

Helsinki, 21 November 2018

Addressee: [REDACTED]

Decision number: TPE-D-2114449858-29-01/F
Substance name: 2,2'-(octadec-9-enylimino)bisethanol
EC number: 246-807-3
CAS number: 25307-17-9
Registration number: [REDACTED]
Submission number: [REDACTED]
Submission date: 09/11/2015
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 pre-mating 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 **30 November 2020**. 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>.

Authorised¹ 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 you submitted.

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

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

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.

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 to be performed with the registered substance with the following justification and specification of the basic study design, following the criteria described in column 2 of Section 8.7.3 of Annex X:

"It is proposed to follow the guideline requirement for a 10 week pre-mating dosing period. There is no specific information on possible effects on reproduction or development of this substance. [...] In the 90 day study carried out on 2,2'-(Octadec-9-enylimino)bisethanol, no treatment related effects were seen from histopathology of the reproductive organs or on the weights of the organs. Also no adverse effects were seen in a histopathological examination of spermatogenesis in the testis and oestrus cycle of the females. The only available information of reproduction and development toxicity is from the related substance 2,2'-(C12-18 even numbered alkyl imino)diethanol (CAS RN 71786-60-2), where in an OECD 422 study which had two weeks pre-mating dosing where no indications of adverse effects on fertility or any other reproductive parameters were seen. Also there were no indications of any adverse histological changes in the reproductive organs or to their weights in that OECD422 or in the 90 day study for this substance. [...] Based on this review there is no requirement for an extension to Cohort 1B to produce and F2 generation." In addition, [...] "There were no effects seen in the OECD422 study on the related substance 2,2'-(Octadec- 9-enylimino)bisethanol or in the 28 day and 90 day studies on this substance 2,2'-(octadec- 9-enylimino)diethanol to indicate any potential for neurotoxicity that would trigger a requirement to include Cohorts 2A and 2B to investigate the potential for development neurotoxicity. The same applies to immunotoxicity so there is no proposal to include Cohort 3 to investigate the potential for developmental immunotoxicity."

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 for which testing is proposed. ECHA has taken these considerations into account.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You did not claim the conditions for expansion of study design were met and ECHA did not identify them either. Thus, ECHA concludes that an extended one-generation reproductive toxicity study according to column 1 of Section 8.7.3., Annex X with the basic study design

is required.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed to "follow the guideline requirement for a 10 week pre-mating dosing period".

To ensure that the study design adequately addresses the fertility endpoint, the duration of the pre-mating 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 pre-mating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

ECHA agrees, that ten weeks pre-mating exposure duration is required because there is no substance specific information in the dossier supporting shorter pre-mating exposure duration.

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.

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, and more specifically via gavage. ECHA agrees that the oral route is the most appropriate route of administration, since the substance to be tested is a liquid.

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: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks pre-mating 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.

Notes for your consideration

The conditions for expansion of the study design are currently not met. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 9 November 2015.

ECHA held a third party consultation for the testing proposals from 1 September 2017 until 16 October 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **2 July 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 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 proposal(s) 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.