Decision number: TPE-D-2114310497-51-01/F

Helsinki, 05 November 2015

DECISION ON TESTING PROPOSALS SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine acetate (1:1), CAS No NS (EC No 939-448-5), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine acetate (1:1), CAS No NS (EC No 939-448-5, submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408), oral route using the analogue substance, 1-Propanamine, 3-((C9-11-iso-,C10-rich)alkyloxy)- (C10i-etheramine).
- Developmental toxicity / teratogenicity study (OECD 414) using the analogue substance, 1-Propanamine, 3-((C9-11-iso-,C10-rich)alkyloxy)- (C10i-etheramine).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year.

This decision does not take into account any updates submitted after the deadline for updating (13 March 2015) communicated to the Registrant by ECHA on 4 February 2015.

This decision does not imply that the information provided by the Registrant in his 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.

ECHA received the registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 25 April 2013.

ECHA held a third party consultation for the testing proposals from 2 June 2014 until 17 July 2014. ECHA did not receive information from third parties.

On 14 November 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 1 December 2014 ECHA received comments from the Registrant on the draft decision.

On 4 March 2015 the Registrant updated his registration dossier [redacted].
The ECHA Secretariat considered the Registrant's comments and update.

On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 3 September 2015 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 proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test methods and the analogue substance [3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine] (EC No 939-485-7):

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats on the analogue substance, 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine (EC No 939-485-7);
2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route on the analogue substance, 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine (EC No 939-485-7)

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **13 November 2017** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance.

0. Read-across approach

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant and information submitted by the Registrant to support the grouping approach and read-across hypothesis

The Registrant has proposed to cover the standard information requirements for a sub-chronic toxicity (90-day) study (Annex IX, 8.6.2.) and pre-natal developmental toxicity study (Annex IX, 8.7.2.) by performing the tests with an analogue substance C10i-etheramine (EC no 939-485-7). The Registrant has provided a read-across justification document which contains the read-across hypothesis, information concerning the structures and purity of the registered and analogue substances, a table containing the molecular chemical profile and estimated properties, a summary and data matrix of the physico-chemical, environmental fate and ecotoxicological properties and classification of the substances. The Registrant has provided the following justification:

> *"The substance C10i-etheramine acetate is produced by neutralising C10i-etheramine with acetic acid. C10i-etheramine is a strong base with a pKa of about 10.14 (ChemAxon estimation). When C10ietheramine acetate dissolves in water or physiological media, the structure of the salt is broken up by water molecules surrounding the charged particles namely, the cationic C10i-etheramine and anionic acetate ions.*
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> *Following oral administration and passing through stomach and intestinal fluids, C10i-etheramine acetate will dissociate. Following the dissociation of the salt the absorption and subsequent systemic availability of the C10i-etheramine is independent of the presence of acetate. The C10i-etheramine structure is much more toxic than the acetic acid part, and therefore it is considered that toxicity profile of C10i-etheramine acetate will be fully driven by its C10i-etheramine content.*
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> *In the evaluation of systemic toxicity, acetate is not considered to contribute to the possible toxicological potential of C10i-etheramine, and thus the information available on the C10i-etheramine itself can be used for the evaluation. C10i-etheramine acetate consists of about 78 w/w% of C10i-etheramine.*
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> *Consequently, due to the identical structures no difference in chemical reactivity or metabolism profile can be expected, and human health and environmental properties will be the same. Only for local effects (on skin and other membranes) the neutralisation by acetic acid can be expected to lead to a possibly different toxicity profile, where due to the neutralisation and lower amount (74%) of C10i-etheramine present in C10i-etheramine acetate product."*
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> *"....C10i-etheramine content (78%), forms a conservative approach".*

b. 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 read-across hypothesis proposed by the Registrant is based on the dissociation of C10i-etheramine acetate (the registered substance) to C10i-etheramine (the analogue substance) and acetate. Acetate is not expected to affect the systemic toxicity and thus C10i-etheramine is claimed to drive the toxicity alone.

ECHA notes that the composition of the registered and analogue substances is similar. The major constituents are C10i-etheramine (the source substance) and C10i-etheramine acetate (the registered substance). In both substances the other constituents are of the

same type: primary alkoxy amines (etheramines C9i and C11i, all branched)/their acetate and their corresponding alcohols (primary iso-alcohols C9i, C10i and C11i, all branched), differing only in the length of the carbon chain. In case of the registered substance the different alkoxy amines form the same type of salt (acetate) as the major constituent. ECHA concludes that the alkoxy amines formed from the registered substance are similar in terms of quality and quantity to the alkoxy amines described in the composition of the analogue substance.

Based on the dissociation constant value provided by the Registrant, ECHA notes that almost complete dissociation is expected to occur immediately in the gastrointestinal tract, and consequently, systemic exposure is expected to be to *"exact same chemical substance"* as claimed by the Registrant. According to the Registrant *"acetate is not considered to contribute to the possible toxicological potential of C10i-etheramine"* and only local effects are expected. ECHA observes that no supporting data is submitted to exclude the influence of the acetate anion. Both substances are classified as Skin Corr. 1B; H314 and acetate is not expected to change significantly the corrosivity of the registered substance.

Based on the information provided by the Registrant, the purities of the registered and analogue substances are [redacted]% and [redacted]%, and typical concentrations of the main constituents are [redacted]% ([redacted]%) and [redacted] % ([redacted]%), respectively. ECHA notes that the Registrant has not addressed the impact of the [redacted]% variation in the composition of the substances on their toxicological profile. However, in any case the concentration of the main constituent (after dissociation) in the proposed source substance is higher than in the target (registered) substance and the concentrations of the other components are in a similar level. Consequently ECHA concludes that testing with the source substance would represent *"conservative approach"* as claimed by the Registrant.

c. Conclusion on the read-across approach

Therefore, ECHA considers that it is plausible that the read-across may be used to predict the properties of the registered substance from the data obtained from the proposed analogue substance C10i-etheramine (EC no 939-485-7). In the case where the tests performed in accordance with the present decision would not confirm the grouping and read-across hypothesis relied upon by the Registrant, this outcome shall not alter the obligation of the Registrant to meet the standard information requirements. Should the read-across strategy be inadequate, it is the responsibility of the Registrant to ultimately submit reliable information or adaptations which is used in a way that does not underestimate hazards of the registered substance in relation to the relevant endpoints.

ECHA therefore concludes that the read-across approach, as presented by the Registrant, can be considered plausible to meet the requirements of Annex XI, 1.5. In any case, following the update of the dossier submitting the information required in the present decision, ECHA will determine whether the documentation provided is sufficient to satisfactorily address the information requirement of Annex IX for the entire category as proposed by the Registrant. If, upon further consideration, the proposed approach does not satisfy the conditions set out in Annex XI, ECHA reserves the right to request the information necessary to fulfil the information requirements for the substance subject to the present decision.

A. Tests required pursuant to Article 40(3)

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.
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.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90 day) via the oral route (EU B.26/OECD 408) to be performed with the analogue substance 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine (EC No 939-485-7) with the following wording: *Testing is proposed on substance 1-Propanamine, 3-((C9-11-iso-,C10-rich)alkyloxy)-(Etheramine C10i) rather than on its acetate salt.*

In light of the physico-chemical properties of the substance, which is a liquid with low vapour pressure classified as corrosive to the skin, and the information provided on the uses and human exposure, i.e., no uses with spray application, ECHA considers that testing by the oral route is most appropriate.

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

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the following study using the analogue substance 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine (EC No 939-485-7) : Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408).

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

a) Examination of the testing proposal

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.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414 to be performed with the analogue substance 3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine (EC No 939-485-7)with the following wording: *Testing is proposed on substance 1-Propanamine, 3-((C9-11-iso-,C10-rich)alkyloxy)-(Etheramine C10i) rather than on its acetate salt.*

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

In light of the physico-chemical properties of the substance, which is a liquid with low vapour pressure classified as corrosive to the skin, and the information provided on the uses and human exposure, i.e., no uses with spray application, ECHA considers that testing by the oral route is most appropriate.

The Registrant did not specify the species to be used for testing. He did not specify the route for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the analogue substance [3-((C9-11-iso,C10-rich)alkyloxy)propan-1-amine (EC No 939-485-7)]: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation, E1

[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.