EUROPEAN CHEMICALS AGENCY

Helsinki, 4 July 2019

Addressee: [redacted]

Decision number: TPE-D-2114465594-39-01/F
Substance name: Propylidynetrimethanol, propoxylated
EC number: 500-041-9
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/10/2018
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 409) using the analogue substance Ethane-1,2-diol, propoxylated (EC 500-078-0) is rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the registered substance.**

While your originally proposed test for Pre-natal developmental toxicity study (EU B.31./OECD TG 414) using the analogue substance Ethane-1,2-diol, propoxylated (EC 500-078-0) is rejected, you are requested to perform:

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbits or rats), oral route using the registered substance.**

You are required to submit the requested information in an updated registration dossier by **12 July 2021** except for the information requested under point 1 for a Sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **11 January 2021**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

This decision does not address the information requirement of the Extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. of the REACH Regulation. The results of the Sub-chronic toxicity study (90-day) will be used, among other relevant information, to decide on the study design of the Extended one generation reproductive

toxicity study. Therefore, your testing proposal for Extended one-generation reproductive toxicity study will be addressed after having received the results of the Sub-chronic toxicity study (90-day).

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] by Wim De Coen, Head of Unit, 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 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the testing proposals related to the following endpoints:

- Sub-chronic toxicity study (90 days)
- Pre-natal developmental toxicity study in a second species

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

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance Propylidynetrimethanol, propoxylated ('the target substance') using data of a structurally similar substance Ethane- 1,2-diol, propoxylated (EC no 500-078-0) (hereafter the 'source substance').

While you have not provided any specific read-across documentation, you included in the registration dossier a document entitled "Proposals for further testing for the NLP 'polyols'". In that document, and in the read-across discussion you have included in the endpoint study summaries in IUCLID, you refer to the grouping of substances, as presented in another document [redacted] That document was however not attached to the dossier, originally assessed by ECHA for the draft decision (Submission number: [redacted] Submission date: 14/06/2018).

However, in your comments on the draft decision, you included several documents supporting your grouping and read-across approach. In addition, you updated your dossier with the current submission (Submission number: [redacted] and Submission date: 31/10/2018) with those documents, which ECHA has assessed for the draft decision.

Read-across hypothesis and category definition

You define your category as "*The target substances are short chain oligomers formed from core molecules containing multiple hydroxyl or amino functional groups or a combination of the two. These functional groups are alkoxylated with propylene oxide or ethylene oxide. The alkoxylation of the core molecules results in multiple free terminal hydroxyl groups, and are therefore these substances are termed as "polyols".*

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: "[redacted] *(2007) set out justification for an initial grouping of all oligomers and polymers using a named core substance, with varying numbers of attached propoxy groups (or propoxy and ethoxy groups). The repeating unit is essentially non-toxic. The properties of the core substance and the repeating unit should be reflected in the oligomers and polymers. If there are toxic properties associated with a core substance, these properties should reduce with increasing numbers of repeating units (i.e. increasing molecular weight)".* Furthermore, you state: "*The biological activity inherent in the members of this category is similar across all endpoints. The available data demonstrates a pattern of similar toxicological properties indicating that the members of the category possess low potential for toxicological hazard including anticipated breakdown products and metabolites*".

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

As an integral part of this prediction, you propose that the source and target substances have similar properties for the above-mentioned information requirements. :*"Since the members of this category have a variety of structures with various anticipated breakdown products and metabolites, Scenario 6 of the ECHA's read-across assessment framework (RAAF, ECHA 2017) (different substances with qualitatively similar properties) was chosen for as the basis of justification for this category"*.

ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is that the structural similarity between the source and target substance is a sufficient basis for predicting the properties of the target substance. Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why a prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

ECHA observes several deficiencies of the read-across adaptation as listed below, and thus there is no basis to predict properties of the target substance from the source substance. First of all, you have not demonstrated why the proposed source substance is the most appropriate substance to be used instead of the target substance when performing the proposed tests. Therefore the choice of source substance cannot be verified.

Furthermore:

A. The impact of the differences in the molecular structures of the source and target substances on physico-chemical or toxicological properties is speculated on in the read-across justification documents which were provided during the commenting phase. Aspects relating to absorption and metabolism of the source and target substances are discussed, but there is no supporting evidence such as conclusive toxicokinetic data from studies on both source and target substances included in the dossier to prove the proposed outcome. In addition, many studies referred to in the category justification document are inconclusive with regard to the likely metabolic mode of action and metabolites of the registered substance, since the tests were conducted with polymers of three and more linear alkoxy repetitions, in contrast to less than three linear alkoxy repeates per chain/arm of the target substance.
B. According to your comments, "*the NLP consortium would like to draw your attention to the metabolism studies that are carried out to prove that the grouping approach is mechanistically justified*". However, the information is currently not available and if submitted, it will be reviewed after the deadline indicated in this decision has passed. Therefore, rapid "(bio)transformation to common compounds", which ensures negligible systemic exposure to the parent compound, has not been demonstrated. Consequently, scenarios 1, 3, 5 in ECHA's read-across assessment framework (RAAF, ECHA 2017) are not applicable.
C. In the absence or in case of hypothesis failure of A, above, there is no (endpoint-specific) comparative toxicological data available to demonstrate that "different compounds have qualitatively similar properties" (scenarios 2, 4 and 6 of the RAAF). In particular, there are no results from e.g. sub-acute toxicity studies with both source and target substance that would enable a comparison of (systemic) toxicological profiles. In addition to the absence of qualitative considerations, also no quantification is possible to reliably predict properties of the target substance.

On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met. Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation and your proposal to use the analogue substance Ethane- 1,2-diol, propoxylated (EC no 500-078-0) as test material in the proposed tests is rejected.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

a) Examination of the testing proposal

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 409 with the analogue substance Ethane-1,2-diol, propoxylated (EC No 500-078-0).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that 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 has evaluated your proposal to perform the test with the analogue substance Ethane-1,2-diol, propoxylated (EC No 500-078-0). However, as explained above in Appendix 1, section 'Grouping of substances and read-across approach' of this decision, your proposal to perform the test with this analogue substance is rejected.

In your comments on the draft decision you disagreed with the rejection of the read-across for this endpoint. You updated your dossier with further documents describing your grouping and read-across approach. ECHA has assessed the documentation, and rejects your adaptations according to Annex XI, Section 1.5. (see Appendix 1, section 'Grouping of substances and read-across approach' of this decision), and did not amend the request. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure. Furthermore, ECHA points out that no repeated dose toxicity study by the oral route is available. Hence, the test shall be performed by the oral route.

Therefore, ECHA considers that a study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

The rat is the preferred species for sub-chronic toxicity tests. ECHA considers this species as being appropriate and testing should be performed with the rat. The test method OECD TG 408 is designed for tests with rodent species, whereas the test method OECD TG 409 is designed for tests with non-rodent species. Therefore, the test shall be performed using the test method OECD TG 408.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 1: The third party has indicated that the studies should be performed in a step-wise manner to avoid unnecessary testing. ECHA agrees with the comment and the timeline has been set to allow for sequential testing. The testing proposal for Extended one-generation reproductive toxicity study will be addressed only after having received the results of the Sub-chronic toxicity study (90-day).

Third party information 2: The third party has indicated "*The substance Propylidynetrimethanol, propoxylated (EC 500-041-9) is part of a broader category. The testing is proposed with another substance of this category: Ethane- 1,2-diol, propoxylated (EC 500-078-0). The justification for applying the results of the proposed testing to other category members by using read-across is included in the dossier. This justification is currently being strengthened further by the NLP Polyols Consortium, by generating additional experimental metabolism data on the individual substances.*
This work is estimated to be completed in 2020. Once this additional information becomes available, it will be incorporated into the dossier."

ECHA notes that it is your responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5 of the REACH Regulation. Therefore, you may assess whether you can justify a read-across as suggested by the third party, for the broader category. If an information requirement can be met by way of adaptation, you may include the adaptation argument with all necessary documentation according to Annex XI, Section 1.5 in the relevant updated registration(s).

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out a study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) while your originally proposed test for Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 409) with the analogue substance Ethane-1,2-diol, propoxylated (EC No 500-078-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration:

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (Annex X, 8.7.3.). However, this testing proposal is not addressed in this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the Extended one-generation reproductive toxicity study. Therefore, you are required to perform the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your testing proposal for the Extended one-generation reproductive toxicity study. The updated testing proposal should include a justification for the design of the Extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the Sub-chronic toxicity study (90-day).

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

a) Examination of the testing proposal

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The registration dossier contains a pre-natal developmental toxicity study in rats in a first species, performed with the analogue substance Ethane-1,2-diol, propoxylated (EC no 500-078-0). In its draft decision on a compliance check of the registration dossier of Propylidynetrimethanol, propoxylated (Communication number CCH-D-2114442414-56-01/D), ECHA rejected the read-across to the analogue substance and requested you to perform a pre-natal developmental toxicity study with the registered substance in a first species (rat or rabbit) (Annex IX, Section 8.7.2.). However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbit) according to OECD TG 414 with the analogue substance Ethane-1,2-diol, propoxylated (EC No 500-078-0).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that 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 has evaluated your testing proposal to perform the test with the analogue substance Ethane-1,2-diol, propoxylated (EC no 500-078-0). However, as explained above in Appendix 1, section 'Grouping of substances and read-across approach' of this decision, your proposal to perform the test with the analogue substance is rejected.

In your comments on the draft decision you disagreed with the rejection of the read-across for this endpoint. You updated your dossier with further documents describing your grouping and read-across approach. ECHA has assessed the documentation, and rejects your adaptations according to Annex XI, Section 1.5. (see Appendix 1, section 'Grouping of substances and read-across approach' of this decision), and did not amend the request.

ECHA considers that a study performed with the registered substance is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

According to the test method OECD 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rabbit or rat as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

b) Consideration of the information received during third party consultation

Third party information 1: As already discussed under point 1.b) above, ECHA received third party information concerning the testing proposal during the third party consultation, which relates to a step-wise approach to the prenatal developmental toxicity tests in the two species. ECHA notes that the timeline in this decision has been set to allow for sequential testing of the pre-natal developmental toxicity study requests made on the first species in a separate decision **CCH-D-2114465595-37-01/F** on a compliance check on the registered substance, and the second species request in this decision.

Third party information 2: The third party has indicated "*The substance Propylidynetrimethanol, propoxylated (EC 500-041-9) is part of a broader category. The testing is proposed with another substance of this category: Ethane- 1,2-diol, propoxylated (EC 500-078-0). The justification for applying the results of the proposed testing to other category members by using read-across is included in the dossier. This justification is currently being strengthened further by the NLP Polyols Consortium, by generating additional experimental metabolism data on the individual substances. This work is estimated to be completed in 2020. Once this additional information becomes available, it will be incorporated into the dossier.*"

ECHA notes that it is your responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5 of the REACH Regulation. Therefore, you may assess whether you can justify a read-across as suggested by the third party, for the broader category. If an information requirement can be met by way of adaptation, you may include the adaptation argument with all necessary documentation according to Annex XI, Section 1.5 in the relevant updated registration(s).

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are thus requested to carry out a study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit or rat), oral route (test method: OECD TG 414) while your originally proposed test for a Pre-natal developmental toxicity study in a second species (rabbit), oral route (test method: OECD TG 414) with the analogue substance Ethane-1,2-diol, propoxylated (EC No 500-078-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

d) *Notes for your consideration*

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species (requested in a separate decision **CCH-D-2114465595-37-01/F** on a compliance check on the registered substance), with all other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation justification.

Deadline to submit the requested information

In the draft decision communicated to you, the time indicated to provide the requested information was 12 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 18 months. You sought to justify this request by explaining that the time span of 12 months for conducting a sub-chronic toxicity study (90-day), oral route (OECD TG 408) is rather challenging and a 18-month time line for the sub-chronic toxicity study would be more adequate. You included proposals from two testing laboratories, presenting their study schedules. ECHA has evaluated your request and the proposals from the laboratories and considers your justifications acceptable. Therefore, ECHA has granted the request and set the deadline for this specific test to 18 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 14 June 2018.

ECHA held a third party consultation for the testing proposals from 5 July 2018 until 20 August 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **7 November 2018**, 30 calendar days after the end of the commenting period.

You updated your registration on 31 October 2018. ECHA took the information in the updated registration into account, and did not amend the draft decision. The updated information is reflected in the Reasons (Appendix 1).

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, 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 but amended the deadline.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.