EUROPEAN CHEMICALS AGENCY

Helsinki, 20 August 2019

Addressee: [redacted]

Decision number: TPE-D-2114479062-50-01/F
Substance name: Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C11-17 and C17 unsatd. alkyl) derivs. and sodium hydroxide and 2-propenoic acid
EC number: 946-533-0
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18/12/2017
Registered tonnage band: 100-1000

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 Pre-natal developmental toxicity study (EU B.31./OECD TG 414) with the analogue substance Amphoacetates C8-C18 (EC no. 931-291-0) is rejected, you are requested to perform:

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

You have to submit the requested information in an updated registration dossier by ***27 August 2020***. You also have to update the chemical safety report, where relevant.

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.

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 for the registered substance Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C11-17 and C17 unsatd. alkyl) derivs. and sodium hydroxide and 2-propenoic acid (Amphopropionates C12-C18), (EC no. 946-533-0); hereafter referred to as "target substance", proposed to be performed with a source substance Amphoacetates C8-C18 (EC no. 931-291-0) on the submitted read-across justification. ECHA has considered first the scientific validity of the read-across hypothesis (preliminary considerations below), before assessing the testing proposed (section 1 below).

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

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

You have proposed to cover the standard information requirement(s) for a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by performing the test with a source substance Amphoacetates C8-C18 (EC no. 931-291-0).

You have provided the following hypothesis/justification:

"This read-across is based on the hypothesis that source and target substances have similar toxicological properties because:
• they are manufactured from similar / identical precursors under similar conditions
• they share structural similarities with common functional groups: tertiary amines, amides, fatty acid chains with comparable length, and short chain carboxylic acids (acetic / propenoic) of comparable length.

Therefore, read-across from the existing acute toxicity, sensitisation, genotoxicity, ecotoxicity, repeated dose and reproductive toxicity studies on the source substances is considered as an appropriate adaptation to the standard information requirements of the REACH Regulation for the target substance, in accordance with the provisions of Annex XI, 1.5 of the REACH Regulation."

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

You have provided a read-across justification as a separate attachment in the registration. Your detailed read-across justification related to pre-natal developmental toxicity can be summarised as follows:

"The structural similarities between the source and the target substances [...] support the read-across hypothesis. Adequate and reliable scientific information indicates that the source and target substances have similar (eco)toxicity profiles."

Further details on structural similarity:

- *"The target and source substances are amphiphilic molecules containing similar amine headgroups and fatty acid chains with comparable C chain distribustions. The target substance Amphopropionates C12-18 and the source substance Amphoacetates C8-C18 have a comparable C chain distribution with C12 representing the majority, whereas the source substance Amphopropionate C8 contains shorter C chains."*

- *"The target substance Amphopropionates C12-18 and the source substance Amphopropionate C8 are manufactured using 2-propenoic acid and thus contain propionate functions (mono- or dipropionate), whereas the source substance Amphoacetates C8-C18 is manufactured using chloroacetic acid and thus contains acetate functions (mono- or diacetate)."*

- *"The source substance Amphopropionate C8 contains shorter C chains, whereas the major C chain in the target substance is C12. In general the absorption declines with increasing alkyl chain length (Ramirez et al. 2001). Therefore the source substances with the shorter alkyl chain lengths are assumed to represent a worst-case scenario due to higher absorption rates than the target substance."*

- *"In contrast to the source substance Amphopropionate C8, the target substance Amphopropionates C12-18 as well as the source substance Amphoacetates C8-C18 contain some amounts of unsaturated C18 chains. An increase in the degree of unsaturation may lead to a slightly higher irritation potential (HERA, 2002; Stillman, 1975; Aungst, 1989). Apart from that, fatty acids irrespective of their degree of unsaturation are in general non-toxic. Irritation studies are available for the target substance itself, thus, for other endpoints, this difference in composition is of no toxicological relevance."*

- *"The target substance Amphopropionates C12-18 contains propionate functions, whereas the source substance Amphoacetates C8-C18 contains acetate functions. The shorter acetate chains might lead to slightly higher absorption."*

"There are no indications for a classification for developmental toxicity and teratogenicity at this time. Evaluation will be reconsidered based on the outcome of the prenatal developmental study with the source substance Amphoacetates C8-C18. The results from this study will be appropriate to cover the endpoint prenatal developmental toxicity based on structural similarities as well as on similar toxicity profiles with regard to acute toxicity and genotoxicity."

In support of your read-across justification you have submitted data matrices covering physicochemical properties, information on classification and labelling, ecotoxicity and environmental fate endpoints, and human health endpoints, for the target substance and two source substances, Amphopropionate C8 (EC no. 264-761-2) and Amphoacetates C8-C18 (EC no. 931-291-0).

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

Based on the information provided, ECHA understands that the proposed read-across hypothesis is based on structural similarity and similar toxicological properties of the target and source substances.

Structural similarity and dissimilarity

ECHA observes that you have provided information to demonstrate and discuss the structural similarities and differences between the target and source substances (as quoted above). ECHA notes however that your assumptions have not been confirmed by experimental data on the relevant substances, and in particular not in relation to pre-natal developmental toxicity. For this specific endpoint it is well known that also minor structural differences may severely impact the toxicity of a substance.

Hence, ECHA concludes that you have not addressed sufficiently the structural differences between the target and the source substances and did not explain why those differences would not lead to differences in the toxicity profile of the registered and source substances in terms of pre-natal developmental toxicity. Given the structural differences between the target and source substances, ECHA considers that there is presently not an adequate/sufficient basis for predicting the properties of the target substance from the source substances.

Toxicological data

In your read-across justification you state that:

- *"No experimental data are available for the target substance Amphopropionate C12 - 18. However, reliable and relevant data on effects to reproductive organs are available with the closely related source substance Amphopropionate C8. In the repeated dose toxicity study performed according to OECD Guideline 407 up to and including the limit dose level of 1000 mg/kg bw/d, no indication of any effects of the substance to reproductive organs were observed."*

- *"No data are available on prenatal developmental toxicity."*

You have proposed that the source substance, Amphoacetates C8-C18 has similar toxicity regarding pre-natal developmental toxicity and therefore the properties of the target substance can be predicted from data obtained from the source substance, Amphoacetates C8-C18. However, ECHA concludes that a comparison of toxicological profiles of the substances regarding pre-natal developmental toxicity cannot be done due to lack of any developmental toxicity data, for example from "reproduction/developmental screening" studies (OECD TG 421 or 422), on the target and the source substances. There is no reproductive toxicity data on the registered substance, and only data on reproductive organs from a "repeated dose toxicity study" (OECD TG 407) for the source substance, Amphopropionate C8. The study protocol OECD TG 407 does not, however, include mating of the animals. Hence, it cannot be used to inform about reproductive performance or pre-natal developmental toxicity.

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, Amphoacetates C8-C18.

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 criteria of Annex XI, 1.5. are met and that read-across approach is plausible to meet the information requirements for pre-natal developmental toxicity (Annex IX, section 8.7.2). Consequently, the testing proposed on the source substance is not appropriate to fulfil the information requirements for the substance subject to the present decision.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first 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 pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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 pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route with the analogue substance Amphoacetates C8-C18 (EC no. 931-291-0).

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 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 has evaluated your proposal to perform the test with the analogue substance Amphoacetates C8-C18 (EC no. 931-291-0). As explained above in Section 0 your read-across adaptation is rejected.

ECHA considers that a study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation. 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 consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You proposed testing by the oral route. ECHA agrees 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 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414) while your originally proposed test for a pre-natal developmental

toxicity study with the analogue substance Amphoacetates C8-C18 (EC number: 931-291-0 is rejected according to Article 40(3)(d) of the REACH Regulation.

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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 18 December 2017.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 7 June 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after 21 November 2018, 30 calendar days after the end of the commenting period.

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 did not receive any comments by the end of the commenting period.

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, or to otherwise fulfil the information requirements with a valid and documented adaptation, 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.