ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 22 November 2018

Addressee
[redacted]

Decision number: TPE-D-2114449866-32-01/F
Substance name: 2,6-dimethyloct-7-en-2-ol
EC number: 242-362-4
CAS number: 18479-58-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 21/02/2018
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.

While your originally proposed test for Extended one-generation reproductive toxicity study in rats, (OECD TG 443) using the analogue substance Geraniol (EC No 203-377-1, CAS RN 106-24-1), is rejected, you are requested to perform:

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 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 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 ***31 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.

ECHA
EUROPEAN CHEMICALS AGENCY

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.

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

Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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 analogue substance Geraniol (EC No 203-377-1, CAS RN 106-24-1), 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:
- *Ten weeks premating exposure duration for the parental (P0) generation;*
- *Cohort 1A (Reproductive toxicity) and Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; without Cohorts 2A and 2B (Developmental neurotoxicity) and without Cohort 3 (Developmental immunotoxicity). As Geraniol does not meet the criteria (b) [...], the conditions to include the extension of Cohort 1B to produce the F2 generation are currently not met. [...] Neither abnormalities of the CNS, nor evidence of adverse effects on the nervous or immune system in studies on adult animals or animals exposed prenatally were observed with Geraniol Extra or structurally analogues. Therefore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified."*

In your comments to the draft decision, you argued that the analogue substance Geraniol also undergoes a testing proposal evaluation process and that those results should be awaited. ECHA notes that the decision for the analogue substance geraniol has not been adopted and ECHA does not base any read-across assessment on future results. In any case this argument does not address the scientific arguments raised by ECHA (see below, the read-across justification is not sufficiently substantiated).

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

You propose the testing to be done with the analogue substance Geraniol (EC No 203-377-1). You have provided a read-across documentation as a separate attachment in the registration dossier, which includes a data matrix, and a group justification for the prediction. Your hypothesis is the following: "*The basis of the analogue approach is*

similarity in structure, physical chemical properties, toxicokinetics, metabolism and toxicological profile between these unsubstituted or formate or acetate-substituted derivatives of monoterpene primary and tertiary alcohols (target and proposed structural analogues)."

ECHA has evaluated your proposal to perform the test with the analogue substance Geraniol on the basis of Annex XI, Section 1.5 of the REACH Regulation. According to this Annex, two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. You have to justify why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA notes that your read-across justification document is a description of the (i) structure similarity, (ii) metabolism similarity, (iii) toxicokinetic similarity ,and (iv) toxicity endpoint similarity. However, you have not demonstrated how each information relate to your hypothesis, i.e. information from geraniol can predict information on the registered substance dihydromyrcenol, nor have you made a specific statement regarding their relevance to the specific reproductive toxicity endpoint. Finally you have not provided any supporting data, which confirms that you can rely on data from geraniol to predict a specific property of the registered substance.

From the data matrix provided in your read-across justification document, ECHA notes that except for eye irritation and *in vitro* genotoxicity, there are no data on the registered substance. In absence of such data ECHA considers that there is no sound scientific basis for the prediction of the extended one-generation reproductive toxicity endpoint, from the source substance to the target/ registered substance. Further, ECHA observes that while you propose to read across from information on geraniol, you then describe studies and observation also from other source substances (linalool, dimyrcetol, nerol, geraniol/nerol mixture), without justifying how these observations are pertinent for the prediction of the reproductive toxicity effects of 2,6-dimethyloct-7-en-2-ol (or dihydromyrcenol, the registered substance)

ECHA concludes that the presented evidence in the data matrix does not support a similar or regular pattern of toxicity as a result of structural similarity. Therefore it cannot be verified that the proposed group/ analogue substance(s) can be used to predict properties of the registered substance.

In your comments to the draft decision, you argued that ECHA should first evaluate the lower-tier test information before assessing the OECD TG 443 testing proposal you have submitted. In addition you considered that findings in such lower tier tests requiring significantly less animals might lead to classification making the OECD TG 443 obsolete: *"Consequently the request for an OECD 443 [...] is premature and not in line with the concepts of REACH and animal welfare ideas."*

ECHA notes that no testing proposal is required for the lower-tier tests and you have thus already the possibility to conduct such testing, taking into account the considerations on the

read-across provided in this decision and your obligation to conduct animal testing only as a last resort (Article 25 of REACH). Therefore your suggestion cannot be taken into account and, in the absence of study data, your proposed adaptation cannot be accepted.

In conclusion, ECHA does not consider that the read-across justification is a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects your adaptation in the technical dossier, and you are recommended to review your read-across approach should it have been used for other endpoints.

Therefore, ECHA requests that the proposed study is performed on the registered substance.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. In your registration dossier, you claimed that the conditions for expansion of study design were not met and ECHA confirms your approach. 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 sufficient. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed to use "*ten weeks premating exposure duration for the parental (P0) generation".*

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.

ECHA notes that there are no repeated dose studies on the registered substance which can be relied upon to set the dose level. Hence, in absence of relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are generated and 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 did not clearly specify the route for testing. However you indicate that "*[a]dministration of the test substance via diet would be the most appropriate route of exposure [...]. Taking*

into account the difficult properties of the test material, additional time will be needed for test substance formulation, palatability testing studies and analysis of stability in vehicle used for oral administration." ECHA agrees that the oral route is the most appropriate route of administration, and more specifically via gavage, since the substance to be tested is a liquid, with possible palatability issues.

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following 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) without extension to mate the Cohort 1B animals to produce the F2 generation.

while your originally proposed test for Extended one-generation reproductive toxicity study (test method OECD TG 443), *with the analogue substance (Geraniol, EC number 203-377-1)* is rejected according to Article 40(3)(d) of the REACH Regulation.

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.

In your comments to the draft decision, you agreed to the basic design indicated and discussed above, and noted that ECHA refers to the lack of repeated dose toxicity study to clarify the study design, quoting the paragraph above.

Deadline to submit the requested information in this decision

In your updated dossier, you requested an extension of the timeline to 40 months, because of the need to "*to perform additional studies*" (e.g. palatability testing studies and analysis of stability in vehicle used for oral administration) "*to select the right doses for the OECD 443 study [...] [due to] the difficult properties of the test material*".

ECHA has only partially granted the request and set the deadline to 30 months, because (i) as you have not sufficiently substantiated (e.g. testing laboratory planning confirming your request) and (ii) preliminary testing which is not subject to compliance with Annexes IX and X (e.g. palability studies, dose range finding,...), and which may support the above request, may be undertaken at your best convenience.

In your comments to the draft decision you re-iterated your request to be granted a longer deadline to provide the requested information. ECHA considers that you have not brought additional arguments (e.g. testing laboratory planning confirming your request) to be discussed. Furthermore you acknowledged that the "*need for additional studies becomes*

even more obvious as the proposed read-across is not considered valid by ECHA", which is already highlighted in the decision.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 9 December 2016.

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 **6 July 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 or the deadline.

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.