Helsinki, 02 September 2020

Addressees
Registrants of Ethylenediamine, propoxylated listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
27/06/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Ethylenediamine, propoxylated
EC number: 500-035-6
CAS number: 25214-63-5

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadlines provided.

A. Requirements applicable to all the Registrants subject to Annex VIII of REACH

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

2. Only if a negative result in Annex VIII, Section 8.4.2. is obtained, in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance;

B. Requirements applicable to all the Registrants subject to Annex IX of REACH

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

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat), oral route with the Substance;

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in points A.1-2. and B.1. above in an updated registration dossier by ***8 December 2021***, and the information requested in point B.2. above by ***8 December 2022***.

You must also update the chemical safety report, where relevant, including any changes to classification and labelling based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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.

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 general considerations

Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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

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 (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.

You read-across between Ethylenediamine, ethoxylated and propoxylated, EC No. 500-047-1 (CAS No. 26316-40-5) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: *"The two substances [...] show similar physicochemical and toxicological properties due to similar chemical structures, common functional groups, common precursors and breakdown products".*

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.

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] 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)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

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

Missing supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[5]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

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

With regard to gene mutation, you have provided a study on *in vitro* gene mutation in bacteria (OECD TG 471, 2001) with the Substance and a mammalian cell gene mutation test (OECD TG 476, 2009) with the source substance.

With regard to clastogenicity, you have provided a mammalian chromosome aberration test (OECD TG 473, 2008) with the source substance. However, you did not provide information with the Substance.

With regard to repeated dose toxicity and developmental toxicity, you have provided the following studies with the source substance: sub-acute toxicity study (OECD TG 407, 2006); sub-chronic toxicity study (OECD TG 408, 2016), and pre-natal developmental toxicity study in rats (OECD TG 414, 2015). However, you did not provide bridging study/studies with the Substance.

In your comments on the draft decision, you indicate your intention to conduct a combined repeated dose toxicity and screening for reproductive/developmental toxicity study (OECD TG 422) with the Substance.

You have not provided new supporting (experimental) data to support a read-across adaptation with your comments. It is not possible to evaluate the supporting information referred to in your comments in absence of sufficient documentation. It is in your discretion to generate and provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH.

Therefore, the data set reported in the technical dossier and through your comments does not include relevant, reliable and adequate information for the Substance and of the source substance(s) to compare the above mentioned toxicological properties, to support your read-across hypothesis.

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

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

Bias in the choice of source substances

In order to make an accurate prediction of ecotoxicological and toxicological properties all relevant information must be considered in the prediction. If not all relevant information is considered then bias may be introduced in the prediction. For example, source substance(s) may be selected incorrectly or incompletely due to a particular selection of source studies.[6]

You have provided information on Ethylenediamine, ethoxylated and propoxylated, EC No. 500-047-1 (CAS No. 26316-40-5) as source substance. You did not provide information on the analogue substance 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol (EC 203-041-4).
The information available on ECHA's website on 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol indicates that this substance is structurally more similar with regard to substituents (no ethoxylation) than the source substance identified by you. Despite these structural similarities no consideration has been provided in the registration dossier on this analogue substance (EC 203-041-4). Furthermore, it is more toxic than the source substance identified by you. Specifically, this analogue shows evidence of neurotoxicity in the central nervous system since *"vacuolation of epithelial cells of the lateral ventricles of the brain"* was observed in all animals of the high dose of an OECD TG 422 study in the absence of further toxicity.

ECHA concludes that not all relevant information have been provided nor considered in your predictions. Therefore, ECHA considers that there is potential for bias in your predictions.

In your comments you indicate your agreement to consider 1,1',1'',1'''-ethylene-dinitrilo-tetrapropan-2-ol, EC No. 203-041-4 (CAS No. 102-60-3) as a further source substance.

B. Conclusions on the read-across approach

As explained above, you have not established, neither in your dossier nor through your comments, 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.

[6] Read-across assessment framework, ECHA 2017, Section 4.5.1.5

Appendix A: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. **In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)**

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

In your comments on the draft decision you agree to this request.

Therefore, the information requirement is not fulfilled.

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

In your comments on the draft decision you agree to this request.

Therefore, the information requirement is not fulfilled.

Appendix B: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII to IX to REACH.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

In your comments on the draft decision you indicate your intention to improve your read-across adaptation. However, as explained in the Appendix on general considerations, your adaptation according to Annex XI, Section 1.5 is rejected based on the currently available information. Your updated dossier will be evaluated after the deadline of this decision has passed.

Therefore, the information requirement is not fulfilled.

A sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance, because although the information indicate that human exposure to the Substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by performing a qualitative assessment for inhalation, local effects.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

In your comments on the draft decision you indicate your intention to improve your read-across adaptation. However, as explained in the Appendix on general considerations, your adaptation according to Annex XI, Section 1.5 is rejected based on the currently available information. Your updated dossier will be evaluated after the deadline of this decision has passed.

Therefore, the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 must be performed in rat as preferred species with oral[7] administration of the Substance.

[7] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 02 October 2018.

The decision making followed the procedure of Articles 50 and 51 of REACH, as described below:

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

ECHA took into account your comments and did not amend the requests and the deadline.

Deadline to submit the requested information in this decision

The timeline indicated in the draft decision to provide the information requested is 12 months for A1, A2 and B1 and 24 months for B2 from the date of the decision.

In your comments on the draft decision, you requested an extension of the timeline stating the following: "*We also kindly ask that ECHA allows 12 months to conduct the intended OECD 422 study with CAS 25214-63-5 and obtain the results before commencing the 12 month and 24 month deadlines for the OECD 408 and OECD 414 in rat. But we would like to point out that in general the time span proposed in the ECHA draft decision of 12 months for conducting a subchronic toxicity study (90 day), oral route (OECD TG 408) is rather challenging, as the assignment of toxicological laboratory can only be conducted after the final decision was sent to the lead registrant. A time span of 18 months for the sub chronic toxicity study would be more adequate.*"

ECHA observes that you indicated that the intended OECD 422 study with CAS 25214-63-5 shall be conducted so as to improve your read across adaptation by submitting missing supporting information. It is at your discretion to perform the abovementioned study and can be commenced at any point in time. The present decision does not require you to perform such test and thereby the imposed deadlines cannot be affected. In addition, the tests under A.1, A.2, B.1 and B.2 may be conducted in parallel and thus the deadlines indicated is still considered adequate. The deadline for the request B.1 is set for the reasons explained in Appendix D.1 of this decision.

Therefore, ECHA has not modified the deadline of the decision.

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 D: Observations and technical guidance

1. The information from the Sub-chronic toxicity study (90-day), requested in the present this decision, is relevant for the design of an Extended one-generation reproductive toxicity study (EOGRTS).

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

3. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

4. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   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: 'How to report robust study summaries'[8].

5. Test material

   Selection of the test material(s) for UVCB substances

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account 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. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

   The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should

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

be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents".

In order to meet this requirement, all the constituents of the test material used for each test must be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.

Technical Reporting of the test material for UVCB substances

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values and other parameters relevant for the property to be tested as the degree of alkoxylation. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website[9].

6. List of references of the ECHA Guidance and other guidance/ reference documents[10]

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 in this decision.

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[11]

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.

[9] https://echa.europa.eu/manuals
[10] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[11] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

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.

OECD Guidance documents[12]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[12] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.