EUROPEAN CHEMICALS AGENCY

Helsinki, 4 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114465595-37-01/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 COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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 registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 1. has negative results;**

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You have to submit the requested information in an updated registration dossier by **13 July 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of 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.

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

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (Genetic toxicity *in vitro*, and Developmental toxicity / teratogenicity).

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 several endpoints:

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

[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.

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.

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 structurally similar substances Glycerol, propoxylated (EC no 500-044-5), D-Glucitol, propoxylated (EC no 500-118-7), 2,2',2''-Nitrilotriethanol, propoxylated (EC no 500-094-8), Propylidynetrimethanol, ethoxylated (EC no 500-110-3) and Ethane-1,2-diol, propoxylated (EC no 500-078-0) (hereafter the 'source substances').

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 is 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 those documents with the current submission (Submission number: [redacted] and Submission date: 31/10/2018), 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*

[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).

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*".

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 substances 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.

More specifically, 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 substances:

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. In the IUCLID endpoint study summary on Genetic toxicity *in vitro* there is a statement *"[...] 2, 2', 2''-nitrilotriethanol, propoxylated is the most bioavailable of the polyols linked by an ether group"*. However, no experimental data is provided to support this claim.
C. 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 only 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.

D. 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.

Furthermore, you have not demonstrated why the proposed source substances are the most appropriate source substances for the toxicological endpoints. Therefore, the choice of all the source substances cannot be verified.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered 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.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

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 as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for *in vitro* Chromosomal Aberration Tests (OECD TG 473, GLP) with the analogue substances Glycerol, propoxylated (EC no 500-044-5), D-Glucitol, propoxylated (EC no 500-118-7), 2, 2', 2''-Nitrilotriethanol, propoxylated (EC no 500-094-8), and Propylidynetrimethanol, ethoxylated (EC no 500-110-3).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments on the draft decision, you agreed to perform the requested test, with the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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 an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for In Vitro Mammalian Cell Gene Mutation Tests (OECD TG 476, GLP) with the analogue substances 2, 2', 2''-Nitrilotriethanol, propoxylated (EC no 500-094-8), and Propylidynetrimethanol, ethoxylated (EC no 500-110-3).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments on the draft decision, you agreed to perform the requested test, with the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 1. has negative results.

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Pre-natal Developmental Toxicity Study (OECD TG 414, GLP) 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 adaptation of the information requirement 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.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

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. However, this

compliance check decision does not contain any request for a sub-chronic toxicity study. Therefore, ECHA has not modified the deadline of this compliance decision. However, the corresponding testing proposal decision does contain a sub-chronic toxicity study (90-day), oral route (OECD TG 408) and due to the information provided, the deadline for this study has been extended to 18 months.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. However, due to your accepted submitted dossier update for the corresponding testing proposal draft decision, your submitted dossier update was also assessed for this compliance check draft decision.

The compliance check was initiated on 8 May 2018.

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 request(s) or 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present 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 your Member State.

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.