Helsinki, 13 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453651-51-01/F
Substance name: 3-C12-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide
EC number: 939-581-9
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26 September 2017
Registered tonnage band: Over 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.

Your testing proposals are accepted and you are requested to carry out:

1. **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 using the registered substance.**

You are additionally requested to perform:

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit or rat), oral route 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 to the REACH Regulation. 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 have to submit the requested information in an updated registration dossier by ***21 June 2021***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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 and scientific information submitted by third parties.

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

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

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.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 by the oral route.

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

You proposed testing in the rat as a first species. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits 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 solid, ECHA concludes that testing should be performed by the oral route.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has indicated that "*there is a REACH Registration Dossier for the structurally-related substance 3-C12-14-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino*

oxide (EC 931-324-9). While this substance does not include a PNDT study, the study proposed for 3-C12-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide could be used as a read-across source assuming confirmation of the testing proposal by ECHA. Using this read-across approach would avoid testing of two structurally similar substances".

ECHA acknowledges that the third party has proposed a read across approach whereby the data proposed to be generated by you on 3-C12-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide, i.e. the substance subject to this decision, might be used as source data to predict pre-natal developmental toxicity properties of the target substance 3-C12-14-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide (EC 931-324-9). However, ECHA considers that this information on potential subsequent use of the data that you proposed to generate does not constitute relevant scientific information in the context of the examination of your testing proposal.

In your comments to the draft decision you suggested a tiered testing strategy including an extended one-generation reproductive toxicity study (requested in a separate compliance check decision) and a pre-natal developmental toxicity study in rabbits as a first tier, and an intermediate dossier update for ECHA to review before proceeding to a pre-natal developmental toxicity study in rats.

ECHA stresses that the sequence for performing the tests requested in this decision and the extended one-generation reproductive toxicity study requested in a separate compliance check decision is at your discretion. The pre-natal developmental toxicity study in a first species requested in this decision and the extended one-generation reproductive toxicity study requested in a separate compliance check decision standard information requirements at your tonnage level. Therefore, the regulatory obligation to perform these studies is not influenced by the outcome of the other study. ECHA will only evaluate the received information when the deadline in the decision has passed. In addition, Pre-natal developmental toxicity studies in a second species is also a standard information requirement for your registration.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: EU B.31./OECD TG 414).

2. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

As outlined above under 1. ECHA has approved your testing proposal for a pre-natal developmental toxicity study in a first species according to OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.).

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement based on the absence of adverse effects on the reproductive organs and tissues in a reproduction/developmental screening study and in 28-day and 90-day repeated dose toxicity studies conducted with the registered substane. You also indicated that "*in a tiered approach, the test substance will be tested in a prenatal development toxicity study according to OECD 414 guideline in a first species, the rat*" and that "*data from this study will be interpreted first*". However, ECHA notes that your adaptation does neither meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2 nor the general rule for adaptation of Annex XI, Section 1.2.

Specifically, the specific rules for adaptation of Annex X, Section 8.7.2., column 2 specify that the studies listed under section 8.7 of Annex X do not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*".
This specific rule for adaptation of the standard information requirement requires three conditions to be met to waive the studies:

i. The substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available): evidence of toxicity has been reported in the 28-day and 90-day repeated dose toxicity studies. The forestomach, the kidney and urinary bladder have been identified as target organs in these studies. Therefore, ECHA considers that the criterion for absence of evidence of toxicity in any of the tests available is not met.
ii. No systemic absorption occurs via relevant routes of exposure as demonstrated by toxicokinetic data: based on physico-chemical properties of the registered substance and taking into account the available toxicological data you concluded in your assessment of the toxicokinetic properties of the registered substance that "*oral absorption is set to 100%*". ECHA considers that the effects observed in the repeated dose toxicity studies conducted with the registered substance demonstrate that the substance is systemically available after oral administration. Therefore, ECHA is of the opinion that the criterion for systemic absorption occurs via relevant routes of exposure is not met.
iii. No or no significant human exposure occurs: based on the information on the uses of the registered substance included in the technical dossier, workers and consumers exposure may occur. However, all risk characterisation ration reported in the technical dossier are inferior to [redacted]. Whilst this suggests that worker and consumer exposure may occur, the significance of such exposure with regard to the safe levels identified for this substance is questionable. Therefore ECHA considers that the criterion for no or no significant human exposure is met.

For the reasons presented above, ECHA considers that the three conditions of the specific rule for adaptation of Annex X, section 8.7 column 2 are not all met. Therefore, ECHA

concludes that the adaptation of the information requirement for a developmental toxicity study according to Annex X, section 8.7 column 2 cannot be accepted.

Furthermore, the absence of adverse effects in repeated dose toxicity studies or in a screening study for reproductive and developmental toxicity do not allow to conclude on whether the registered substance has or has not developmental toxicity properties. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected. 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 consideration, ECHA considers testing should be performed in a second species (rabbit or rats), depending on the species tested in the first pre-natal developmental toxicity study.

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 solid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you suggested a tiered testing strategy. Please see ECHA's response under Section 1. of this decision.

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 second species (rabbit or rat), oral route (test method: OECD TG 414).

Notes for your consideration

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

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.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 36 months. You sought to justify this request by suggesting a tiered testing strategy including an intermediate evaluation by ECHA and studies requested in a parallel compliance check decision. You also provided documentary evidence from testing laboratories with indicative timelines for the

performance of the requested pre-natal developmental toxicity studies in this decision and of the requested extended one-generation reproductive toxicity study in a separate compliance check decision.

The pre-natal developmental toxicity study in a first species requested in this decision and the extended one-generation reproductive toxicity study, requested in a parallel compliance check decision, can be performed simultaneously. However, considering the indicative timelines provided by the testing laboratories, ECHA has modified the deadline of the decision from the original 24 months to 30 months. The deadlines in this decision and the parallel compliance check decision are set to 30 months, each.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 26 September 2017.

ECHA held a third party consultation for the testing proposals from 26 March 2018 until 11 May 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **27 August 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 took into account your comments and did not amend the requests, but amended the deadline in the decision.

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.