ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 27 April 2018

Addressee: [redacted]

Decision number: CCH-D-2114407994-41-01/F
Substance name: Ethanaminium, 2-hydroxy-N-(2-hydroxyethyl)-N,N-dimethyl-, esters with C16-18 and C18-unsatd. fatty acids, chlorides
EC number: 620-174-7
CAS number: 1079184-43-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 03/04/2017
Registered tonnage band: Over 1000

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]

1. **Spectral data (Annex VI, Section 2.3.5.) on the registered substance;**

2. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.) on the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex X, 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 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.

[1] No testing for endpoints listed in Annexes IX or X to the REACH Regulation may be started or performed at this moment: A decision only becomes legally effective and binding for you after it has been adopted according to Article 51 of the REACH Regulation. ECHA will take the decision either after the date it has become clear that Member State competent authorities have not made any proposals to amend the draft decision or, where proposals to amend it have been made, after the date the Member State Committee reached a unanimous agreement on the draft decision.

You have to submit the requested information in an updated registration dossier by **4 May 2020**. 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[2] by Kevin Pollard, Head of Unit, Evaluation E1

[2] 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

INFORMATION ON THE IDENTITY OF THE SUBSTANCE

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

1. Spectral data (Annex VI, Section 2.3.5.)

Spectral data (ultra-violet, infra-red as well as nuclear magnetic resonance or mass spectrum) are necessary to be reported in a registration dossier to confirm the structural formula of a substance. For UVCB-substances, spectral data are relevant to provide the spectral "fingerprint" (the characteristic spectral signals/bands related to functional groups) of the constituents of the substance.

You provided in your dossier the description of the methods for ultra-violet, infra-red and nuclear magnetic resonance spectroscopy, however the respective spectra are not reported.

Therefore, it is missing to be reported spectra that verify the identity of the reported groups of constituents in section 1.2.

Accordingly, ECHA requests you to provide in your IUCLID dossier the respective spectra (ultra-violet, infrared and nuclear magnetic resonance or mass spectrum) that provide the spectral "fingerprint" of the constituents of the substance.

You should report the required spectra of your substance in IUCLID Section 1.4. Technical instructions on how to report the requested information in section 1.4 of your dossier are available in the manual "How to prepare registration and PPORD dossiers" section 9.4.4. (version 4.0, May 2017).

In your comments on the draft decision, following the procedure set out in Article 50(1) of the REACH Regulation, you mentioned that spectral data was provided for the substance in the dossier submitted on the 10 December 2009 and that this data was lost in the following dossier updates. You also mentioned that you submitted a dossier update containing the spectral data but that this submission failed the ECHA technical completeness check.

You are reminded that this draft decision does not take into account any updates submitted after the notification to you of the draft decision. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

2. High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.)

You are required to report either a high-pressure liquid chromatogram or a gas chromatogram in your registration dossier such that it confirms the substance composition and identity as factual evidence.

This means that the information included in the chromatography report needs to enable understanding how you identified and quantified the constituents reported in the composition section of the IUCLID dossier. If appropriate, you may provide other suitable methods to verify the composition of the substance.

You provided in your dossier the description of a high-pressure liquid chromatography method. However, the related chromatogram is missing and you provided no other quantification method in your dossier.

Therefore, ECHA requests you accordingly to provide a chromatogram and the related description of the method or any other suitable method that allows verification of the composition of your substance.

More specifically, you shall describe how you identified and quantified the constituents and groups of constituents present in the registered substance, including the relative content of the different fatty acids in terms of the carbon chain length and backbone type (e.g. saturated or unsaturated).

You shall provide also an explanation on how you translated the results of the analytical methods into the composition in section 1.2, including peak tables, identification of the peaks, area percentages, and calculations used. Based on the analytical data, you should also revise the composition of your substance in section 1.2. of the dossier, if relevant.

Taking into account the complexity of the composition of the registered substance, information on the identification and quantification of its groups of constituents may be derived by combining information on the manufacturing process and results of the qualitative and quantitative analysis of the starting materials.

You should report the required chromatography method and/or any other suitable analytical method to quantify your substance in IUCLID Section 1.4.
Technical instructions on how to report the requested information in section 1.4 of your dossier are available in the manual "How to prepare registration and PPORD dossiers" section 9.4.4. (version 4.0, May 2017).

In your comments on the draft decision, following the procedure set out in Article 50(1) of the REACH Regulation, you mentioned that a high-pressure liquid chromatogram was provided for the substance in the dossier submitted on the 10 December 2009 and that this data was lost in the following dossier updates. You also mentioned that you submitted a dossier update containing the chromatogram but that this submission failed the ECHA technical completeness check.
You are reminded that this draft decision does not take into account any updates submitted after the notification to you of the draft decision.

All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

TOXICOLOGICAL INFORMATION OF THE SUBSTANCE

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

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.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with 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. 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 the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have sought to adapt this information requirement according to Annex XI, Section 3.2 (a). To further support your adaptation you have provided the following information:

Endpoint study record 1: *"Performance of an EOGRTS is not necessary in accordance with Annex XI (3.2 (a)) of REACH Regulation (EC) No 1907/2006 based on a quantitative assessment. The results of exposure and risk assessments covering all relevant exposures throughout the life cycle of the substance demonstrate a low exposure and a RCR value below 1 in all scenarios of manufacture, formulation, professional use, consumer use and indirect exposure of humans via the environment. The very small spectrum of identified uses as referred to in Annex VI section 3.5 is documented in chapters 9 and 10 in this CSR. The exposure assessment and risk characterisation according to Article 14(4) and Annex I, 5 of REACH Regulation (EC) No 1907/2006 have been conducted solely for the purpose of justifying this waiver, given that the substance is not classified as dangerous or as PBT/vPvB according to any of the Regulation's criteria. Strictly conservative DNELs have been derived from results of the available test data which include a pre-natal developmental study and sub acute and sub-chronic studies with evaluation of reproductive endpoints. No substance-related adverse effects were found in any of the tests conducted and the NOAELs used to derive the DNELs correspond to the maximum doses tested. The DNELs fertility have been derived from results of the sub-chronic repeated dose toxicity study, taking full account of the potential increased uncertainty resulting from the omission of the information requirement by applying an additional assessment factor. These derived DNELs are relevant and appropriate both for the information requirement to be omitted and for risk assessment purposes. The exposure and risk assessments are included in chapters 9 and 10 of this CSR.*

The final conclusion is based on the risk characterisation ratio (RCR). Comparison of all the derived DNELs with the results of the exposure assessment shows that exposures in all life cycle stages of the substance are well below the derived DNELs even under the precautionary assumptions applied".

Endpoint study record 2: Supporting study: "*28 day Oral Toxicity (Intubation) Study in Rats*", rat, oral (OECD TG 407; GLP) with the registered substance, [redacted], 1994 (study report), reliability 1

Endpoint study record 3: Supporting study: "*13 Week Subchronic Oral (Intubation) Study in Rats*", rat, oral (OECD TG 408; GLP) with the registered substance, [redacted], 1994 (study report), reliability 1

ECHA has evaluated your adaptation according to the criteria set in Annex XI, Section 3.2(a), and concluded the following:

ECHA notes that the exposure scenario covers all relevant exposures for the identified uses and shows no significant exposure, thus the criteria (i) of the Annex XI Section 3.2(a) is met.

However, the criteria (ii) and (iii) are not met. This is because, the current DNEL for reproductive toxicity is derived from the sub-chonic toxicity study ([redacted], 1994) and the information from the sub-chronic toxicity study do not provide equivalent information as the extended one-generation reproductive toxicity. More specifically, the information on reproductive toxicity from a sub-chronic toxicity study is limited to information on organ weights and histopathological changes of the reproductive organs. Much more information on reproductive toxicity can be gained from an extended one-generation reproductive toxicity study than from a sub-chronic toxicity study. For instance, information on sexual function and fertility (such as functional fertility after 10 weeks exposure covering spermatogenesis and folliculogenesis, sperm parameters, oestrous cyclicity) and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation is obtained. Similarly, 28-day and prenatal developmental toxicity studies do not provide the same critical information on reproduction; information is limited to organ weight and histopathology of reproductive organs, maintenance of pregnancy, and prenatal developmental toxicity. Thus, relevant information on reproductive toxicity is lacking and it is not possible to conclude on the reproductive toxicity properties of the substance. The use of an additional assessment factor cannot take into account missing relevant information which may e.g. lead to hazard classification. This is illustrated in the footnote of criteria (ii) describing that a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit an extended one-generation reproductive toxicity study[3]. In comparison, the currently available information on toxicity to reproduction provides even less information than what a screening test for reproductive/developmental toxicity (OECD TG 421/422) would provide. Thus, the available information does not meet the criteria specified under (ii) and (iii). Subsequently, the DNEL derived from the results of the sub-chronic toxicity study shall not be considered appropriate to omit an extended one-generation reproductive toxicity study.

[3] Even though the text of the footnote still refers to the two-generation reproductive toxicity study, this information requirement was changed by the Commission Regulation 2015/282. Based on the Regulation the new information requirement is the extended one-generation reproductive toxicity study.

Therefore, your adaptation does not meet the general rule for adaptation of Annex XI; Section 3.2(a), and your adaptation of the information requirement is rejected.

In your comments on the draft decision, following the procedure set out in Article 50(1) of the REACH Regulation, you acknowledge ECHA's request for the extended one-generation reproductive toxicity study has a formal reason. However, by taking together all the provided data and the low exposures of the substance in all life stages, you indicate that the study is therefore not scientifically justified and the request completely ignores animal welfare.

ECHA acknowledges your comments on the draft decision, however, you have not provided further scientific justified reasoning and/or new information to justify the reason why the requested study needs not to be performed. As outlined above, ECHA has assessed the results of your submitted adaptation(s), and has found it does not meet the information requirement. It is the responsibility of you to ensure that the results of the adaptation are sufficiently justified.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier and your comments on the draft decision does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3., is required. The following refers to the specifications of this required study.

b) The specifications for the study design

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* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 conducted 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.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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 6.0, July 2017) Chapter R.7a, Section 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.

c) Outcome

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: 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

Notes for your consideration

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 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. 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

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 8 June 2017.

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.

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 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.