read-across justification document contains information which provides an indication that the substance may be a (developmental) neurotoxicant. The OECD TG 422 study (2009) with the analogue substance 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol (EC No. 203-041-4) shows evidence of neurotoxicity in the central nervous system. A vacuolation of epithelial cells of the lateral ventricles of the brain was observed in all animals of the high dose in the absence of further toxicity.

32 You proposed to include Cohort 2A and 2B.

33 ECHA agrees that the inclusion of Cohort 2A and 2B are necessary.

1.4. Outcome

34 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test, as specified above.

1.4.1. Further expansion of the study design

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

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2023).
Guidance on intermediates; ECHA (2010).

All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs); ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 1 July 2022.

ECHA held a third-party consultation for the testing proposal(s) from 22 September 2022 until 7 November 2022. ECHA did not receive information from third parties.

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

The deadline to provide the requested information takes into account the deadline set to provide the information requested in ECHA's compliance check decision of 2 September 2020 for the source substance 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol (EC number 203-041-4). That decision requested the registrants concerned to submit among others an Extended One Generation Reproductive Toxicity study on the source substance by 8 December 2023. The present decision is adopted close to that deadline. ECHA therefore considers that a period of six months from the date of the adoption of the present decision should be sufficient time for you to obtain relevant information on that study from the registrants of the source substance and to submit this information with ECHA.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

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 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. 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:

- its representativeness towards the specified analogue substance,
- it supports the read-across prediction as presented in the read-across justification document,
- 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.

(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 the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP

[2] https://echa.europa.eu/practical-guides

(ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm 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 (https://echa.europa.eu/manuals).

2. General recommendations for conducting and reporting new tests

References to Guidance on REACH and other supporting documents can be found in Appendix 1.