EUROPEAN CHEMICALS AGENCY

Helsinki, 27 October 2016

Addressee: [redacted]

Decision number: TPE-D-2114347176-48-01/F
Substance name: 2-Propyn-1-ol, reaction product with 1-2.5 moles of oxirane
EC number: 941-793-1
CAS RN: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23.03.2015
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408) using the analogue substance 2-propyn-1-ol compound with methyloxirane (CAS RN 38172-91-7) is rejected, you are requested to perform:

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

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **4 May 2018**. You shall also update the chemical safety report, where relevant.

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

Appeal

Applicable only for the final decision: 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, shall 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 Claudio Carlon, Head of Unit, Evaluation E2

[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

0. Grouping of substances and read-across approach

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance 2-Propyn-1-ol, reaction product with 1-2.5 moles of oxirane (EC No 941-793-1; hereafter referred to as "target substance"), proposed to be performed with a source substance 2-propyn-1-ol compound with methyloxirane (CAS RN 38172-91-7). ECHA has considered first the scientific validity of the read-across hypothesis (preliminary considerations below), before assessing the testing proposed.

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

0.1 Description of the grouping and read-across approach proposed by you

You have provided a testing proposal for an oral sub-chronic study according OECD 408 in rats, gavage administration with the analogue substance 2-propyn-1-ol compound with methyloxirane (CAS RN 38172-91-7) to meet the the standard information requirement for a sub-chronic study (90 days; Annex IX, Section 8.6.2.) by applying a read-across adaptation following REACH Annex XI, Section 1.5.

In your justification for the analogue read-across approach, you have drawn the following conclusion: "in accordance with Article 13 (1) of Regulation (EC) No 1907/2006, "*information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)." According to the general rules for grouping of substances and read-across approach laid down in Annex XI, Item 1.5, of Regulation (EC) No 1907/2006, substances may be considered as read across source substance if their physico-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. The source substance used here is considered to apply to these general rules and the similarity is justified on basis molecular structure, physico-chemical properties and toxicological profile, supported by QSAR calculation. In detail there is convincing evidence that these source substances is adequate to be used as read across information source based on the following key points:*

(i) Common route of synthesis: derived from the same linear Alkohol (2-Propyn-1-ol) which is epoxylated or propoxylated.
(ii) Similar structural features: ethoxylated or propoxylated Propargylalcohol
(iii) Similar physico-chemical properties: log Pow < 3, low vapour pressure, very high or high water solubility.
(iv) Common (as far as possible) toxicological profile: Comparable acute toxicity and same irritation behaviour.

(v) Common metabolic pathways: Based on comparable physico-chemical properties a same pathway can be expected."

ECHA considers this as the hypothesis under which you make predictions for subchronic toxicity.

0.2 Information/documentation submitted to support the grouping and read-across hypothesis

You have provided a read-across justification as a separate document attachment to the CSR.

In addition you have provided a study record on a dose-range finding study for the OECD TG 422 screening study ([redacted], rel. 2) performed with the analogue substance 2-propyn-1-ol compound with methyloxirane (CAS RN 38172-91-7), and a study record on the OECD TG 422 screening study study ([redacted], rel. 1) performed with the same analogue substance.

0.3 ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

ECHA understands that the read-across approach for repeated dose toxicity is based on structural similarity ("*the only difference between the target and source substance is a methyl group which is attached to the ethoxygroup*"), on similar physico-chemical properties and on similarities in acute toxicity and skin and eye irritation/corrosion for which information on source and target substance have been compared in the read-across justification document.

With regard to the proposed predictions ECHA has the following observations:

(i) Substance characterisation of source and target substances

ECHA notes that the target substance is a UVCB substance consisting of 2-propyn-1-ol alcohols with variying degree of ethoxylation. The ranges of these constituents are relatively wide. The target substance seems to be also a UVCB substance consisting of 2-propyn-1-ol alcohols with mexthoxyirane and other constituents. The source substances used in the OECD TG 422 screening study provided consists of propanol with methyloxirane, water, and propylene glycol and higher alcoxylated products. However, the analogue/read-across justification document submitted does not contain information regarding the composition of the source substance. Furthermore, the comparison including the composition of the two substances has not been made. In addition, the structural similarity suggested in the read-across justification document concerns "some representative structures", according to you.

Thus, it is clear that there are structural differences, which have not been addressed by you and the multi-constituent nature of these two substances severely limits the possibility of reliable read-across.

Currently the composition of the target substance and its impurity profile cannot be sufficiently assessed using the information provided in the registration dossier and the suitability of the substances for read-across purposes cannot be verified. Therefore ECHA cannot reach a conclusion whether the source substances can be used to predict properties for the registered substance.

(ii) Structural similarity and dissimilarity

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA notes the following observations:
You conclude that the only difference between the target and source substance is a methyl group which is attached to the ethoxygroup of the source substance and therefore, "*structure concerned behaviour is assumed*".

ECHA notes that there seems to be a relatively close structural similarity, but only between the main constituents of source and target substance. The main consituent of the source substance has a methyl-group, which is absent in the main constituent of target substance. However, you did not justify adequately whether the differences in the methy group could bring divergent outcomes in terms of predicting toxicological properties for the source substance in comparison to the target substance.

Furthermore, there are other constituents in both substances, and a proper comparison - to support/address the structural similarity - of the two substances, is missing. As indicated above, the chemical composition of the source substance is different from that of the target substance. However, you did not justify adequately whether the differences in the composition could bring divergent outcomes in terms of predicting toxicological properties for the source substance in comparison to the target substance.

ECHA concludes that you have not addressed the obvious structural differences between the source substances and the target substance and did not explain why those differences would not lead to differences in the toxicity profile of target and source substances and thus affect the possibility to predict the properties of the target substance from the data of the source substance.

(iii) Support of a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.* One prerequisite for a prediction based on read-across therefore is that the substances involved are structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

There is no information on systemic repeated dose toxicity study provided with both substances to support the proposed read-across for repeated dose toxicity. In fact there is no such data on the target substances of the read-across. The OECD TG 422 screening study provided (and the dose range finding study for 14 days) with the source substance are the only repeated dose toxicity studies available in the registration dossier. Therefore, it can be concluded that the proposed read-across approach for repeated dose toxicity is not supported by any relevant toxicological data derived with the target substance.

ECHA concludes that while similarity is observed on relevant physico chemical data, acute toxicity, skin and eye irritation/corrosion, the presented evidence of toxicological information on repeated dose toxicity is insufficient and does not allow an assessment of

whether human health effects (repeated dose toxicity) of the target substance can be predicted from the source substance. Therefore it cannot be verified that the proposed group/analogue substance(s) can be used to predict properties of the registered substance.

(iv)Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

No data is given for toxicokinetics of the two substances. Only theoretical and preliminary assumptions are presented. You assume that "*Due to the similar phys.-chem. values and structure information of both source and target molecule the assumed kinetic behaviour is comparable*". The registration dossier does not have repeated dose toxicity study with the target substance (e.g. a 28 day study) to compare the systemic availability of the target substance with the source substance.

Therefore, ECHA concludes that you did not address important aspects such as the toxicokinetics of the parent substance and their metabolic fate / (bio)tranformation and the resulting possible difference in the metabolite profile. Consequently, it is not possible to verify the substances which are likely to govern the toxicity profiles of source and target substances.

In the absence of such information ECHA therefore considers that there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

0.4 Conclusion on the read-across approach

Based on the data submitted by you, ECHA concludes that you have not provided adequate and reliable information to demonstrate that the read-across approach is plausible for the endpoints in consideration.
As explained above in this Appendix, ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the the adaptation for the sub-chronic toxicity study does not comply with the general rules of adaptation as set out in Annex XI, 1.5..

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

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 EU B.26./OECD TG 408 with the analogue substance 2-propyn-1-ol compound with methyloxirane (CAS RN 38172-91-7).

ECHA has evaluated your proposal to perform the test with the analogue substance 2-propyn-1-ol compound with methyloxirane (CAS RN 38172-91-7). However, as explained above in Appendix 1, section 0 of this decision, the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

You proposed testing by the oral route. 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 4.1, October 2015) 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, the exposure concentrations reported in the chemical safety report for the inhalation route is low (maximum 1.94 mg/m^3). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408), while your originally proposed test for Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408) in rats using the analogue substance 2-propyn-1-ol compound with methyloxirane (CAS 38172-91-7) is rejected according to Article 40(3)(d) of the REACH Regulation.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 23 March 2015.

ECHA held a third party consultation for the testing proposal(s) from 17 April 2015 until 4 June 2015. ECHA did not receive information from third parties.

The examination of the testing proposal was initiated on 28 January 2016.

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

On 18 May 2016 ECHA notified you of the draft decision and invited you to provide comments. You did not provide comments within the timeline indicated by ECHA.

On 8 September 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.