ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465662-44-01/F
Substance name: Isononanoic acid, C16-18 (even numbered)-alkyl esters
EC number: 601-141-6
CAS number: 111937-03-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/03/2018
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 proposal is accepted and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by **2 November 2021**. 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.

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)**

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

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral route with the following justification and specification of the study design:

*"There is already some basic information available indicating that a basic module OECD 443 is sufficient to achieve the missing information. Based on the available 90d study with extended reproduction parameter ([redacted], 2018) investigation weekly physical examinations including detailed clinical signs did not show any signs of neurotoxicity which could be correlated to the treatment with the test item. Concluding no DNT module is necessary. Further no toxicologically significant changes in hematology occurred in this study nor histopathological changes in immune correlated tissues are reportet. Hence, no further investigation of immuntoxicity is suggested. Concluding no DIT module is proposed. Additional no effects on fertility/development were only observed in a 90d study with extended reproduction ([redacted] 2018) or in a teratogenicity study ([redacted] 1997), concluding no additional cohort is proposed."*

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). 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 designs is appropriate to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to column 1 of Section 8.7.3., Annex X is required. The following refers to the specifications of this required study.

*Premating exposure duration and dose-level setting*

You propose a duration of two weeks for the premating exposure. To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). Ten weeks exposure duration is supported also by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

*Extension of Cohort 1B*

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include an extension of Cohort 1B and provided a justification stating that "*no effects on fertility/development were only observed in a 90d study with extended reproduction ([redacted] 2018) or in a teratogenicity study ([redacted] 1997), concluding no additional cohort is proposed*".

ECHA agrees that the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017) are not met and concludes that Cohort 1B must not be extended.

*Cohorts 2A and 2B*

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of Section 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You proposed not to include Cohorts 2A and 2B and provided a justification stating that "*Based on the available 90d study with extended reproduction parameter ([redacted] 2018) investigation weekly physical examinations including detailed clinical signs did not show any signs of neurotoxicity which could be correlated to the treatment with the test item. Concluding no DNT module is necessary*".

ECHA agrees that the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017) are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

*Cohort 3*

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

You proposed not to include Cohort 3 and provided a justification stating that "*no toxicologically significant changes in hematology occurred in this study nor histopathological changes in immune correlated tissues are reportet. Hence, no further investigation of immuntoxicity is suggested. Concluding no DIT module is proposed*".

ECHA agrees that the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017) are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

*Species and route selection*

You proposed testing in rats. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

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.

In your comments to the draft decision you state that you will perform the testing as requested by ECHA.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

*Notes for your consideration*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

**Deadline to submit the requested Information**

In a draft decision requesting an Extended one-generation reproductive toxicity study (Annex IX/X, Section 8.7.3.; test method: OECD TG 443) in rats, the deadline indicated to provide the requested information is set to 24 months from the date of adoption of the decision. You have included in your current registration dossier, a request for a deadline for the "extended one- generation study" of 40 months. In order to justify why an extension of the current standard draft decsion deadline for this endpoint to 40 months is required, you in part outline your own experimental laboratories capacity is limited to a few extended one-generation studies per year due to your current number of scheduled studies and your current number of testing proposals with EOGRTS. ECHA requested you to submit documentary evidence indicating the scheduling timelines for the study in question in order to justify why in this case, 40 months is required. In your response received on 12 October 2018, you indicated that detailed information with a timeline scheduling for the proposed study from the laboratory facility could currently not be provided at this point in time. The detailed planning of the study with all necessary steps can only start after you receive the basic input (draft decision) from ECHA, including the set-up of the study itself, e.g. which modules are requested. In general, you consider a prolongation of the deadline from 24 to 40 months appropriate taking into account the logistics of setting up this type of test.

ECHA considers currently you have not justified your request to prolong the deadline from 24 months to 40 months. Therefore, ECHA has set the deadline of the decision to 24 months.

In your comments on the draft decision, you requested for a deadline extension for the "extended one-generation study" from 24 months to 40 months. In addition to your comments you have justified your extension by submitting documentary evidence indicating the scheduling timelines for the "extended one- generation study".

ECHA has considered your comments and documentary evidence and in light of your raised palatability and related dose range investigations issues, ECHA has prolonged the deadline from 24 months to 30 months. Therefore, ECHA has set the deadline of the decision to 30 months.

**Appendix 2: Procedural history**

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 27 March 2018.

ECHA held a third party consultation for the testing proposals from 18 June 2018 until 2 August 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **21 December 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 amended the deadline.

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 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.