EUROPEAN CHEMICALS AGENCY

Helsinki, 5 February 2020

Addressee
Registrant of JS_91648-19-0 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
24 April 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-C12-14 acyl derivs., hydroxides, inner salts
EC number: 293-878-1
CAS number: 91648-19-0

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 ("REACH" or the "REACH Regulation"), ECHA requests that you submit the information listed below by the deadline of ***14 February 2022***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with the Substance;

2. 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 Substance;

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance;

Your originally proposed tests using an analogue substance 1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,Ndimethyl-3-sulfo-, N-(C8-18(even numbered) acyl) derivs., hydroxides, inner salts], EC 939-455-3 (CAS 68139-30-0 or CAS 70851-08-0; C8-18) are rejected, according to Article 40(3)(d) of the REACH Regulation:

- Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408)
- Pre-natal developmental toxicity study (EU B.31./OECD TG 414)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210)

Conditions to comply with the requests

The Appendix on general considerations addresses issues relevant for several requests while Appendix A states the reasons for the requests for information to fulfil the requirements set out in Annex IX of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and

provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 on general considerations

1. Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5 REACH.

You seek to adapt the following standard information requirements by applying read-across approaches in accordance with Annex XI, Section 1.5 of the REACH Regulation:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

I. Predictions for (eco)toxicological properties

You have provided a read-across justification in IUCLID Section 13.

In your read-across justification you have identified two structurally similar source substances:

- Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C8-18(even numbered) acyl) derivs., hydroxides, inner salts; EC number: 939-455-3 (CAS No 1469983-49-0; C8-18 cocamidopropyl hydroxysultaine), and
- Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C12-18(even numbered) acyl) derivs., hydroxides, inner salts; EC number: 939-457-4 (CAS No 1469983-50-3; C12-18 cocamidopropyl hydroxysultaine).

The source substances and the Substance contain C10, C12 and C14 alkyl chains, while the source substances contains shorter (C8) and longer alkyl chains (C18).

You have provided the following reasoning for the prediction of (eco)toxicological properties: "*The substances are structurally similar and available data indicates that the compositions of the three different substances are comparable. It can therefore be concluded that an analogue Read-Across approach is viable.*"

ECHA understands that you predict the properties of the Substance using a read-across

[2] ECHA Guidance R.6
[3] Read-Across Assessment Framework (RAAF)
[4] RAAF - considerations on multi-constituent substances and UVCBs

hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

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

i. Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[5]. It should explain why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in chemical composition between the source substances and the Substance is a sufficient basis for predicting the properties of your Substance for other endpoints.

While ECHA agrees that the source substances and your Substance share the common main constituents, you fail to explain why the stated differences in the chemical composition should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern.

In your comments on the draft decision you acknowledge the identified deficiencies in the read-across hypothesis regarding the failure to explain the impact of structural differences on the predictions for (eco)toxicological properties.

In conclusion, you have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source substances and your Substance.

ii. Missing 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).

[5] ECHA Guidance, Chapter R.6.
[6] ECHA Guidance, Chapter R.6, Section R.6.2.2.1.f

Supporting information must include bridging studies to compare properties of the Substance and source substances.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances with similar composition cause the same type of effects.

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).

To support your hypothesis, for environmental properties you have provided short-term fish and *Daphnia* toxicity studies with the source substance C12-18 cocamidopropyl hydroxysultaine (EC number 939-457-4) and with your Substance.

However, for the studies claimed to be conducted with the Substance, you have not provided qualitative nor quantitative compositional information of the individual constituents of the test substances to establish that they are representative of your Substance.

In your comments to the draft decision, you propose to attempt obtaining this information for the studies with the source substance.

You further indicate that the absence of compositional information of the test material is not expected to affect the read-across predictions. To support this, you indicate that the (eco)toxicological properties of the different constituents are likely to be similar hence differences in their distribution is not affecting the predictions. You also indicate that the currently available bridging studies (short-term fish and short-term *Daphnia*) show that the source substance and the Substance have similar toxicity.

ECHA notes that compositional information of the test material is already available in your dossier for the source studies, while it is missing for the studies conducted with the Substance, as explained above. You have not provided this information in your comments.

In the absence of information on test substance composition for the studies conducted with the Substance, the data set reported in the technical dossier does not allow to compare the properties of the Substance and of the source substance(s).

Consequently, you have not established that the Substance and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

iii. Relevance of the supporting information

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*".

In order to support your claim that your Substance and source substance C8-18 cocamidopropyl hydroxysultaine have similar properties for the endpoints under

[7] ECHA Guidance R.6, Section R.6.2.2.1.f

consideration in the read-across approach, you refer to their acute toxicity and bacterial mutagenicity properties.

In your comments on the draft decision, you propose to generate (Q)SAR data to add further weight of evidence to the read across justification.

Whilst the data set suggests that the substances may have similar properties for acute toxicity and bacterial mutagenicity, these studies do not provide information on the developmental toxicity properties of the Substance and source substance. Accordingly, these information are not considered as relevant to support the prediction of all the endpoints under consideration.

Predictions from (Q)SAR models may be of value in supporting read-across approaches, providing that the applicability domain of the models are appropriate[8]. However considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as reproductive or developmental toxicity, it is likely that QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints.

II. 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 source substances. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. REACH and your grouping and read-across approach is rejected.

2. Consideration on uses of the substance in relation to the tests requested in the decision

In your comments to the draft decision you also claim that the Substance is utilised as a cosmetic ingredient and therefore the unnecessary testing on vertebrate animals should be avoided.

ECHA points out that according to the ECHA factsheet available on the interface between REACH and Cosmetics Regulations, which was developed jointly with the European Commission[9], the Cosmetics Regulation does not restrict testing under REACH, if this testing is required for environmental endpoints or the substance is also registered for non-cosmetic uses. In the Chemical Safety Report (CSR) you have reported many product categories/market uses for the registered substance, such as washing, cleaning and disinfecting products, metal surface treatment products, polishes and wax blends, and use of emulsifiers and foaming agents. Furthermore, even if a substance is registered exclusively for cosmetic use, the animal testing requirements continue to apply to tests needed to assess the risks from exposure to workers in the Chemical Safety Assessment. Such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation; see Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135)).

Further information is available at https://www.echa.europa.eu/-/clarity-on-interface-between-reach-and-the-cosmetics-regulation.

[8] ECHA Guidance R.7a, Section R.7.6.4.1.2
[9] Please see https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf

Appendix A: Reasons for the requests applicable to comply with Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted for the Substance, proposed to be performed with a source substance [Popanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C8-18(even numbered) acyl) derivs., hydroxides, inner salts; EC number: 939-455-3 (CAS No 1469983-49-0; C8-18 cocamidopropyl hydroxysultaine).

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to RACH.

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

A sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX, Section 8.6.2. to REACH.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route according to OECD TG 408, to be performed with the analogue substance C8-18 cocamidopropyl hydroxysultaine (EC number: 939-455-3; CAS No 1469983-49-0).

ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance C8-18 cocamidopropyl hydroxysultaine. As explained in the Appendix on general considerations, Section 1, your adaptation according to Annex XI, Section 1.5 to REACH is rejected.

Therefore, your proposal to test the analogue substance, C8-18 cocamidopropyl hydroxysultaine, is rejected according to Article 40(3)(d).

You proposed testing by the oral route. ECHA agrees with your proposal. Based on the ECHA guidance, the most appropriate route of administration is the oral route[10] since the Substance is a liquid of very low vapour pressure and no uses with spray application that could potentially lead to aerosols of inhalable size, are reported. You did not specify the species to be used for testing. According to OECD TG 408, the rat is the preferred species.

According to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the proposed test, with the Substance.

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, Section 8.7.2 to REACH.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414, to be performed with the analogue substance C8-18 cocamidopropyl hydroxysultaine (EC number: 939-455-3; CAS No 1469983-49-0).

[10] ECHA Guidance R.7a, Section R.7.5.4.3

ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance C8-18 cocamidopropyl hydroxysultaine. As explained in the Appendix on general considerations, Section 1, your adaptation according to Annex XI, Section 1.5 to REACH is rejected.

Therefore, your proposal to test the analogue substance, C8-18 cocamidopropyl hydroxysultaine, is rejected according to Article 40(3)(d).

You proposed testing with the rat as a first species. You may select between the rat or the rabbit because both are preferred species under the OECD TG 414. You did not specify the route for testing. The oral route is the most appropriate route of administration to investigate reproductive toxicity.

According to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the proposed test with the Substance.

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Long-term toxicity testing on fish is a standard information requirement in Annex IX, Section 9.1.6 to REACH.

You have submitted a testing proposal for a Fish, early-life stage toxicity test according to OECD TG 210, to be performed with the analogue substance C8-18 cocamidopropyl hydroxysultaine (EC number: 939-455-3; CAS No 1469983-49-0).

ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance C8-18 cocamidopropyl hydroxysultaine. As explained in the Appendix on general considerations, Section 1, your adaptation according to Annex XI, Section 1.5 is rejected.

Therefore, your proposal to test the analogue substance, C8-18 cocamidopropyl hydroxysultaine, is rejected according to Article 40(3)(d).

According to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the test with the Substance.

Appendix B: Procedural history

ECHA received your registration containing the testing proposals for examination on 24 April 2018.

ECHA held a third party consultation for the testing proposals from 18 June 2018 until 2 August 2018. ECHA did not receive information from third parties.

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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 C: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

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(s).

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[11].

4. Test material

   Selection of the test material(s)

   While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[12].

5. List of references of the ECHA Guidance and other guidance/ reference documents[13]

   QSARs, read-across and grouping
   Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

[11] https://echa.europa.eu/practical-guides
[12] https://echa.europa.eu/manuals
[13] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

ECHA Read-across assessment framework (RAAF, March 2017)[14]

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents
Guidance Document on aqueous –phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[14] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.