ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 June 2019

Addressee: [redacted]

Decision number: TPE-D-2114475934-35-01/F
Substance name: Terpineol
EC number: 701-188-3
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/07/2018
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 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 by gavage with the registered substance specified as follows:

- **At least two 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.**

You shall also submit with the new endpoint study record, a valid scientific justification relating to 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 have to submit the requested information in an updated registration dossier by **5 July 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, 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 proposal submitted by you.

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[2].

For completeness, ECHA also assesses whether the extended one-generation reproductive toxicity study would also be triggered under Annex IX of the REACH Regulation. ECHA notes that adverse effects on male sexual function and fertility are observed in the OECD TG 422 study (GLP, Thacker, 2010 b). More specifically, male rats became infertile at the high-dose group (750 mg/kg bw/day) and reduced testis and epididymal weights with flaccid testis were observed. As the condition of Annex IX, Section 8.7.3. of the REACH Regulation is fulfilled, an EOGRTS is an information requirement for the registered substance also pursuant to column 1 of Section 8.7.3., Annex IX to 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 EOGRTS according to EU B.56./OECD TG 443 by the oral (dietary) route of administration in rats with ten-week premating exposure duration to be performed with the registered substance. You have provided a detailed justification for this study design, according to the criteria described in column 2 of Section 8.7.3. of Annex X and detailed in ECHA's Guidance[3] and available as an attachment in Section 7.8.1 of the submitted registration dossier.

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.

ECHA considers that the proposed study design requires modification to fulfil the information requirement according to columns 1 and 2 of Section 8.7.3., Annex X. The following refers to the specifications of this required study.

[2] ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R. 7.6 (version 6.0, July 2017)
[3] As per ref. 3

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[4], 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 proposed that premating exposure duration should be 10 weeks. In this respect, ECHA emphasises that 10 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[5]. In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance[6]. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

In general, 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.

With respect to dose-level setting, you proposed that "*the doses used in the EOGRTS will be based on the results of a previous 2-week preliminary study and an OECD 422 screening study*".

ECHA notes that the provided OECD TG 422 study was conducted by gavage dosing. As the requested extended one-generation reproductive toxicity study shall be also conducted via oral route by gavage, ECHA considers that this OECD TG 422 gavage study can be used for identifying appropriate dose levels.

In this respect, ECHA emphasises the following:
In order to be compliant and not to be rejected due to too low dose levels, 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.
In this case, the selection of top dose level should be based upon a dose level which causes observed fertility effects, in order to confirm the findings related to sexual function and fertility observed in the OECD TG 422 study for the purpose of classification and labelling. It should be avoided to completely ablate fertility in the top dose, and it is indeed recommended to set a top dose level where there is both a statistically-significant drop in fertility and also where there are offspring produced for the EOGRTS cohorts. For this purpose, the setting of such a dose level should be based upon robust empirical evidence.

[4] As per ref. 3
[5] As per ref. 3
[6] As per ref. 3

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

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. You claimed that the registered substance has no genotoxic effects in somatic cells, is rapidly absorbed, has no bioaccumulation potential and has no endocrine (disrupting) mode of action. You therefore concluded that column 2 conditions of 8.7.3., Annex X are not met and that an extension of Cohort 1B to produce a F2 generation is not justified.

ECHA does not agree with your proposal and considers that the criteria to extend the Cohort 1B are met.

Firstly, Column 2, Section 8.7.3 of Annex X outlines that extension of Cohort 1B needs to be included if the substance has uses leading to significant exposure of consumers and professionals. In your justification, you did not provide any comments regarding this condition. ECHA notes that the use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by professionals (PROCs 1, 2, 3, 4, 5, 7, 8a, 8b, 9, 10, 11, 13, 14, 15, 16, 19, 21, 24) and consumers in coatings and inks, cosmetics, washing and cleaning products, detergents, biocides, polishes, wax blend, air care products, fragrance components.

Secondly, you conclude that the registered substance has no endocrine (disrupting) mode of action, as no adverse effects are observed on endocrine organs (pituitary, mammary gland, thyroid and adrenal glands). However,there are other indications for endocrine-disrupting modes of action, as described in ECHA Guidance[7]. More specifically, the combined repeated dose toxicity with the reproduction /developmental toxicity screening study [redacted] 2010; according to OECD TG 422) provided in the dossier shows changes in male reproductive organs. Decreased testes weights, low epididymal weights, reduced numbers or complete absence of spermatozoa accompanied by the presence of degenerate spermatogenic cells in ducts in the epididymis were reported in the high-dose group. As no females became pregnant in that group, there are indications that the testicular and epididymal effects observed in males would have been sufficient to prevent fertilisation.According to ECHA Guidance, these effects indicate relevant mode(s) of action related to endocrine disruption.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and the provided screening study indicates endocrine-disruption modes of action for the registered substance.

Species and route selection

[7] As per ref. 3

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 dietary route because gavage dosing in the OECD TG 422 study resulted in male infertility at the high dose due to a bolus effect. Furthermore, you proposed that gavage administration would not be relevant:
"Oral route by gavage is excluded because of the specific an irrelevant effects observed by this route of exposure on male fertility, which would compromise the mating phase and the integrity of the study".

You concluded that oral gavage route of administration is not relevant for human exposure as the effects are unlikely to occur (or have not been seen) when administered via inhalation, dermal or oral (dietary) routes of exposure and that no classification for reproductive effects is therefore warranted.

ECHA notes that, according to ECHA Guidance[8], the selected route must be the most appropriate for identification of intrinsic hazardous property of the substance leading to the highest exposure. In this case, adverse effects on male reproductive tissues (reduced testis and epididymal weights with flaccid testis), leading to infertility in the high-dose group in the absence of systemic toxicity is the major concern in the OECD TG 422 gavage study; the claim that these effects are irrelevant is not substantiated and cannot be accepted. These effects must be further investigated following the same route of administration.

ECHA therefore concludes that oral gavage is the most relevant route to investigate the intrinsic hazard for sexual function and fertility of the registered substance.

Hence, testing should be performed in rats via the oral route by gavage administration.

In your comments to the draft decision you provided a summary of data on the registered substance already considered for this decision and additionally a "new"14 days toxicokinetics study (referred to as [redacted] (2018) in your comments and as [redacted] (2018) in your updated dossier) and maintained your proposal to conduct the study by dietary route of administration.

You considered that comparative combined gavage/feeding and feeding studies as well as toxicokinetic studies show that via dietary route of administration less adverse or non-adverse effects on male testis were observed and that a high dose via gavage administration causes saturation of excretion and/or metabolism pathways; this leads to internal over exposure to at least one of the metabolites and to the induction of severe adverse testicular effects. You further referred to limit dose concept and indicated that some high doses may induce non-relevant effects considered outside the criteria which lead to classification.

You referred to ECHA Guidance on dose level selection for repeated dose toxicity studies, especially regarding saturation of absorption and detoxification mechanism and other possible sources for non-linear kinetics. Finally, you considered the advantages and disadvantages of gavage dosing, including a potential "bolus effect" which might pose adverse effects not relevant for risk assessment and/or hazard classification as not being likely for human exposure. You concluded that testicular toxicity, although intrinsic effects,

[8] As per ref. 3

observed in the OECD TG 422 study after oral gavage administration of the registered substance should be considered as irrelevant for human exposure, risk assessment and classification, and hence further testing should be performed via dietary route of administration.

As already indicated above, ECHA considers that the selection of the administration route to investigate reproductive toxicity should allow the identification of intrinsic hazardous property of the substance. ECHA considers that, based on the available data, the dietary route of administration seems not to be able to detect the intrinsic hazardous properties of the substance similarly like the gavage dosing does. You have also not demonstrated that peak exposures are irrelevant to humans.

ECHA further stresses that provided data does not support your hypothesis. Based on the toxicokinetics study conducted according OECD 417 (GLP, [redacted] 2013, oral (gavage)) with [isopropyl methyl-14C]-alpha-terpineol, the substance is rapidly metabolised and eliminated from the body. ECHA notes that toxicokinetic data after repeated dosing ([redacted] 2018), provided in the updated dossier and analysed in your comments, are not consistently reported and hence cannot be relied on. More specifically, in your comments you claim that "*after 14 days of treatment, the exposure to the metabolite was 13 -fold higher than expected at 750 mg/kg bw/day*", while robust study summary of the same study refers to 1.3- fold difference. Based on the information given in your comments and updated dossier, ECHA calculates that 1.3-fold difference is the correct value and does not support a non-linear internal exposure leading to "*internal overexposure*". Furthermore, ECHA notes that one component of the registered substance only, alpha-terpineol and its glucuronide metabolite, were used in toxicokinetic studies. No comparison is given for toxicokinetics after dietary dosing and other aspects such as enterohepatic circulation have not been considered. ECHA further considers that an excessive internal dose of the registered substance and/or its metabolite(s) would also lead to excessive general systemic toxicity which is not the case here.

With regard to your reference to the concept of the limit dose addressed in the CLP Regulation, ECHA notes that the dose levels in OECD TG 422 are below the limit dose specified (1000 mg/kg bw/day) and not above any hazard classification criteria for reproductive toxicity. ECHA Guidance for reproductive toxicity highlights that the selection of appropriate route of administration depends on the most appropriate route for identification of the intrinsic properties of the substance for reproductive hazard.

In summary, ECHA does not agree with you that the effects on testes should be disregarded and considered as a non-relevant finding in determining the intrinsic properties of the substance for hazard classification. ECHA therefore maintains its conclusion that oral gavage is the most relevant route to investigate the intrinsic hazard for sexual function and fertility of the registered substance and therefore testing must be performed via oral gavage.

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 by gavage, according to the following study-design specifications:

- At least two 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.

Notes for your consideration

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 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[9]. 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.

[9] As per ref. 3

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 30 September 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 **13 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 did not amend the request.
You updated your registration on 27 July 2018. ECHA took the information in the updated registration into account, and did not amend the draft decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-65 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

ECHA
EUROPEAN CHEMICALS AGENCY

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.