EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 12 January 2021

Addressee: [redacted]

Decision number: CCH-D-2114538542-50-01/F
Substance name: Fatty alcohols C13-15 (odd numbered, linear and branched), reaction products with ethylene oxide, sodium chloroacetate and ethanolamine
EC number: 931-915-1
CAS number: NS
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 18/03/2020

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-2114449968-26-01/F of 5 November 2018 ("the original decision") ECHA requested you to submit information by 12 November 2019 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement(s):

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance

You are therefore still required to provide this information requested in the original decision.

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.

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance)[1].

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.

Approved[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA
[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

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

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

In the compliance check decision you were requested to submit information derived with the Substance for pre-natal developmental toxicity one species (rat or rabbit), via oral route.

In the updated registration dossier subject to follow-up evaluation, you have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

You have provided a prenatal developmental toxicity study (OECD TG 414) conducted with analogue substance 'Fatty alcohols C12-14 (even numbered, linear and branched), reaction products with ethylene oxide and chloroacetic acid, sodium salt' ('Alkyl Ether Carboxylate', 'AEC') ([redacted] 2012).

Furthermore, in support of your read-across approach, you have provided the following *in vitro* studies:

i) Human pluripotent stem cell-based assay measuring changes in cellular metabolism to predict developmental toxicity *in vitro* (devTOXqP-iPS Cell Assay); conducted with the Substance

ii) Human pluripotent stem cell-based assay measuring changes in cellular metabolism to predict developmental toxicity *in vitro* (devTOXqP-iPS Cell Assay); conducted with AEC.

We have assessed this information and identified the following issues:

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. 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.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

You have registered the Substance as a UVCB (Unknown or Variable composition, Complex reaction products or Biological materials). According to the IUCLID dossier, the Substance consists of [redacted] constituents. The main constituents are:

- Fatty alcohols C13 (linear and branched), reaction products with ethylene oxide, sodium chloroacetate and ethanolamine [redacted]
- Fatty alcohols C15 (linear and branched), reaction products with ethylene oxide, sodium chloroacetate and ethanolamine [redacted]
- Acetamide, 2-(C13 (branched and linear)-alkyloxy)-N-(2-hydroxyethyl)-, (≥ 8 ≤ 12 % (w/w))
- Alcohols, C13 (branched and linear) [redacted]
- Alcohols, C15 (branched and linear) [redacted]

i) Information in the dossier

You predict the properties of the Substance from the structurally similar substance Alkyl Ether Carboxylate (i.e. the source substance), which you claim to be the main constituent of the Substance. ECHA therefore understands that you refer to a constituent-based approach, i.e. the source data comes from test results obtained with the individual constituent(s) of the target substance[3].

The source study that you have used in your read-across approach, prenatal developmental toxicity study ([redacted], 2012), is performed according to the OECD TG 414 with the source substance Alkyl Ether Carboxylate, i.e. Fatty alcohols C12-14 (even numbered, linear and branched), reaction products with ethylene oxide and chloroacetic acid, sodium salt (CAS No. 33939-64-9).

While you have not provided a read-across justification document in your dossier, IUCLID section 7.8 and the CSR indicate the following reasoning for the prediction of toxicological properties: "*Based on the results of this study conducted with the source substance, the dose level of 1000 mg/kg bw/day [...] corresponds to 2400 mg/kg bw/d of the target substance based on the molecular weight of the main constituent (which is the source substance) and its concentration in the target substance. This constituent is considered to be the main constituent driving the potential toxicity of the target substance if some could occur (see the RAAF document).*"

Furthermore, in IUCLID section 7.8 and in the CSR it is stated that "*both substances have similar results profiles in an in vitro study for the developmental potential where metabolic perturbation at concentrations similar to those that impacted cell viability was observed. Therefore, it can be concluded that the metabolic disturbance was a consequence of cytotoxicity and that there is no evidence for any potential for developmental toxicity for AA 15 and AEC.*"

ii) Your comments

With your comments, you provided a read-across justification document (dated 7 November 2019). The read-across justification document explains that the source substance is a (bio)transformation product of the main constituent of the Substance: "*This read-across is based on the hypothesis that different substances give rise to common compounds to which the organism is exposed. The common compound is the source substance (AEC) and the (bio)transformation product of the major compound of the target substance*".

Furthermore, in your comments you explain that you "*took a read-across approach that is different from your interpretation.*" ECHA notes that the read-across approach, specifically the identity of the source substance, in the read-across justification document provided with your comments is different from the dossier: In your comments you explain that the source substance (AEC) is a (bio)transformation product of the main component of the Substance, instead of being the main component itself, as stated in the dossier.

iii) Conclusion

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be similar to those of the source substance.

ECHA notes the following shortcomings with regards to the predictions of toxicological properties, irrespective of whether the source substance is considered to be the (bio)transformation product of the main component or the main component of the target substance itself.

[3] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

Characterisation of the source substance(s)

Annex XI, Section 1.5 of the REACH Regulation provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as group.*"

According to the ECHA Guidance, "*the purity and impurity profiles of the substance and the structural analogue need to be assessed*", and "*the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded*". The purity profile and composition can influence the overall toxicity/properties of the Substance and of the source substance(s).[4] Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

Furthermore, whenever the Substance and/or the source substance(s) are UVCB substances, qualitative compositional information of the individual constituents of the substances needs to be provided; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable.[5]

The source study and supporting study (ii) are conducted with the source substance, i.e. an UVCB substance defined as 'Fatty alcohols C12-14 (even numbered, linear and branched), reaction products with ethylene oxide and chloroacetic acid, sodium salt' (CAS No. 33939-64-9).

Neither the dossier nor the read-across justification document provides any qualitative compositional information of the individual constituents of the source substance, or quantitative characterisation in the form of concentration of the individual constituents of the source substance. Without this information, comparative assessment of the compositions of the Substance and of the source substance cannot be completed. Therefore, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the composition of the source substance.

Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[6]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include e.g. information on the impact of exposure to all constituents of the Substance on the prediction, and bridging studies to compare properties of the Substance and source substance.

Missing information on the impact of non-common compounds

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.3.1
[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.5.5
[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

Exposure to the Substance may also lead to exposure to other compounds than the main constituent of the Substance or the (bio)transformation product of the main constituent, i.e. the claimed source substance. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

According to the dossier, the Substance consists of [redacted] constituents. Based on the concentration ranges given for each constituent in the dossier, ECHA understands that the main constituent, with a concentration range of [redacted] is 'Fatty alcohols C13 (linear and branched), reaction products with ethylene oxide, sodium chloroacetate and ethanolamine'.

a) No information on further constituents

i. Information in the dossier

According to your read-across hypothesis in the dossier, the source substance is the main constituent of the Substance, and this constituent is the main driver of potential toxicity for the Substance. However, the dossier contains no justification why the source substance, which you claim to be the main constituent, would be the only toxicologically relevant constituent of the Substance. No experimental data or other adequate and reliable information addressing the impact of exposure to the other ten constituents of the Substance is provided.

ii. Your comments

In the read-across justification document provided with your comments, you consider that the toxicological concern should be addressed to the main (first) constituent since it represents approximately [redacted] of the target substance, more precisely the ethoxylated ether part.

The read-across justification document further assumes that the potential toxicity of "*the second constituent, Acetamide, 2-(C13-15 (odd numbered, branched and linear)-alkyloxy)-N-(2-hydroxyethyl)-, which is present at an average rate of* [redacted] *in the target substance*" is covered by the main (first) constituent based on the high similarity of their structures. In reference to the first and second constituents, the read-across justification document refers to Fiume *et al.* (2015)[7] for the safety assessment of ethanolamides. This publication concludes that "*No data on the reproductive and developmental toxicity or carcinogenicity of the ethanolamides included in this report were found.*"

You also address "*the third constituent of the target substance*", i.e. Alcohols, C13-15 (odd numbered, branched and linear), which is present at an average rate of [redacted] You consider that long chain alcohols (C6-C22) have been extensively tested, and that these chemicals do not show evidence of activity in the reproductive system.

ECHA notes that the information provided in the read-across justification addresses three components of the Substance. You consider that none of these constituents show activity or toxicity in the reproductive system.

iii. Conclusion

Thus, there is no information to support your claim that the source substance, which you claim to be either the (bio)transformation product of the main constituent of the Substance or the main component of the target substance itself, is the only toxicologically relevant constituent of the Substance.

[7] Fiume et al. (2015). Safety Assessment of Ethanolamides as Used in Cosmetics. Int J Toxicol. 2015 Jul-Aug;34(1 Suppl):18S-34S

Further, irrespective of whether the source substance is considered to be the (bio)transformation product of the main component or the main component of the target substance itself, neither the read-across justificaton document nor the information in the dossier address all the remaining components of the Substance. Therefore, it is impossible to predict the properties of the Substance which originate from the further constituents.

b) No information on ethanolamine

According to the information in your dossier and read-across justification document, the source substance characterised as 'Fatty alcohols C12-14 (even numbered, linear and branched), reaction products with ethylene oxide and chloroacetic acid, sodium salt' does not appear to include ethanolamine, which, according to IUCLID section 1.2, is part of the main constituent of the Substance (cf. 'Fatty alcohols C13 (linear and branched), reaction products with ethylene oxide, sodium chloroacetate and ethanolamine'; emphasis added).

In the read-across justification document provided with your comments you explain that the source substance is a (bio)transformation product of the main constituent of the Substance. The document does not address ethanolamine.

Ethanolamine itself is suspected of damaging fertility or the unborn child[8]. You have not provided any information addressing the impact of exposure to ethanolamine, justifying why the source substance, which does not contain ethanolamine, does not underestimate the hazard prediction of the Substance. ECHA concludes that the source substance is not representative of the main constituent of the Substance.

In the absence of such information, you have not substantiated why the source substance would be "*the main constituent driving the potential toxicity of the target substance*", and you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Absence of adequate supporting information to compare properties of the substances

According to the information in your dossier, you consider the source substance to be the main constituent of the Substance, and that the main constituent would be driving the potential toxicity for the Substance.

According to your read-across hypothesis provided with your comments, the source substance is a (bio)transformation product of the main constituent of the Substance, and this constituent is the main driver of potential toxicity for the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

In order to support your claim that your Substance and source substance(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to their "*similar results profiles in an in vitro study for the developmental potential*". You have provided two human pluripotent stem cell-based assays measuring changes in cellular metabolism to predict developmental toxicity *in vitro* (devTOXqP-iPS Cell Assay): one study conducted with the Substance, and one study conducted with the source substance 'Fatty alcohols C12-14 (even

[8] https://echa.europa.eu/substance-information/-/substanceinfo/100.004.986

numbered, linear and branched), reaction products with ethylene oxide and chloroacetic acid, sodium salt'.

Both the dossier and the read-across justification document provided with your comments address the above-mentioned *in vitro* studies, concluding that "*there is no evidence for any potential for developmental toxicity for AA 15 and AEC.*"

This *in vitro* data set provides some information that the source and target substances may have similar properties *in vitro*. However, in view of the complexity of the reproductive process and large number of potential targets/mechanisms associated with this broad area of toxicity, *in vitro* studies provide only limited information. A negative *in vitro* result predicting absence of a particular property for a substance alone cannot be interpreted as demonstrating the absence of a reproductive hazard with the same confidence as an animal study[9].

In the absence of reliable and adequate bridging studies allowing to compare the properties of the Substance and of the source substance, you have not established that the Substance and the source substance are likely to have similar properties in relation to reproductive toxicity. Therefore you have not provided sufficient supporting information to strengthen the rationale for read-across.

Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

Based on the above, the information you provided do not fulfil the information requirement, and you are still required to provide information on the prenatal developmental toxicity study in a first species (rat or rabbit), oral route (Annex IX, Section 8.7.2); test method: EU B.31/OECD TG 414, with the Substance.

In your comments you, as the only registrant of the Substance, indicate your willingness to submit an updated technical dossier.

[9] ECHA Guidance R.7a, section R.7.6.4

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision CCH-D-2114449968-26-01/F. The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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 of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

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.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Production volume
In your comments you indicate a possible future reduction in your production volume. However, registrants that have lowered their tonnage band after the adoption of the initial evaluation decision continue to be bound by the requirements relevant for the tonnage band at which they were addressed in the initial evaluation decision. ECHA notes that at the time of adoption of the original decision, your production volume was 100-1000 tpa. Therefore, you are still required to provide the requested information irrespective of a possible future tonnage downgrade[10].

[10] ECHA's practical guide "How to act in dossier evaluation" (April 2020), section 6: https://echa.europa.eu/documents/10162/13643/pg_dossier_evaluation_en.pdf/5788b5ee-f6c0-df56-c7ea-c693740acf87

Appendix 3: Further information, observations and technical guidance

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

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.