ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 21 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114366342-52-01/F
Substance name: Terpineol
EC number: 232-268-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18.04.2016
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species that is appropriate, via oral route with the registered substance;**

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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **30 July 2018**. You also have to update the chemical safety report, where relevant.

The reasons of 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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material. However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt this information requirement. You provided the following justification for the adaptation: "*Further testing is not required under Annex IX, column 2, section 8.7.2. since no adverse effects were observed in OECD guideline 414 and OECD guideline 422 studies conducted in rats. Also, Terpineol has antimicrobial and antifungal properties (Singh et al., Antimicrobial activity of some promising plant oils, molecules and formulations. Indian J Exp Biol. 2012 Oct;50(10):714-7) therefore it is not expected to be well tolerated by rabbits, whose digestive tract is particularly sensitive to such molecules. As excessive toxicity may occur and prevent from accurately discriminate between potential developmental toxicity and species-specific toxicity, no further developmental toxicity study in the rabbit is deemed necessary.*"

ECHA notes that you propose an adaptation referring to Annex IX, Section 8.7.2., column 2, which requires that "*a decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data.*" However, for Annex X dossiers a pre-natal developmental toxicity study in a second species is a standard information requirement. Therefore, for an Annex X dossier, an adaptation based on Annex IX, Section 8.7.2., column 2 cannot be accepted. Instead, ECHA evaluates your arguments with respect to Annex XI, Section 1.2., weight of evidence.

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation. Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as investigated in a pre-natal developmental toxicity study (EU B.31/OECD TG 414), particularly in a second species.

The existing OECD TG 414 and OECD TG 422 studies, together or separately, do not meet this condition because both studies were performed with the same species and the OECD TG 422 study is a screening study that does not address pre-natal developmental toxicity with sensitivity and depth of investigations (e.g. external, skeletal and visceral alterations) which would allow concluding on prenatal developmental toxicity equal to an OECD TG 414 study.

You argue that a pre-natal developmental toxicity study in rabbit is not deemed justified due to assumed extensive species-specific toxicity preventing accurate discrimination of potential developmental toxicity. In your adaptation you stated that the digestive tract of rabbits might show a particular sensitivity to terpineol due to its antimicrobial and antifungal properties.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you maintained that a pre-natal developmental toxicity study in rabbit is not deemed justified, by providing further information with references on the antimicrobial activity of terpineol for *Escherichia coli* and *Staphylococcus aureus*. You further argued that "*The effects of antibacterial substances on rabbit gastrointestinal flora are well known and lead to excessive maternal toxicity which makes difficult the interpretation of potential toxic effects on fetuses and dams. Signs of maternal toxicity occur secondary to the sensitivity of the rabbit gastrointestinal system to antibiotics and include diarrhea, decreased food consumption and body weight that can result in abortions, resorption and malformations. Also, rabbits are susceptible to intestinal tract disturbances and diarrhea with oily substances [6]. Therefore, Terpineol multiconstituent is expected to disrupt the rabbit intestinal flora which can secondarily lead to altered development in utero due to an indirect, local and species-specific adverse maternal toxic effect. In addition, in a developmental toxicity study in rats, Terpineol multiconstituent did not show any teratogenic effects when rats were treated with Terpineol multiconstituent at dose levels up to 600 mg/kg bw/day by gavage [7]. Based on the antimicrobial activities of α-terpineol, the species-specific sensitivity of rabbit to antimicrobial agents as well as the absence of developmental toxicity in rats, DRT considers that the requested developmental toxicity study in the rabbits is not necessary.*"

ECHA notes that the original technical dossier and your comment(s) on the draft decision provide information on effects of terpineol on bacteria and generic considerations on the effects of antibacterial substances on the gastro-instestinal tract of rabbits. Based on this information, ECHA notes that the rabbit may not be an appropriate species to investigate prenatal developmental toxicity with the registered substance.

ECHA notes further that REACH requires for dossiers registered at Annex X level testing for pre-natal developmental toxicity in a second species. The test method OECD TG 414 and ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, section R.7.6.2.3.2, Stage 4.5 indicate that the rat and the rabbit are the *preferred* species. However, ECHA Guidance further indicates that "*The selection of the species for the prenatal developmental toxicity study should be made taking into account substance-specific aspects. If a species other than the rat and the rabbit is selected as the first or second species, the selection should be justified.*"

ECHA concludes that the argued species-specific toxicity of the registered substance in rabbit, which may disturb assessment of developmental toxicity, *per se* and even if demonstrated is not a justification to adapt the standard information requirement of a pre-natal developmental toxicity study in a second species, but it may indicate that another species than the rabbit should be used.

Therefore, your adaptation of the information requirement is rejected. Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding the selection of the species, the test in the first species was carried out with rats. According to the test method EU B.31./OECD TG 414, the rat and the rabbit are the preferred species. According to ECHA Guidance R.7.a "*if both or one of the default species (the rat or the rabbit) are not suitable species for prenatal developmental toxicity testing, a more suitable species considering the human relevancy should be selected for testing. An adequate justification must be provided for other species other than the rat or the rabbit*". Therefore, considering that the rabbit may not be a suitable species for testing the registered substance, you should select an appropriate species.

ECHA considers 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) R.7a, chapter 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 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species that is appropriate by the oral route.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 2 November 2016.

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 did not amend the request(s).

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

ECHA received proposals for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-54 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present 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 your Member State.

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.