~~Confidential~~

Helsinki, 10 November 2023

Addressee
Registrant listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
23/10/2015

Registered substance subject to this decision ("the Substance")
Substance name: N-(2-aminoethyl)-1,3-propanediamine
EC number/List number: 236-882-0

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 ***18 November 2024***.

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

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

The reasons for the request(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 of the decision and its corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 request(s)
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 request(s)

Contents

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

1 An in vitro gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

1.1. Information provided

2 You have provided an in vitro gene mutation study in bacteria (1990) with the Substance.

3 In addition, you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an *in vitro* gene mutation study in bacteria (2012) with 1, N1,N1'-1,2-ethanediylbis(1,3-propanediamine), EC 234-147-9 // N4 Amine;

(ii) an *in vitro* gene mutation study in bacteria (1997) with Ethane-1,2-diamine; prop-2-enenitrile, CAS No 68909-99-9 // N3/N4 Amine.

1.2. Assessment of the information provided

1.2.1. The provided study on the Substance does not meet the specifications of the test guideline(s)

4 To fulfil the information requirement, a study must comply with OECD TG 471 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the test is performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

5 In the provided study on the Substance (study i):

a) the test was performed with the strains *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (i.e., the strain E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 is missing).

6 The information provided does not cover the specification required by the OECD TG 471.

1.2.2. Read-across adaptation rejected

7 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.

8 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

9 You provide a read-across justification document in IUCLID Section 13.

10 You predict the properties of the Substance from information obtained from the following source substances:

- N4 Amine, N1,N1'-1,2-ethanediylbis(1,3-propanediamine, EC 234-147-9 (source substance 1);
- N3/N4 Amine, Ethane-1,2-diamine; prop-2-enenitrile, CAS No 68909-99-9 (source substance 2);

11 You provide the following reasoning for the prediction of toxicological properties: "*Due to structural and physic-chemical similarities, toxicological data from the source substances N4 Amine and N3/N4 Amine can be used for the assessment of human health hazard of the target substance*".

12 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

13 We have identified the following issues with the predictions of in vitro gene mutation in bacteria:

1.2.2.1. Inadequate read-across hypothesis

14 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must include an explanation why the properties of the Substance may be predicted from other substances in the group, i.e. a read-across hypothesis. This hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). It should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

15 Your read-across hypothesis is only based on structural similarities and similarities in the physico-chemical properties of the source substances. You consider that these elements are a sufficient basis for predicting in vitro gene mutation in bacteria.

16 You have not substantiated how structural and physico-chemical similarity alone would explain similarity in the predicted endpoints and thus be sufficient to justify the prediction.

17 While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar toxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for toxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances, and thus why the properties of the Substance may be predicted from information on the source substances.

1.2.2.2. Missing supporting information to compare the properties of the substances

18 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substances (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

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

20 For the source substances, you provided in the registration dossier acute the Ames tests used for the prediction. Apart from these studies, your read-across justification or the registration dossier does not include any bridging studies for the Substance that would confirm that both substances cause the same type of effects for the following endpoint: gene mutation in bacterial cells (5th strain).

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

1.2.2.3. Conclusion on the read-across approach

22 Based on the above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Your read-across approach under Annex XI, Section 1.5. is rejected.

23 Therefore, the information requirement is not fulfilled.

24 In the comments to the draft decision, you agree to perform the requested study.

1.3. Specification of the study design

25 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471) is considered suitable.

2. Short-term toxicity testing on aquatic invertebrates

26 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

2.1. Information provided in your registration dossier

27 You have provided a short-term toxicity study on daphnia magna (1989) with the Substance.

2.2. Assessment of the information provided in your registration dossier

2.2.1. The provided study does not meet the specifications of the test guideline(s)

28 To fulfil the information requirement, a study must comply with OECD TG 202 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Characterisation of exposure

a) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available.

29 In the provided study:

Characterisation of exposure

a) no analytical monitoring of exposure was conducted.

30 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically no analytical monitoring was performed. In the absence of analytical monitoring you have not demonstrated that exposure was satisfactorily maintained throughout the test. The fact that the Substance is miscible and has a low capacity to adsorb and a low Henry's Law Constant (HLC) does not guarantee that initial concentrations and concentrations throughout the test were maintained within 20% nominal.

31 On this basis, the specifications of OECD TG 202 are not met.

32 In your comments on the draft decision, you consider that "*the information on the physicochemical properties of the Substance and its fate gives a good indication if test concentrations can be maintained over the exposure period*". Furthermore, you explain to you intend "*to perform a growth inhibition test with algae with analytical monitoring according to OECD TG 201*" which, according to you, "*will allow to conclude on the stability of the test item in the study on the immobilisation of Daphnia magna*". Therefore, you disagree to perform the requested study.

33 ECHA emphasizes that conducting an analytical verification of exposure concentrations is a mandatory requirement of the OECD TG 202. More specifically, paragraph 23 of the OECD TG 202 specifies that "[t]*he concentration of the test substance should be measured, as a minimum, at the highest and lowest test concentration, at the beginning and end of the test*". As the test concentrations must be analytically verified at the beginning of the test, the purpose of analytical monitoring is not only to assess the stability of exposure concentrations over the exposure period but also to demonstrate that the method used to prepare the test solutions led to initial concentrations that are consistent with nominal concentrations. Conducting a new OECD TG 201 study would not provide any supporting evidence that initial exposure concentrations were satisfactory in the existing short-term toxicity study on aquatic invertebrates. Furthermore, it is noted that experimental conditions (e.g., test medium composition) differ in the OECD TG 201 and OECD TG 202 which may have an impact on the stability of exposure concentrations. Therefore, the information provided in your comments does not change the assessment outcome.

2.3. New adaptation provided in your comments on the draft decision

34 In your comments on the draft decision you provide the following documents:

- the KATE model, document "A2_01_13531-52-7_KATE2020_v3.0_2022-12-09"
- ECOSAR, document "A1_01_13531-52-7_ECOSAR_v2.2_2022-12-05".

35 ECHA therefore understands that you may intend to adapt this information under Section 1.3 of Annex XI and has assessed the provided information against the corresponding legal provision.

2.4. Assessment *of the new adaptation provided in your comments on the draft decision*

2.4.1. (Q)SAR adaptation rejected

36 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

(1) the substance must fall within the applicability domain of the model, and

(2) adequate and reliable documentation of the method must be provided.

2.4.1.1. The substance is outside the applicability domain of the model KATE

37 Under Guidance on IRs and CSA R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

38 The applicability domain of the KATE model is defined as substance having a logP ranging from -0.56 to 4.47.

39 The Substance used as input for the prediction has the following properties related to the estimation of applicability domain: logP = -1.67.

40 The substance used as input for the prediction is outside the applicability domain of the model KATE as indicated in the document "[redacted]".

41 Therefore, you have not demonstrated that the Substance falls within the applicability domain of the KATE model.

2.4.1.2. Inadequate documentation of the prediction (QPRF)

42 Guidance on IRs and CSA R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

43 For the prediction based on the KATE model, you provided an EC50 for Daphnia, the identification of the substance modelled and information on the applicability domain of the model.

44 For the prediction based on the ECOSAR model, you provided an EC50 for Daphnia, the identification of the substance modelled and the max log Kow both for the classes aliphatic amines and neutral organics.

45 In both cases, the information you provided about the predictions lacks the following elements: the identities of close analogues including considerations on how predicted and experimental data for analogues support the prediction.

46 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

47 Based on the above, your adaptation is rejected.

48 Therefore, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

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 (2012).
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

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 14 March 2022.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 6 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

ECHA took into account your comments, amended the decision by removing the request for Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.). Furthermore, on 12 January 2023, you downgraded the tonnage band of your registration from 10-100 tpa to 1-10 tonnes per year (tpa). As a result, this decision no longer addresses the following information requirements:

- Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.)
- In vitro micronucleus study (Annex VIII, Section 8.4.2.)
- in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

As a result, ECHA has amended the deadline from 24 months to 12 months.

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

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

Appendix 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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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

(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 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.

(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, in this case purity and presence of impurities

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance.

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