EUROPEAN CHEMICALS AGENCY

Helsinki, 24 April 2018

Addressee: [redacted]

Decision number: TPE-D-2114407364-56-01/F
Substance name: Menthol
EC number: 201-939-0
CAS number: 89-78-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22/05/2017
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: EU B.56./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 some 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 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 **4 May 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.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

[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.

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

Examination of the testing proposal

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 EU B.56./OECD TG 443 by the oral route with the registered substance.

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, based on the currently available information, the proposed study method according to EU B.56./OECD TG 443 is appropriate to fulfil the information requirement of Section 8.7.3, Annex X, of the REACH Regulation with the exception that the proposed premating exposure duration requires modification as described below.

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

The specifications for the study design

Premating exposure duration

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.

You propose two weeks premating exposure duration by providing substance specific justification as follows: you state that "*based on the available toxicokinetic data rapid metabolism and excretion mainly as glucuronides is reported. Menthol glycuronic acid appeared in the urine of rabbits in less than an hour after gavage dosing menthol, and 90 per cent of the conjugated acid was found to be excreted in 6 hours when 2 g of menthol were feed. Even when larger doses were given over 90 per cent of the total amount excreted appeared in the urine during the first 24 hours. In another study after a single oral administration of 1 g/kg bw of menthol racemic to rabbits, 59 % of the applied test substance was excreted as glucuronide with the urine within 2d (see chapter Toxicokinetics). Repeated dose sub-acute, sub-chronic and chronic toxicity studies are available in rats and mice. These studies indicate that toxicity to menthols are not time dependent (see chapter Repeated dose toxicity). The default pre-mating period according to the ECHA guidance documents is 10 weeks, but compound specific data should be taken into account to define the pre-mating time. Overall, taking into account the available data on toxicokinetics and repeated dose toxicity studies a 2 week premating as indicated in the OECD TG 443 is considered to be appropriate and sufficient for this substance*".

ECHA notes that your substance specific argument to justify the two weeks premating exposure duration is fast elimination of the registered substance based on the toxicokinetics data, thus the toxicity is not dependent on length of exposure duration.

However, the provided information on toxicokinetics are only for rabbits. Hence, you have not demonstrated whether similar toxicokinetic profile will be applicable for rat as the extended one-generation is to be conducted using rats. Furthermore, you have not demonstrated whether the registered substance will not reach in gonads and accessory sex organs neither explained why a repeated dosing would not affect the spermatogenesis and folliculogenesis.

In addition, the available data in the technical dossier do not allow to conclude on the pattern of toxicity for the registered substance at different length of exposure duration. More specifically, no NOAEL was assigned in the 28-day oral study as there were no effects at any dose levels. In addition, the oral chronic studies (105 weeks) in rats and mice were not performed upto limit dose level and did not show any effects.

Furthermore, no information provided on fertility or mating after ten weeks of premating exposure duration. The available repeated dose toxicity studies provide information on organ weights and histopathology but not on mating.

Therefore, ECHA considers that ten weeks premating exposure duration is required because your justification is not sufficient to justify 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).

Dose-level setting

You propose that the basis for dose level selection "*will be determined based on the available data and a pilot study conducted as a dose-range finding study*".

ECHA accepts your proposal. ECHA would like to highlight that the highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of 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 justifications as follows: "*there is no indication from the available studies that would justify an extension of cohort 1B. Histopathological examinations of the reproduction organs of rats and mice showed no changes in repeated dose toxicity studies with D/L-menthol and also in carcinogenicity studies with D/L menthol. Hence there is no indication of a potential of D/L-menthol to interfere adversely with reproduction*".

ECHA notes that the currently available information do not meet 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).

Therefore, ECHA agrees that the criteria to extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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 an extension of Cohorts 2A and 2B and provided justifications as follows: "*histopathological examinations of the developmental toxicity relevant organs (e.g. thyroid, brain) of rats and mice showed no changes in repeated dose toxicity studies with D/L-menthol and also in carcinogenicity studies with D/Lmenthol. Hence there is no trigger to include the developmental neurotoxicity cohorts*".

ECHA notes that the currently available information do not meet 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).

Therefore, ECHA agrees that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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 justifications as follows: "*histopathological examinations of the immune-toxicity relevant organs (e.g. spleen) of rats and mice showed no changes in repeated dose toxicity studies with D/L-menthol and also in carcinogenicity studies with D/L menthol. Hence there is no trigger to include the immunotoxicity cohort*".

ECHA notes that the currently available information do not meet 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).

Therefore, ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

You proposed testing in rats. According to the test method EU B.56./ 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 solid, ECHA concludes that testing should be performed by the oral route.

Outcome

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 EU B.56./ 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 some 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 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 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. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 22 May 2017.

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 15 January 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 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.