EUROPEAN CHEMICALS AGENCY

Helsinki, 5 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114465580-48-01/F
Substance name: Aspartic acid, N-(3-carboxy-1-oxo-sulfopropyl)-N-(C16-C18 (even numbered), C18 unsaturated alkyl) tetrasodium salts
EC number: 939-704-6
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09/06/2016
Registered tonnage band: 100-1000

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. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered 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 registered substance;**

You have to submit the requested information in an updated registration dossier by ***12 July 2021.*** You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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[1] by Wim De Coen, Head of Unit, 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.

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Appendix 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

TOXICOLOGICAL PROPERTIES

Your registration dossiers contain adaptation arguments which are based on a grouping and read-across approach in accordance with Annex XI, Section 1.5. of the REACH Regulation. You have grouped registered substances and formed a category subgroup of 'N3 sulphosuccinates' to predict missing (eco)toxicological properties within this group.

Within your category there are read-across adaptations for the following standard information requirements:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Pre-natal developmental toxicity study (Annex IX, Section 8,7.2);

ECHA has considered the scientific rationale of your grouping (i.e. category) approach before assessing the validity of your read-across predictions for the individual endpoints. The read-across assessment analyses all predictions made within the category.

Grouping of substances and read-across approach

You have sought to adapt information requirements listed above by applying a read-across approach in accordance with Annex XI, Section 1.5. 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). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration.

Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework[2][3] foresees that there are two options which may form the basis of the read-across hypothesis- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

A. Description of your grouping approach

You seek to adapt the human health information requirements for a screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) and for a pre-natal developmental toxicity study (Annex IX, Section 8,7.2) by applying a read-across approach according to Annex XI, Section 1.5.

You propose to read-across between the substance subject to this decision, Aspartic acid, N-(3-carboxy-1-oxo-sulfopropyl)-N-(C16-C18 (even numbered), C18 unsaturated alkyl) tetrasodium salts (EC No. 939-704-6, CAS not available), and the two following structurally similar substances:

[1] butanedioic acid, 2(or 3)-sulfo-, 4-[2-[(1-oxo(C12-C18(even numbered) and C18unsaturated)alkyl))amino]ethyl]esters, disodium salts (EC No. 939-637-2) (N2 group), and
[2] butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate (EC No. 209-406-4, CAS No. 577-11-7)(di-ester group).

You have provided two justification documents as separate attachments in IUCLID: a read-across justification document for the group of sulfosuccinates named "READ ACROSS ARGUMENTATION FOR THE SULFOSUCCINATES" and a justification document for the N3-subgroup "Read across justification N3-subgroup". Both documents are dated 1st June 2016. You outline in the read-across justification document 'read-across argumentation for the sulfosuccinates' the general structures of "*5 subgroups considered for the detailed read across argumentation*" and make a general characterisation of the sulfosuccinates.

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://echa.europa.eu/publications/technical-scientific-reports

Your read-across justification document 'Read across justification N3-subgroup' attached to the registration dossier covers:

- general compositional information for the registered substance;
- the reasoning for the grouping based on general low toxicity;
- general information to support the read-across approach based on physico-chemical properties;
- general information to support the read-across approach based on similarity or regular pattern in toxicological and ecotoxicological properties; and
- general data matrices showing the available physico-chemical, environmental fate and (eco)toxicological data and how the data is to be read across within the category.

You state in that document that the registered substance is the only member of the N3 subgroup and that the registered substance forms *"a separate subgroup because the structure of the tertiary amide is not completely comparable to the structure of the N1-subgroup which are simple secondary amide structures."*

You use the following arguments to support the prediction of properties of the registered substance from data for source substances:

"For the toxicological endpoints, there was a general low toxicity profile in this subgroup as seen for N1 and N2 subgroup. The substance was not predicted irritating nor tested sensitising for skin (NC), but showed signs for eye irritation (CLP category 2 subgroup classification proposed). LD50 values for oral and dermal are above 2000 mg/kg bw, and NOAEL for repeated dose toxicity varied from 500 to 1000 mg/kg bw. The combined repeated dose toxicity/reproduction and developmental toxicity study from the N2 subgroup did not show reproductive toxicity effects. This lack of effects was further supported by the absence of reproductive and developmental findings for other sulfosuccinates as they were tested from the Di-ester subgroup."

You also indicated the following with respect to reproductive toxicity and developmental toxicity:

"Finally, based on the structural, kinetic/metabolic and toxicological similarity between subgroups, read across was also performed with the Di-ester subgroup substance CAS 577-11-7 for:

- *reproductive toxicity* [...]
- *developmental toxicity* [...]"

According to you the source and registered substances have similar properties for the above-mentioned information requirements.

You submitted a revised read-across justification documentation with your comments to the draft decision. In this documentation, (1) you specified the compositions and the concentration ranges of the constituents of the target and the source substances, (2) you provided more detailed information on sub-acute toxicity of the source substance [1], and (3) you provided a comparison of the observed effects with that of the sub-chronic toxicity study with the target substance. You conclude that the source substances are of higher toxicity than the target substance, and hence, the source substances can be considered as 'worst case' substances for read-across.

In your revised read-across justification document you also confirm that your read-across hypothesis is based on structurally similar substances which have similar toxicological properties. However, in your comments, you re-phrased your initial read-across hypothesis by stating: "*The Registrant does not further claim that read-across for reproductive and developmental toxicity endoints is performed with the substances based on the structural, kinetic/metabolic and toxicological similarity between subgroups. The hypothesis is based on the hypothesis that source and the target substance have a "safe and similar toxicity profile for systemic toxicity" and that therefore the properties of the target substance can be predicted from data on the substance*".

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from source substances.

B. ECHA analysis of your predictions of toxicological properties in light of the requirements of Annex XI, Section 1.5

Since the N3-subgroup is only composed of the target substance, ECHA considers your adaptation as an analogue approach whereby you use information on the source substances described above to predict the properties of the target substance as follows:

Information requirement: reproductive toxicity
- Key study: "*combined repeated dose toxicity study with the reproduction/developmental toxicity screening test*" (according to OECD TG 422) with substance [1] (study report from 2012)
- Key study: "*two-generation reproductive toxicity study*" (equivalent or similar to OECD TG 416) with substance [2] (study report from 1986)

Information requirement: pre-natal developmental toxicity study
- Key study: "*prenatal developmental toxicity study*" (equivalent or similar to OECD TG 414) with substance [2] (study report from 1976)

ECHA understands that you consider that the substance [1] and the target substance have a "*safe and similar toxicity profile for systemic toxicity*" and that therefore the properties of the target substance can be predicted from data on the substances [1] and [2].

According to the information provided in the revised read-across justification document for N3 subgroup, the similarity in toxicity profiles between the source and the target substances is based on information on acute toxicity, eye irritation, skin sensitisation, genotoxicity. You also point at the outcome of repeated dose toxicity studies conducted with the substance [1] and the target substance. In your comments to draft decision you compared the effects observed in the sub-chronic toxicity study (90-day) with the registered substance and in the screening study (OECD 422) with substance [1]. You also compare the NOAELs of the developmental toxicity study with substance [2] and the screening study with [1].

ECHA acknowledges the similarities with respect to repeated dose toxicity but notes that there is still no relevant information on the registered substance that would enable comparison of reproductive or developmental toxicity with the source substances.

Consequently, as your claims that "*the N2 source substance is considered to be a worst case substance for read-across*" and that the source and target substances have "*safe and similar toxicity profile for systemic toxicity*" are not supported by information relevant to

reproductive or developmental toxicity endpoints, ECHA considers that this information does not constitute relevant supporting information in the context of a read-across approach intended to predict developmental and reproductive toxicity properties.

C. Conclusion

As explained above, there is not sufficient data with the registered substance to support your hypothesis that the source and target substances have similar reproductive and developmental toxicologic properties. Consequently, your hypothesis is not a reliable basis whereby the properties of the substance subjected to this decision may be predicted by interpolation from other substances in the group. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5 and is rejected.

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing

- key study: study record for a "*combined repeated dose toxicity study with the reproduction/developmental toxicity screening test*" (according to OECD TG 422) with substance [1] (study report from 2012)
- key study: study record for a "*two-generation reproductive toxicity study*" (equivalent or similar to OECD TG 416) with substance [2] (study report from 1986)
- supporting study: study record for a "*two-generation reproductive toxicity study*" (equivalent or similar to OECD TG 416) with substance [2] (study report from 1970)

However, as explained above in Appendix 1, section 'Grouping of substances and read-across approach' of this decision, your adaptation of the information requirement is rejected.

ECHA notes further that the provided two-generation reproductive toxicity studies do not cover all the key parameters foreseen to be investigated in a reproduction/developmental screening test (according to OECD TG 421/422) and therefore cannot be used to fulfill the current standard information requirement. More specifically, the provided two-generation reproductive toxicity studies lack the following parameters:

- parental (P) generation: histopathology and weight of reproductive organs, histopathology and weight of major non-reproductive organs (OECD TG 422 only)
- offspring (F1): certain parameters for endocrine modes of action

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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 solid, ECHA concludes that testing should be performed by the oral route.

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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

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

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a

- key study: study record for a "*prenatal developmental toxicity study*" (equivalent or similar to OECD TG 414) with the analogue substance [2] (study report from 1976)
- supporting study: study record for a "*combined repeated dose toxicity study with the reproduction/developmental toxicity screening test*" (according to OECD TG 422) with the analogue substance [1] (study report from 2012)
- supporting study: study record for a "*prenatal developmental toxicity study*" (equivalent or similar to OECD TG 414) with the analogue substance calcium bis{1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate} (EC No. 204-889-8, CAS No. 128-49-4) (study report from 1976)

However, as explained above in Appendix 1, section 'Grouping of substances and read-across approach' of this decision, your adaptation of the information requirement is rejected.

ECHA further notes that a "*combined repeated dose toxicity study with the reproduction/developmental toxicity screening test*" (test method: OECD TG 422) does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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 solid, ECHA concludes that testing should be performed by the oral route.

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: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

Deadline to submit the requested information in this decision

In your comments to the draft decision you request "*prolongation of the deadline to at least 24 months from the date of the final decision*" if ECHA does not accept the updated read-across justifications. You submitted a letter from a contract research organisation outlining a realistic schedule for conducting the requested studies. Furthermore, you note that testing of other sulphosuccinate compounds of various subgroups are currently under testing which needs to be discussed in the consortium for the read-across strategy. ECHA acknowledges your comments and has prolonged the decision deadline to 24 months.

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 24 July 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 request(s). The deadline of the decision was extended.

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.