EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002645-72-04/F Helsinki, 20 December 2012

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

For 3-C12-14-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide, List number 931-324-9, 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 proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 3-C12-14-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide, EC No 931-324-9, by [redacted] (Registrant), latest submission number [redacted] for the tonnage band of 1000 tonnes or more per year:

- Sub-chronic oral toxicity test, repeated dose 90-day oral toxicity study in rodents (EU B.26) using analogue substance 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide.

On 18 February 2011, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposal set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposal from 1 September 2011 until 17 October 2011. ECHA did receive information from third parties (see section III below).

On 24 January 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 17 February 2012 ECHA received comments from the Registrant to ECHA's draft decision and on 27 March 2012 the Registrant updated his registration dossier.

ECHA considered the Registrant's comments received. On basis of the comments, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 19 July 2012 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 to amend the draft decision within 30 days of the receipt of the notification. Subsequently, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 22 August 2012 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposal for amendment received and decided to amend the draft decision.

On 3 September 2012 ECHA referred the draft decision to the Member State Committee.

The Registrant did not provide any comments on the proposed amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 8 October 2012 in a written procedure launched on 26 September 2012 and ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

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 to initiate a compliance check on the registration at a later stage.

II. Testing required

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test method and the analogue substance 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide:

Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2., test method: EU B.26/OECD 408).

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **20 June 2014** an update of the registration dossier containing the information required by this decision.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance on the analogue substance 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide, submitted read-across justification and data matrix and scientific information submitted by third parties.

Sub-chronic toxicity study (90-day)

a) Read-across approach

In relation to the testing proposal subject to the present decision, the Registrant has proposed using the read-across approach, in accordance with Annex XI, 1.5, and to perform the relevant test on another substance than the registered substance. ECHA has considered first the scientific validity of the proposed read-across approach, before assessing the testing proposed.

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 information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

The original draft decision sent to the Registrant contained a request to conduct the initially proposed study by using the registered substance.

The Registrant updated his dossier on 27 March 2012 and changed the testing strategy by proposing a read-across approach, i.e. testing an analogue substance instead of the registered substance in a Sub-chronic toxicity study (90-day).

In the updated dossier the Registrant provided justification for the read-across approach composition of the substance to be tested with concentration ranges a data matrix containing information on the physicochemical properties environmental fate and ecotoxicity and mammalian toxicity of the source and target substances and a certificate of analysis of the constituents and their relative concentrations in the source substance to be tested.

The registrant has proposed to test a substance with the following chemical names: Amides, C12-C18 (even numbered), N-[3-(dimethylamino) propyl], N´-oxides (common name) and 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide (IUPAC name) and provided a table to describe the substance composition. ECHA notes, that the name Amides, C12-C18 (even numbered), N-[3-(dimethylamino) propyl], N´-oxides can be used to describe the substance to be tested if the chain lengths C8-C10 are expected to be present in the substance statistically at concentrations of less than 10 %. Similarly, the chain lengths C16-C18 are expected to be present in the substance statistically at concentrations of more than 10 %. ECHA uses the name 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide to describe the substance composition provided by the Registrant in their justification for the read-across approach.

The Registrant's read-across justification is based on the following:
"*The analogue Amides, C12-C18 (even numbered), N-[3-(dimethylamino) propyl], N´-oxides which shares the same functional groups with the substance Amides, C12-C14 (even numbered), N-[3-(dimethylamino) propyl], N´-oxides, has comparable values for the relevant molecular properties. For the source substance, in the chemical structure, the RCO- is substituted by C8-C18 (predominantly C12 and C14, about 60-70% of the total) and for the target substance the RCO is substituted by C12-C14. In addition, as the functional groups are the same in the source and target substances, the toxicological effects and metabolic pathways are expected to be the same. In addition, the target substance has been self-classified based on the source substance.*"

ECHA considers that the justification given demonstrates that it is plausible that the requirements of Annex XI, section 1.5 in conjunction with article 13(1) and Annex IX, third introductory paragraph, of the REACH Regulation may be met. Specifically, adequate and reliable documentation of the applied read-across approach has been provided, and ECHA considers that there appears to be a scientific justification that human health effects for repeat-dose toxicity may be predicted from data for the substance 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide through the read-across approach. However, a final conclusion on the validity of the suggested approach to adapt the standard information requirement will only be possible when it has been demonstrated on the basis of test results that the conditions set out in Annex XI section 1.5 are met for this endpoint.

ECHA emphasises that it is the Registrant's responsibility to amend and substantiate read-across and category justification according to Annex XI, section 1.5 and to use all relevant available data.

Following the update of the dossier based on the present decision, ECHA will decide whether the documentation provided is sufficient to satisfactorily address the information requirement for the substance subject to this decision 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.

In addition, ECHA notes that the current conclusion reached on the read-across approach is valid only in relation to the substance to be tested as provided by the Registrant in the dossier. The proposed read-across approach can only be accepted provided that the substance identity information of the test sample describes the test substance accurately. Therefore, the Registrant is reminded that according to the "Sub-chronic oral toxicity test: repeated dose 90-day oral toxicity study in rodents" guideline (EU B.26), the test report shall contain the following information on the test substance: physical nature, purity and physico-chemical properties and identification data (and vehicle, if other than water). This information shall be included in the robust study summary to be submitted to ECHA by the deadline indicated under Section II. Testing required.

b) Information requirement

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 generate the data for this endpoint.

The Registrant proposed testing by the oral route. In the light of the physico-chemical properties of the registered substance and its close structural similarity to the analogous substance and the information provided on the uses and human exposure for the registered substance, ECHA considers that testing by the oral route is appropriate.

The Registrant did not specify the species to be tested. According to the test method EU B.26 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the analogue substance 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide.

c) Consideration of the information received during third party consultation

Third party information 1:

A third party has suggested testing an analogous substance instead of the registered substance and to use the generated data in a read-across approach to cover the Sub-chronic toxicity study endpoint in this registration dossier.

ECHA has evaluated the information submitted by the third party and concludes that the provided information does not fulfil the requirements for a read-across approach as stated in Annex XI, section 1.5 of the REACH regulation. Therefore, ECHA considers that the provided information is not sufficient to fulfil the information requirement for this endpoint.

Third party information 2:

A third party states that *in vitro* metabolism studies with the registered substance could give additional information for estimation of systemic toxicity without conducting the proposed oral 90-day study.

The third party has proposed a weight-of evidence / read-across approach for ECHA to consider before further tests on vertebrate animals are requested. As part of this approach, the third party refers to existing 28-day and screening studies conducted with a read-across substance Amides, coco, N-[3-(dimethylamino)propyl], N-oxides (CAS no. 68155-09-9), and provided results from 28-day, 90-day and screening studies according to OECD Guidelines 407, 408 and 422 for cocamidopropyl betaine and several amine oxides, specifically 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS 1643-20-5). In addition, the third party has presented comments on dose selection for the proposed sub-chronic toxicity (90-day) test due to the irritant/corrosive characteristics of the registered substance, and proposes that doses higher than 100 mg/kg bw/day should not be included in the 90-day study protocol. Consequently, the informative value of the proposed study would be limited.

ECHA considers that although the information provided by the third party might be scientifically valid, it is still not sufficient for ECHA to conclude that the conditions of Annex XI of the REACH Regulation are met.

Even if ECHA cannot draw a definitive conclusion from the information provided it acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities. This would require that the Registrant demonstrates a sufficient justification from several independent sources of information leading to the assumption/conclusion that a substance has or has not particular dangerous properties, according to the criteria laid down in Annex XI of the REACH Regulation.

The Registrant is reminded that according to the EU B.26/OECD 408 test guideline selection of dose levels should take into account any existing toxicological and toxicokinetic data for the test compound or related materials. Furthermore, the test guideline stipulates that highest dose levels should be chosen with the aim to induce toxicity but not death or severe suffering.

Therefore, ECHA does not consider this to be at the moment a sufficient basis to fulfil the information requirements for this endpoint.

d) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the analogue substance 3-C8-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

IV. Adequate identification of the composition of the tested material

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in the registration dossier was sufficient to confirm the identity of the registered substance for the purpose of assessing the testing proposal. It is noted, however that this information, or the information submitted by other Registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed test, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all the joint registrants of the same substance to agree with the test proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint registrant. Finally, the study must be shared by the joint registrants concerned.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. 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://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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