EUROPEAN CHEMICALS AGENCY

Helsinki, 18 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114363811-50-01/F
Substance name: 1-phenylethanol
EC number: 202-707-1
CAS number: 98-85-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04.10.2016
Registered tonnage band: 10-100T

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. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

2. **Robust study summary for In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; in conjunction with Annex I, Section 1.1.4.) for the registered substance;**

3. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD [421/422]) in rats, oral route with the registered substance;**

4. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) 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 **25 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 Claudio Carlon, Head of Unit, Evaluation E2

[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. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

In the technical dossier you have provided study records for publications from 1987, 1976 and 1958 performed with the following strains: S. typhimurium (TA1535, TA1537, TA97 and TA100), E. coli, strain: P3110, DNA polymerase deficient strain: P3478 (Pol A+ and pol A- strains) and E. coli Sd-4-73. However, these studies do not provide the information required by Annex VIII, Section 8.4.1., because they are all non-guideline studies and are not conducted according to GLP. The test guideline OECD 471 specifies the recommended strains to be used and how the data shall be reported. Furthermore, in the key study from year 1987 the sole positive control used with metabolic activation is not as specified in the test guideline and all data reporting on the results is missing as well as confirmation of negative results. The study from year 1976 is performed using three concentrations and only with metabolic activation. In the study from 1958 only one (incorrect) strain is used. Since the tests were conducted, significant changes have been made to OECD TG guideline 471 so that testing on at least five strains including testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided studies do not meet the current guideline, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

In your comments to the draft decision you argued that this request should be removed from the decision. However, what you provided in your comments is a summary of the study record that is already present in the dossier, upon which ECHA drafted its request. As you have not addressed any of the deficiencies outlined above and you have not provided any additional and relevant information, ECHA considers that your request cannot be accepted.

As explained above, 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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

2. Robust study summary for In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3. in conjunction with Annex I, Section 1.1.4.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the Practical Guide on "How to report robust study summaries".

An *In vitro* gene mutation study in mammalian cells is a standard information requirement as laid down in Annex VIII, Section 8.4.3. 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. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 1.1.4. if there are several studies addressing the same effect, then, having taken into account possible variables (e.g. conduct, adequacy, relevance of test species, quality of results, etc.), normally the study or studies giving rise to the highest concern shall be used to establish the DNELs and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment.

You have provided a study record for an *In vitro* gene mutation study in mammalian cells ([redacted], 2015) to meet the standard information requirement of Annex VIII, Section 8.4.3.

However, ECHA notes that, contrary to Article 3(28) of the REACH Regulation, the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. The reporting of this recent study is inadequate, in particular, the following elements are missing: e.g.

- The data, for both treated and control cultures, should include the number of cells at the end of treatment, the number of cells plated immediately following treatment, and the colony counts. Data should include cytotoxicity (expressed as relative survival, RS) and all the data needed to calculate the mutant frequency both for treated and control cultures. RS for each culture should be expressed as a percentage relative to the concurrent solvent control.

- Individual culture data should be provided. Additionally, all data should be summarised in tabular form.
- The tables 1A and 1B in the technical dossier include inadequate information (0/4 and N/A).
- Data for both treated and control cultures, should include: (1) the number of cells plated with and without selective agent (at the time the cells are plated for mutant selection), and (2) the number of colonies counted from the plates with and without selective agent. The presentation of results should also include all of the data needed to calculate the mutant frequency. The mutant frequency should be expressed as the number of mutant cells per million viable cells. Currently the mutation frequencies are missing.
- The negative and positive control data should induce responses that are compatible with historical negative and positive control data.
- The criteria for selecting the concentrations are missing.

Therefore, you need to provide a complete robust study summary with the above missing elements for this study.

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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Robust study summary for the *In vitro* gene mutation study in mammalian cells ([redacted], 2015).

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2. In the technical dossier you have provided study records for one generation reproductive toxicity study (1986, 1990) in rats and mice via oral and dermal route and a publication (1983) performed with an analogue substance via oral route.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. because no details on mating, no data on oestrous cycle, no sperm

parameters, no litter observations, no data on offspring examinations, and no data on reproductive indices are available. Furthermore, these are all non-guideline studies and the studies are not conducted according to GLP.

Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision you argued that this request should be removed from the decision. However, what you provided in your comments is simply a summary of the study record that is already present in the dossier, upon which ECHA drafted its request. As you have not addressed any of the deficiencies outlined above and you have not provided any additional and relevant information, ECHA considers that your request cannot be accepted.

As explained above, 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.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

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.

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:
- Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 4.1, October 2015).

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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.

In the technical dossier you have provided a study record for a OECD 201 (Alga, Growth Inhibition test). However, this study does not provide the information required by Annex VII, Section 9.1.2., because due to the following reasons it is considered not reliable:

- The study is not conducted according to GLP;
- No analytical monitoring has been conducted;
- Number of control replicates seems fewer than recommended (only 3 replicates used, although OECD 201 TG recommends that twice the number of test substance replicate to be used; i.e. at least 4);
- In between replicate variation very high in some samples (10^4-10^5);
- Control 3 does not show exponential growth, but a decreasing with time thus not meeting the validity criteria (i.e. exponential growth in control);
- When variation for section-by-section specific growth rate in control is calculated based on the data provided, the CV is not within the range defined by the validity criteria (it should be <35%).

Therefore, the results of the test cannot be considered reliable.

In your comments to the draft decision you argued that this request should be removed from the decision. However, what you provided in your comments is simply a summary of the study record that is already present in the dossier, upon which ECHA drafted its request. As you have not addressed any of the deficiencies outlined above and you have not provided any additional and relevant information, ECHA considers that your request cannot be accepted.

As explained above, 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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

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: Algae growth inhibition test, EU C.3./OECD TG 201).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 18 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a short term repeated dose toxicity 28-day study (Annex VIII, Section 8.6.1.). As this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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 01 Decenber 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 proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

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.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

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

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2018.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. 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.

4. 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.