EUROPEAN CHEMICALS AGENCY

Helsinki, 13 September 2018

Addressee: [redacted]

Decision number: TPE-D-2114440097-52-01/F
Substance name: 6-[(1-oxomethyloctyl)amino]hexanoic acid
EC number: 276-173-3
CAS number: 71902-23-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 24/03/2017
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.

Your testing proposal is accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the analogue substance 6-(isononanoylamino)hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1).**

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 **20 September 2019**. 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.

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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 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

The decision of ECHA is based on the examination of the testing proposals submitted by you.

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 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 6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``-nitrilotriethanol (CAS 85702-79-0).

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

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 and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance 6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``-nitrilotriethanol (CAS 85702-79-0).

Grouping and read-across approach for toxicological information

Your registration dossier contains for the developmental toxicity endpoint an adaptation argument in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach for the individual endpoint.

You have sought to adapt the required information for developmental toxicity by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration. The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

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

You have proposed to cover the standard information requirements for a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by performing the test with a source substance 6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``nitrilotriethanol (CAS No 85702-79-0).

You have provided a read-across justification as a separate attachment in the registration dossier. Furthermore you have provided a data matrix with the physico-chemical properties as well as the available human health data (acute toxicity, genetic toxicity, 7-days repeated dose range finding study, and peroxizome proliferation studies) for both, the target and source substances. In addition, in the Annex I of the read-across justification a toxicity summary on 2,2`,2``-nitrilotriethanol is provided.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group.
6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``nitrilotriethanol (CAS No 85702-79-0) and 3,5,5-trimethylhexanoic acid (CAS No 3302-10-1; hereafter source substance 2) should exhibit comparable toxicity profiles. You propose that 6-

(isononanoylamino)hexanoic acid, compound with 2,2`,2``nitrilotriethanol (CAS No 85702-79-0) is a salt of the target chemical, and 3,5,5-trimethylhexanoic acid is a presumed metabolite.

For the source substance, you further propose that when it is dissolved in an aqueous system or in a biological fluid, an immediate dissociation occurs to give the target chemical and the base, thereby explaining the expected comparable toxicity profile to that of target chemical. A significant toxicity contribution of 2,2`,2``-nitrilotriethanol is not expected.

Moreover, you support this hypothesis with comparison of existing toxicity data for the source and target substance. As an integral part of this prediction, you propose that the source and registered substance(s) have comparable toxicity profiles for the above-mentioned information requirements.

ECHA considers that all this information is your read-across hypothesis.

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

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

Based on the information provided, ECHA understands that the proposed read-across hypothesis is based on the argument that the source 6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``-nitrilotriethanol is a salt of the target chemical which when dissolved in an aqueous system or in a biological fluid, gives the target chemical and the base by an immediate dissociation. Furthermore you argue similar MoAs and toxicological properties of the target and source substances.

Given the fact that by dissociation the source substance results in the target and the base, there is clearly structural similarity. Given additionally the fact that the target and the source substances have comparable effects in a limited number of studies, then the proposed read-across approach is a plausible basis for predicting the properties of the registered substance. The source substance dissociates into the target and an additional substance, 2,2`,2``-nitrilotriethanol. Hence the properties of 2,2`,2``-nitrilotriethanol will also contribute to the human health properties of the source substance. While a summary on the toxicity of 2,2`,2``-nitrilotriethanol is provided, no study summaries were provided. This may lead to a worst case scenario in the event that 2,2`,2``-nitrilotriethanol is more toxic than the registered substance, but this is acceptable to ECHA. ECHA notes that the molecular mass of the target substance is 271.4 Da, whereas the molecular mass of the source substance is 420.6 Da, and further notes a dose ensuring exposure to sufficient target substance upon the dissociation of the source must be used. Moreover, in deriving DNELs for the target substance from studies obtained with the source substance, it will be necessary to correct for the molecular mass of source and target substance.

You have proposed that the source substance 6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``nitrilotriethanol 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. ECHA concludes that the data provided provide sufficient evidence to conclude that your hypothesis is plausible.

iii. Conclusion on the read-across approach

For the reasons as set out above, ECHA considers that this grouping and read-across approach may provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance.

Hence, this approach is considered plausible for the purpose of the testing proposal evaluation. ECHA emphasises that any final determination on the validity of the read-across, including the grouping approach proposed by you, would be premature at this point in time. The eventual validity of the read-across hypothesis and grouping approach will be reassessed once the requested information is submitted.

You proposed testing in the rat as a first species. According to the test method EU B.31./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 liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the analogue substance 6-(isononanoylamino)hexanoic acid, compound with 2,2`,2``nitrilotriethanol (CAS 85702-79-0): Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: EU B.31./OECD TG 414).

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.

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 23 January 2017.

ECHA held a third party consultation for the testing proposals from 10 March 2017 until 25 April 2017. ECHA did not receive information from third parties.

On 28 April 2017, ECHA notified you of a draft decision, which had been based on the previous registration dossier (submission number [redacted]).

However, ECHA's evaluation had not taken into account the update of your registration that you submitted on 24 March 2017 (submission number [redacted]).

As this update included relevant information, ECHA decided to re-evaluate the information submitted by you, and a new draft decision replacing the prior draft was submitted to you on **28 March 2018**.

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 carrying out the tests 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 tests must be suitable to assess these.

   Furthermore, 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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.