~~Confidential~~

Helsinki, 20 January 2022

Addressees
Registrants of borethanolamin listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
26/11/2020

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction products of monoethanolamine and boric acid (1:1)
EC number: 701-025-6
CAS number: NS

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 ***26 April 2024***.

The requested information must be generated using the Substance unless otherwise specified.

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) by oral route, in one species (rat or rabbit)

Your originally proposed tests using Reaction products of monoethanolamine and boric acid (1:3) are rejected, according to Article 40(3)(d):

- Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408)
- Extended one-generation reproductive toxicity study in rats, (EU B.56./OECD TG 443)

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

- Appendix entitled "Reasons to request information required under Annex IX of REACH".

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.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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

Appeal

This decision 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.

Approved[1] under the authority of Mike Rasenberg, 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. Sub-chronic toxicity study (90-days)

A sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH (Section 8.6.2.).

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for a Sub-chronic toxicity study (90 day) according to OECD TG 408. In the testing proposal in IUCLID section 7.5.1 and in the read-across justification provided in the category section of IUCLID, you state that *"A read-across approach is proposed between of Reaction products of monoethanolamine and boric acid (1:1) and Reaction products of monoethanolamine and boric acid (1:3), with the sub-chronic toxicity to rats in a 90-day study (via the oral route) only to be conducted on the 1:3 ratio."* Therefore, ECHA understands that the study is proposed to be conducted using the test substance Reaction products of monoethanolamine and boric acid (1:3), EC 701-024-0 (i.e. MEA polyborate 1:3).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Repeated dose toxicity. 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 a 90-day study 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 (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].

You have provided a read-across justification 'MEA Polyborates' under IUCLID section Linked Categories.

You propose read-across between the substance Reaction products of monoethanolamine and boric acid (1:3), EC No. 701-024-0 as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties:

"A read-across approach is applied [….] for the human health endpoints due to the structural

[2] ECHA Guidance R.6: QSARs and grouping of Chemicals.
[3] Read-Across Assessment Framework (RAAF). 2017
[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017

similarity of the two reaction products (Scenario 6 in ECHA's RAAF document), both resulting from the same starting materials (only the ratio is different), and through the same manufacturing process.

The existing physico-chemical, toxicological, environmental fate and ecotoxicological data already showed good correlation with no significant differences between the two ratios.".

You state that "*we expect no differences in test results of the proposed higher tier studies*."

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

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

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).

Supporting information must include bridging studies to compare properties of the Substance and source substances.

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 is necessary to confirm that both substances 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.

In your technical dossier you indicate that the available supporting information "*is primarily physico-chemical properties that influence the absorption and distribution of the substance in the body. This data provides limited information indicating a read- across approach between the reaction products of MEA Polyborate 1:1 and 1:3 for the human health endpoints is likely justified for repeated dose studies including 90-day toxicity studies. However, since no data is available on the metabolism of MEA Polyborate, additional data is needed to inform if read across is justified for repeated dose studies*". In order to increase the robustness of your proposed prediction, you indicate that "*data from dose range finding studies for the proposed developmental toxicity and 90-day toxicity studies will provide the requisite information to determine if read-across is justified for repeated dose toxicity studies*".

You further state that "*we intend to conduct developmental toxicity studies (OECD 414) in rat, on both ratios, to identify any potential differences in effects*".

ECHA agrees that there is currently no information establishing that the Substance and the source substance are likely to have similar properties after repeated administration. Additional

[5] ECHA Guidance R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

data is needed to support the proposed prediction and to compare the properties of the Substance and of the source substance.

You have proposed to use data from the proposed PNDT study and the dose range-finding studies for the developmental toxicity and 90-day toxicity studies to support the read-across.

ECHA observes that the PNDT study is conducted only in female animals following exposure to the test substance for approximately 14 days during gestation. In addition, the study does not typically cover haematology, clinical biochemistry or full organ and tissue weight and histopathology evaluated in the repeated-dose toxicity studies such as OECD TG 408. Furthermore, while you have not provided any details on the design of the proposed dose range-finding (DRF) studies, the DRF studies in general have very limited exposure duration and set of parameters examined. Rather, these studies are primarily intended to identify the highest dose which can cause toxicity but not mortality. ECHA considers that as these studies have limited duration and may only inform on a very limited set of parameters, they cannot constitute, on their own, a reliable basis for establishing that the substances may have similar properties for the sub-chronic toxicity (90-day).

As a conclusion, in the absence of any other information to support the rationale for the read-across, your read-across hypothesis as currently documented cannot be confirmed.

For these reasons, your proposed read-across adaptation is rejected.

1.3. Specification of the study design

According to the OECD TG 408, the rat is the preferred species. Therefore, the study must be conducted in the rat.

The oral route of administration is the first choice for investigating systemic toxicity (ECHA Guidance R.7a, Section R.7.5.4.3.2.).

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 with the Substance, as specified above.

You have proposed a tiered strategy with the developmental study (OECD TG 414) conducted prior the 90-day study (OECD TG 408). You propose that "*As part of this tiered strategy the developmental study (EU B.31/OECD TG414) will be conducted prior the 90-day study (OECD TG 408)*." and indicate the following reasons:

i. "*Results from one test may render a subsequent test unnecessary, as appropriate classification and labelling information and risk management measures may be able to be derived from these without other tests.*
ii. *Results from one test may help as range finders for subsequent tests and/or may help in refining the protocol.*
iii. *On the grounds of animal welfare […] Utilisation of a tiered testing strategy, in which additional tests are potentially avoided dependent on the results of preceding tests, is desirable and consistent with the aims and objectives of REACH*."

Regarding points i. and iii. above, ECHA points out that the information requirements of Annex IX, 8.6.2 and 8.7.2 for a sub-chronic toxicity study and a pre-natal developmental toxicity study, respectively, cannot be adapted based on the outcome of the other study.

Regarding point ii. and the use of the PNDT as a dose range finder for the sub-chronic toxicity study (90-day), ECHA observes that the PNDT study is conducted only in pregnant female animals following exposure to the test substance for approximately 14 days during gestation. Therefore, this study may not provide reliable information on the tolerability of the virgin females and males to the Substance.

Despite the above, ECHA considers that you are free to perform the testing sequentially as long as you provide the requested information by the deadline set in this decision.

In your comments to the draft decision, you agree that repeated dose data are needed to justify the proposed read-across testing strategy for the sub-chronic toxicity study, and that the developmental toxicity data from an OECD 414 study in pregnant females has limited utility for the design or conduct of a sub-chronic OECD 408 study (90 day). You have clarified your testing strategy and, to substantiate the read-across approach, you propose to conduct extended dose range finding (DRF) studies (28-day) with the target and the source substances supported by the OECD 414 studies (bridging studies). You indicate that depending on the findings in bridging studies, the 90-day study would be conducted with either one (worst case) or with both the source and the target substances.

However, you have not provided any of the proposed supporting information. Therefore, as this strategy relies on a read-across approach that has not yet been fully described and justified, as well as on data which is yet to be generated for the proposed source substance and the Substance (bridging studies), no conclusion on the compliance of the proposed adaptation can be made.

2. Pre-natal developmental toxicity study

A pre-natal developmental toxicity (PNDT) study (OECD 414) in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for a PNDT study according to OECD TG 414 by the oral route with the Substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA agrees that a PNDT study in a first species is necessary.

1.2. Specification of the study design

You proposed testing in the rat as a first species. You may select between the rat or the rabbit because both are preferred species under the OECD TG 414 (ECHA Guidance R.7a, Section R.7.6.2.3.2.).

You proposed testing by the oral route. ECHA agrees with your proposal because this route of administration is the most appropriate to investigate reproductive toxicity (ECHA Guidance R.7a, Section R.7.6.2.3.2.).

1.3. Outcome

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

In your comments to the draft decision, you agree to conduct the study as requested. The proposed sequential testing strategy is addressed above under section 1, Sub-chronic toxicity study (90-days).

3. 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.

You have indicated that the "*Testing of the Extended One Generation Reproductive Toxicity of rats (via the oral route) on MEA Polyborates 1:3 will address the requirement of Section 8.7.1 of Annex VIII of REACH.*". However, currently your dossier does not contain any repeat dose toxicity studies or other evidence which indicates that the Substance causes adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Therefore, there is no need for an EOGRTS.

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for an EOGRT study according to OECD TG 443 with the analogue substance Reaction products of monoethanolamine and boric acid (1:3) (EC No 701-024-0).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. 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 considers that an EOGRTS is not necessary at this tonnage band on the basis of the information currently available.

1.2. Outcome

Under Article 40(3)(d) of REACH, the proposed test is rejected.

In your comments to the draft decision, you agree that as there is currently no data in the dossier indicating that the Substance, MEA polyborate 1:1, causes adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity, an EOGRTS is not necessary.

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[6].

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:

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) 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

a) 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.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (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[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix C: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 4 July 2019, following the necessary clarification of the identity of your substance.

ECHA held a third party consultation for the testing proposal(s) from 27 January 2020 until 12 March 2020. ECHA did not receive information from third parties. No further testing proposals were submitted following the dossier update of 26 November 2020.

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 within the notification period.

ECHA took into account your comments and amended the deadline.

Deadline to submit the requested information in this decision

In your comments to the draft decision, you have indicated that the provided deadline of 18 months is not sufficient to finalise the requested studies. You have provided documentary evidence from the CROs indicating that 24 months are required to conduct the requested studies, considering capacity and administrative issues. On this basis, ECHA has extended the deadline with six months from 18 months to 24 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 D: List of references - ECHA Guidance[8] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[9]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[10]

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.

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[11]
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.

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

Appendix E: 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
[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.