EUROPEAN CHEMICALS AGENCY

Helsinki, 21 November 2018

Addressee:
[redacted]

Decision number: TPE-D-2114449854-37-01/F
Substance name: Dimethylamine
EC number: 204-697-4
CAS number: 124-40-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/07/2018
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, inhalation 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 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 extending, or not, Cohort 1B, 3) termination time for F2 generation, and 4) reasons for including, or not, Cohorts 2A/2B and/or Cohort 3.

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 ***28 May 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 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.

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 inhalation route in the rat, to be performed with the registered substance, according to the basic study design. You have provided the following justification, according to the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA Guidance[2]:

"*- Premating exposure duration for parental (P0) animals: 10 weeks [...]*
- Basis for dose level selection: preliminary dose range finder [...]
- exclusion of extension of Cohort 1B (the conditions to include the extension of Cohort 1B are currently not met [...])
- Termination time for F2: not applicable
- exclusion of developmental neurotoxicity Cohorts 2A and 2B (No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified [...]
- exclusion of developmental immunotoxicity Cohort 3 (No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified [...]

Background information used to conclude on the study design:
- Uses and exposure assessment for professional workers and consumers: no consumer uses identified, several professional uses identified, which do not lead to significant exposure
- Genotoxicity: the substance has been shown to be not genotoxic [...] and in conclusion no classification as mutagenic)
- Bioaccumulation: there are no indications that an extended exposure durcation is needed to reach the steady state kinetics, as the substance has been shown to have a very low potential for bioaccumulation in aquatic and terrestrial organisms [...].
- Repeated-dose toxicity: The olfactory sensory cell is highly sensitive to the toxic effects of DMA, with minor lesions being produced in rodents even at the current threshold limit value of 10 ppm. [...]
- Neurotoxicity: there is no data available which rises a concern for dimethylamine and its potential to induce neurotoxicity [...]

[2] ECHA Guidance *on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

- Immunotoxicity: there is no data available which rises a concern for dimethylamine and its potential to induce immunotoxicity [...]
- Endocrine effects and modes of action: there is no data available which rises a concern for dimethylamine and its potential to induce endocrine effects [...]."

ECHA agrees to the proposed basic study design.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). 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.

Therefore, 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 for premating exposure duration, dose level setting, species and route selection of this required study.

Premating exposure duration and dose-level setting

You proposed that *"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"*, and that the dose level selection must be based on a preliminary dose range finding study.

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.

ECHA agrees, that ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating 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 to conduct a range-finding study (or range finding studies) ant to report its results 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. ECHA agrees that testing should be performed in rats, since it is the preferred species, according to the test method OECD TG 443.

You proposed testing by the inhalation route. ECHA agrees that the inhalation route is the most appropriate route of administration, since the substance to be tested is a gas.

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, inhalation 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.

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*. 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

In your comments on the draft decision, you agreed to perform the requested test. In addition you requested an extension of the timeline to 36 months instead of the the time indicated in the draft decision communicated to you (24 months from the date of adoption of the decision). You sought to justify this request by the following reasons: i) additional time is needed to appoint an appropriate contract research laboratory (CRO) having sufficient capabilities to conduct the requested OECD TG 443 study via inhalation route and ii) additional time is needed to conduct an appropriate dose range finding study via inhalation route.

ECHA considers that you can start the process of appointing a CRO and initiate the setting of the dose-range finding study while thedecision making process is ongoing. Therefore, ECHA has partially granted the request and set the deadline to 30 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 11 January 2018.

ECHA held a third party consultation for the testing proposals from 28 February 2018 until 16 April 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **1 August 2018**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the deadline.

You updated your registration on 31 July 2018 (submission number [redacted]). ECHA took the information in the updated registration into account, and did not amend the request in the draft decision as the updated information did not impact the outcome of the proposed testing.

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.