ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 20 November 2018

Addressee: [redacted]

Decision number: TPE-D-2114449852-41-01/F
Substance name: Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene
EC number: 270-128-1
CAS number: 68411-46-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/11/2017
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 proposal is modified and you are requested to carry out:

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 systemictoxicity at the highest dose level;**
- **Cohort 1A (Reproductive toxicity);**
- **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation; and**
- **Cohorts 2A and 2B (Developmental neurotoxicity)**

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.

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 ***27 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 you submitted.

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: "*Modules for DNT and DIT are not considered relevant for this substance. The need for mating of the F1 generation will be determined in the course of the study.*"

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 design requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation. Based on professional and consumer uses, thyroid effects as well as accumulation potential, extension of Cohort 1B to produce a second filial generation is requested. Furthermore based on the reported thyroid effects, also (developmental) neurotoxicity Cohorts 2A and 2B are requested.

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 columns 1 and 2 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

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 if 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). In this specific case, a ten-week exposure duration is supported 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 to determine the need for mating of the F1 generation in the course of the study. However, as outlined here below, ECHA considers that the criteria for extending Cohort 1B to produce the F2 generation are already met by the available information on the registered substance.

The use of the registered substance is leading to significant exposure of consumers and professionals because the registered substance is used by professionals as adhesives and sealants (PROCs 8a and 10; including use in private households), as lubricants, greases, hydraulic fluids and heat-transfer fluids (PROCs 8a, 10, 11, 13, 17 and 18), and as stabilisers (PROCs 4, 5, 8a, 10, 11, 13, and 14), and by consumers as lubricating agents and greases.

Furthermore, there are indications for endocrine-disrupting modes of action because a decrease in total thyroxine (T4, both sexes), an increase in thyroid-stimulating hormone (TSH, both sexes, all groups) and microscopic findings in the thyroid gland of the males in all treated groups were observed in the provided OECD TG 422 study on the registered substance.

Additionally, there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure because the calculated $\log K_{ow}$ for the registered substance is above 4.5 (calculated $\log K_{ow} \geq 5$ at 25°C, with $\log K_{ow}$ values of up to 10.8 for constituents of the UVCB).

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because (1) the uses of the registered substance is leading to significant exposure of professionals and consumers, (2) the OECD TG 422 study on the registered substance indicates endocrine-disruption modes of action (thyroid) and (3) there are indications that the internal dose will reach a steady state in the test animals only after an extended exposure.

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 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, without any justification.

However ECHA notes that existing information on the registered substance derived from an available *in vivo* OECD TG 422 study show evidence of thyroid disruption: Decrease in total thyroxine (T4, both sexes), increase in thyroid-stimulating hormone (TSH, both sexes, all groups) and microscopic findings in the thyroid gland of the males in all treated groups were observed.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

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 (feed). 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)(b) of the REACH Regulation, you are requested to carry out the modified 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) with extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity).

Notes for your consideration

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including 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 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 due to the need for an initial planning phase (6 months) and conducting palatability and dose-range finding studies (12 months), whereas the timeline to conduct the extended one-generation reproductive toxicity study is 18 months. ECHA considers that you can already initiate the palatability and dose-range finding studies without awaiting the adopted decision, and thus that a 6–month extension of the deadline is sufficient. Therefore, ECHA has only 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 23 March 2012.

ECHA held a third party consultation for the testing proposals from 25 October 2017 until 11 December 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 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, 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.