EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 28 April 2021

Addressee of the decision: [redacted]

Registration number subject to the decision: [redacted]
Registration number of the new Lead Registrant: [redacted]

Decision number: TPE-D-2114551148-49-01/F
Substance name: Acetic acid, chloro-, sodium salt, reaction products with 4,5-dihydro-2-undecyl-1H-imidazole-1-ethanol and sodium hydroxide
EC number: 271-794-6
CAS number: 68608-66-2
Submission number subject to follow-up evaluation: [redacted], updated by the new Lead Registrant
Submission date subject to follow-up evaluation: 24/08/2020, updated by the new Lead Registrant

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

By decision TPE-D-2114359615-42-01/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 (rat or rabbit), 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 as provided in the Analogue Approach for REACH Registration of ALKYLAMPHOACETATES, section 4.2.

	Amphoacetate C12 EC 271-794-6 (target)	Amphoacetates C8-C18 EC 931-291-0 (source)
Monoacetate/Diacetate ratio	Monoacetate form only	Monoacetate form and Diacetate form
Distribution of alkyl derivatives constituents		
C8		
C10		
C12		
C14		
C16		
C18+C18:1		

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 alkyl derivative is the similar main constituent between the substances. Differences in the concentrations of this constituent is identified. More specifically, the Substance has a higher concentration in C12 than the

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

source substance.

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

A mono acetate only form 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 whether 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 and target substances. 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 determine the extent of the structural similarities and differences between the substances.

Missing information to substantiate worst-case consideration

According to the ECHA Guidance[7] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

As indicated above, your read-across hypothesis is based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of 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 a conservative prediction of the properties of the Substance from the data on the source substance(s). Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

You identify elements of structural similarities between the substances in section 4.1.1 of your read-across justification document "*Furthermore all analogous structures 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. This similarity will result in similar behaviour of the analogues in the eco-system and in the body after uptake*". 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,*

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

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."

In the category justification document (Section 4.1.1) you also specify that "*The ratio of the (potential) structures contained in the surfactant part of the substance have been found to play a role with regard to the eco-toxicological properties of the substances, for the individual endpoints the influence is addressed and follow-up testing (where applicable) is done with the worst case.*"

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, a monoacetate C8-C18 and a diacetate C8-C18 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, that you followed up with a sub-chronic study.

While ECHA understands that the choice of the diacetate form for the OECD TG 408 and 414 studies is based on a worst-case approach for the source study, there is no information on whether this also applies for a different composition, i.e. with different distribution of alkyl chain length. Additionally, there is no information on the composition of the C8-18 sample tested in the source studies which is presented as diacetate C8-18.

In the absence of information on these aspects, it remains unclear which constituents of these substances are systemically available. Consequently, a plausible mechanistic explanation cannot be presented on why and how test results from the source substance can be used to predict systemic properties for the target substance. ECHA considers that you have not established that the properties of these substances relating to systemic toxicity are likely to be similar or follow a regular pattern.

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

In your comments on the draft decision, submitted on behalf of the co-registrants, you noted your intention to improve the read-across approach in a future dossier update, but you have not provided any further information.

You remain responsible for complying with this decision.

B. 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, you express an intention to strengthen your read-across approach by conducting 'bridging studies' (OECD TG 407 or 422) with the Substance.

You remain responsible for complying with this decision.

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, you agree to perform the requested study. You intend to provide a dossier update with this information by December 2022.

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-2114359615-42-01/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.

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 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.