EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2016

Addressee: [redacted]

Decision number: TPE-D-2114350809-40-01/F
Substance name: 2-phenylethanol
EC number: 200-456-2
CAS number: 60-12-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28.04.2016
Registered tonnage band: 100-1000T

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 accepted and you are requested to carry out:

1. **Viscosity (Annex IX, Section 7.17.; test method: OECD TG 114) using the registered substance.**

While your originally proposed two-generation reproductive toxicity study according to OECD TG 416 in rats by the dermal route using the registered substance is rejected, you are requested to perform:

2. **Extended one-generation reproductive toxicity study (Annex IX, 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 of the REACH Regulation. In order 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 are required to submit the requested information in an updated registration dossier by **21 December 2018**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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 proposal(s) submitted by you and scientific information submitted by third parties.

1. Viscosity (Annex IX, Section 7.17.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

"Viscosity" is a standard information requirement as laid down in Annex IX, Section 7.17 of the REACH Regulation. The information on this endpoint is not available for the registered substance subject to the present decision but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and you need to provide information for this endpoint.

You have submitted a testing proposal for a viscosity study according to OECD TG 114 (Viscoxity of Liquids). ECHA considers the proposed test appropriate and testing should be performed with the registered substance.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed test using the registered substance: Viscosity of liquids (test method: OECD TG 114).

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

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.

a) Examination of the testing proposal

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 IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX 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 ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

ECHA considers that adverse effects on reproductive organs or tissues are observed in the provided sub-chronic dermal toxicity study according to OECD TG 411 because a "*significant increase in relative organ weight of ... gonads occurred at 2.00 ml/kg*". As the condition of Annex IX, Section 8.7.3. is fulfilled, an extended one-generation reproductive toxicity study is an information requirement for the registered substance pursuant to Annex IX, Section 8.7.3.

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 a two-generation reproductive toxicity study according to EU B.35./OECD TG 416, in rats, by the dermal route using the registered substance. ECHA notes that a two-generation reproductive toxicity study is no longer an information requirement in REACH Regulation. It has been replaced by the requirement for an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443), if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity pursuant to Annex IX, Section 8.7.3. Hence, ECHA considers that the proposed study is not appropriate to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation.

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 IX 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 because 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* R.7a, chapter R.7.6 (version 4.1, October 2015).

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 existing 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 IX 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.

As outlined above, you proposed a two-generation reproductive toxicity study instead of an extended one-generation reproductive toxicity study and, therefore, you did not provide any justification for the existence or non-existence of triggers for the extension of Cohort 1B to include the F2 generation following the criteria described in column 2 of Section 8.7.3 of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

However, ECHA concludes that the criteria to extend Cohort 1B are not met.

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 IX . When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

As outlined above, you proposed a two-generation reproductive toxicity study instead of an extended one-generation reproductive toxicity study and, therefore, you did not provide any justification for the existence or non-existence of triggers for including Cohorts 2A and 2B following the criteria described in column 2 of Section 8.7.3 of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

However, ECHA concludes that the criteria to include Cohorts 2A and 2B are not met. 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 IX.

As outlined above, you proposed a two-generation reproductive toxicity study instead of an extended one-generation reproductive toxicity study and, therefore, you did not provide any justification for the existence or non-existence of triggers for including Cohort 3 following the criteria described in column 2 of Section 8.7.3 of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

However, ECHA concludes that the criteria to include Cohort 3 are not met. 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.

For the proposed two-generation reproductive toxicity study, you proposed testing by the dermal route. However, ECHA does not consider that the dermal route is the most appropriate route of administration for reproductive toxicity because only a minor fraction (7.55%) was absorbed through human skin and most of the dose (ca. 90%) was lost from the surface of the skin due to evaporation (see IUCLID section 7.1.1, endpoint study record for [redacted], 1987). Furthermore, the absorption rate by dermal administration was much lower compared to the absorption rate by oral administration (see IUCLID section 7.1.1, endpoint study record for [redacted], 1990).

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 4.1, October 2015) 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.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party summarised the findings of the endpoint study record of Huntingdon, 1985 which is available in the registration dossier of the registered substance (see IUCLID section 7.8.2) and of two sub-chronic toxicity studies by Vollmuth et al, 1995[2] and Owston et al., 1981[3] without providing further information how this information can be used to meet the information requirements according to Annex IX, Section 8.7.3.

ECHA observes that none of the provided studies fulfils the information requirement for an extended one-generation reproductive toxicity study. Furthermore, ECHA notes that it is your responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions for specific adaptation possibilities according to column 2 of Section 8.7.3. of Annex IX, or general adaptation possibilities according to Annex XI. Therefore, you may assess whether you can justify an adaptation based on the information provided by the third party. If the information requirement can be met by way of adaptation (e.g. column 2 adaptation or weight-of-evidence), you may include the adaptation argument with all necessary documentation in an updated registration.
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 30 months. You sought to justify this request by possible delays in laboratory availability. ECHA requested you to provide documentary evidence from a contract research organisation in support of such a request. In your response to the ECHA request you stated that "*the testing decision is still in draft status, so no study has yet been scheduled; hence it is not practical at this stage to get 'documentary evidence' of a delay by the CRO. When the final decision is made therefore and the study is scheduled, we will specify whether a deadline extension is necessary and provide documentation to support this.*" Therefore, ECHA has not modified the deadline of the decision.

[2] Vollmuth T.A., Bennett, M.B., Hoberman, A.M. and Christian, M.S. (1995) An Evaluation of Food Flavoring Ingredients Using an In Vivo Reproductive and Developmental Toxicity Screening Test. Teratology, 41(5), 597.
[3] Owston E., Lough R. and Opdyke D.L. (1981) A 90-day study of phenylethyl alcohol in the rat. Fd and Cosmet Toxicol, 19(6), 713-715.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional 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;

while your originally proposed test for two-generation reproductive toxicity study according to OECD TG 416 is rejected according to Article 40(3)(d) of the REACH Regulation.

Note for your considerations

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 IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7.a, chapter R.7.6 (version 4.1, October 2015). 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 proposal(s) for examination pursuant to Article 40(1) on 13 March 2013.

ECHA held a third party consultation for the testing proposal(s) from 15 April 2014 until 30 May 2014. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **29 June 2016**, 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 did not amend the requests or 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) 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 test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.