~~Confidential~~

Helsinki, 28 April 2021

Addressee: [redacted]

Decision number: TPE-D-2114551150-64-01/F
Substance name: Reaction products of 1H-imidazole-1-ethanol, 4,5-dihydro-, 2-(C11-C13 odd-numbered alkyl) derivs. and sodium hydroxide and chloroacetic acid
EC number: 938-645-3
CAS number: NS
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 16/12/2019

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

By decision TPE-D-2114359618-36-01/F of 27 April 2017 ("the original decision") ECHA requested you to submit information by 6 May 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):

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance.**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using 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].

[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

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

[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 on general considerations

(i) Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

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 (addressed under 'Predictions for toxicological properties').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4,5].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13: 'Analogue Approach for REACH Registration of ALKYLAMPHOACETATES'.

You read-across between the structurally similar substance, Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C7-C17 odd-numbered, C17-unsatd. alkyl) derivs. and sodium hydroxide and chloroacetic acid (EC No 931-291-0, 'Amphoacetates C8-C18') as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties:
"It is concluded that based on the similar composition and structural similarity of the components present and their water solubility, partition coefficient, vapour pressure and surface activity, the analogous substances will be distributed similarly in the environment and in the human body and may have similar (eco)toxicological properties."

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

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 based on a worst-case approach.

ECHA notes the following shortcomings with regards to predictions of toxicological properties.

Characterisation of the structural similarities and differences between the substances

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"*. In order to determine the structural similarities and differences between the substances included in a read-across approach, and in particular when these substances are UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) 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[6].

You highlight differences in the composition of the substance relating to the distribution of the alkyl derivative constituents between the source and target.

You elaborate on the main differences and similarities for the substances as follows (Table 1):

Table 1. Identification for Amphoacetates C8-C18 and Amphoacetate C12-C14 as provided in the 'Analogue Approach for REACH Registration of ALKYLAMPHOACETATES', section 4.2.

	Amphoacetate C12-C14 EC 938-645-3 (target)	Amphoacetates C8-C18 EC 931-291-0 (source)
Monoacetate/Diacetate ratio	Monoacetate form and diacetate form ([redacted])	Monoacetate form [redacted] and diacetate form ([redacted])
Distribution of alkyl derivatives constituents		
C8	[redacted]	[redacted]
C10	[redacted]	[redacted]
C12	[redacted]	[redacted]
C14	[redacted]	[redacted]
C16	[redacted]	[redacted]
C18+C18:1	[redacted]	[redacted]

A wider range of carbon chain length spanning from C8 to C18 is included in the composition of the source substance compared with the Substance. The C12 and C14 alkyl derivatives are the

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

similar main constituents between the substances. Differences in the concentrations of these constituents are identified. More specifically, the Substance has a higher concentration in C12/14 than the source substance.

Furthermore, you report different "forms", i.e. mono acetate and diacetate forms for each of the substances. ECHA understands from this information that there may be two different possible situations/forms of a substance depending on the amount of chloroacetic acid being used in the manufacturing process.

A [redacted] ratio of monoacetate/diacetate for each carbon chain length is the only "form" existing for the Substance. In addition to this configuration, for the source substance a "monoacetate form" can exist where [redacted] of the alkyl derivatives are in the mono-acetate form and [redacted] are in the di-acetate form.

It is unclear whether the concentrations reported for each "form" of the substances correspond to average concentrations for the entire set of alkyl constituents or whether these concentrations apply to each alkyl derivative individually. For example, in a [redacted] mono-acetate[redacted] diacetate form, it is unclear whether there are [redacted] of each C-chain length as mono-acetates or is there an average of [redacted] of all the alkyl chain derivatives with varying concentrations of different c-chain length are mono-acetates, with this concentration for some constituents being [redacted] and for others [redacted]

In order to establish the compositional similarities, it is important to provide a breakdown of the ratio of mono-diacetate for each carbon chain length for source substance and for the Substance. ECHA notes the technical difficulties mentioned in your dossier in providing an analytical characterisation of the substances. However this is particularly important since the prediction is based on diacetates alkyl chain derivatives being a worst-case.

In the absence of this information, it is not possible to characterise qualitatively and quantitatively the constituents included in the composition of the substances and to determine the extent of the similarities between the substances.

Missing supporting information to compare properties of the substances

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*"[7]. 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 bridging studies to compare properties of the Substance and source substance.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). 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 substances 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).

[7] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

You identify elements of structural similarities between the substances in section 4.1.1 of your read-across justification document "*The ratio of the (potential) structures contained in the surfactant part of the substance is not expected to play a significant role with regard to the (eco)toxicological properties of the substances, because the structures all have the same functional groups, i.e. one or two aminoglycinate (-NH-CH2-COONa) functions (i.e. terminal acetate) and hydroxyl, linked to a fatty chain by an amide bond*".

You also highlight differences in their compositions "*All analogous substances contain a main alkylamphoacetate fraction, as well as sodium chloride, sodium glycolate and residual water, all in comparable amounts. Because of the decreasing proportion of other alkyl chains, the Amphoacetates C12-C14 and Amphoacetates C12 have an increasing content in the C12 alkyl structures compared to the Amphoacetates C8-18. C8 Amphoacetates has a high percentage of C8 alkyl chains.*"

You provide information to establish that diacetates are a worst case for C8-18. More specifically, you conducted two OECD TG 422 studies with the source substance (EC 931-291-0) using two different testing materials ([redacted]), a monoacetate C8-C18 and a diacetate C8-C18, respectively, in order to cover both forms of the substance. In the one study conducted with the mono-acetate, you derived a NOAEL of 1000 mg/kg bw/day based on the absence of adverse effects at the highest dose, while in the study with the diacetate, effects were observed, which you followed up with a sub-chronic study.

The choice of the diacetate form for the OECD TG 408 and 414 studies with the source substance is based on the outcome of the two OECD TG 422 studies. The observation of different effects in the OECD TG 422 studies conducted with the mono-acetate and with the diacetate form of the source substance suggests that the mono-acetate and diacetate forms of a substance may have different toxicological properties. Their ratio in the composition of the substances may play a role in the toxicological properties of the substance as a whole. This is in contradiction with your claim that "*The ratio of the (potential) structures contained in the surfactant part of the substance is not expected to play a significant role with regard to the (eco)toxicological properties of the substances*".

The data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and of the source substance to support your read-across hypothesis whereby these structurally similar substances cause the same type of effect(s).

Therefore, ECHA considers that you have not provided an adequate scientific basis according to which the properties of Amphoacetates C12-14 for the endpoints sub-chronic toxicity and pre-natal developmental toxicity may be predicted from data generated using Amphoacetates C8-18.

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.

Appendix 1: Reasons

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

In the original decision you were requested to submit information derived with the Substance for sub-chronic toxicity study (90-day), in rats, via oral route.

In the updated registration dossier subject to follow-up evaluation, you have adapted the standard information requirement mentioned above according to Annex XI, section 1.5.

In support of your adaptation, you have provided a study according to OECD TG 408, conducted with the analogue substance [redacted], i.e. the diacetate C8-C18 (EC no. 931-291-0).

As explained above, in the Appendix on general considerations, 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.

Therefore, the information you provided does not fulfil the information requirement, and you are still required to provide information on sub-chronic toxicity study (90-day), in rats, oral route (Annex IX, Section 8.6.2); test method: EU B.26./OECD TG 408 with the Substance.

In your comments, submitted in alignment with the Amphoacetates consortium, you agree to perform the requested study. You intend to provide a dossier update by December 2022 with the requested information.

2. 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 original decision you were requested to submit information derived with the Substance for pre-natal developmental toxicity study in a first one species (rats or rabbits), via oral route. In the updated registration dossier subject to follow-up evaluation, you have adapted the standard information requirement mentioned above according to Annex XI, section 1.5.

In support of your adaptation, you have provided a study according to OECD TG 414, conducted with the analogue substance [redacted], i.e. the diacetate C8-C18 (EC no. 931-291-0).

As explained above, in the Appendix on general considerations, 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.

Therefore, the information you provided does not fulfil the information requirement, and you are still required to provide information on pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (Annex IX, Section 8.7.2); test method: EU B.31./OECD TG 414 with the Substance.

In your comments, submitted in alignment with the Amphoacetates consortium, you agree to perform the requested study. You intend to provide a dossier update by December 2022 with the requested information.

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 TPE-D-2114359618-36-01/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 40 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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

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.

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.