EUROPEAN CHEMICALS AGENCY

Helsinki, 21 May 2018

Addressee: [redacted]

Decision number: CCH-D-2114408304-61-01/F
Substance name: Butanedioic acid, 2(or3)-sulfo-, 4-[2-[(1-oxo(C12-C18(even numbered) and C18 unsaturated)alkyl)amino]ethyl]esters, disodium salts
List number: 939-637-2
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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with 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 with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **28 May 2020**. You also have to update the chemical safety report, where relevant.

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 **Claudio Carlon**, Head of Unit, Evaluation **E2**

[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 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.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1 and 2).

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- a sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.) with Aspartic acid, N-(3-carboxy-1-oxo-sulfopropyl)-N-(C16-C18 (even numbered), C18unsaturated alkyl) tetrasodium salts (EC 939-704-6)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) with Butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate (CAS 577-11-7) and calcium bis{1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate} (CAS 128-49-4).

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[2]. 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,

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

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 foresees that there are two options which may form the basis of the read-across hypothesis[3]- (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.

You consider to achieve compliance with the REACH information requirements for the registered substance Butanedioic acid, 2(or3)-sulfo-, 4-[2-[(1-oxo(C12-C18(even numbered) and C18 unsaturated)alkyl)amino]ethyl]esters, disodium salts (EC 939-637-2) using data of structurally similar substances Aspartic acid, N-(3-carboxy-1-oxo-sulfopropyl)-N-(C16-C18 (even numbered), C18unsaturated alkyl) tetrasodium salts (EC 939-704-6), Butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate (CAS 577-11-7) and calcium bis{1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate} (CAS 128-49-4) (hereafter the 'source substances').

You have provided a read-across documentation as two separate attachments in the registration dossier.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: on the basis of structural similarity, similarity in physico-chemical, ecotoxicological and toxicological (including kinetic/metabolic) properties in certain endpoints, it is possible to predict the human health properties of the registered substance for other endpoints. As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical/ ecotoxicological/ toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical/ ecotoxicological/ toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on structural similarity, similar physico-chemical, ecotoxicological and toxicological properties has not established why the prediction is reliable for the human health end-points for which the read across is claimed.

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

You have also claimed that there is kinetic/ metabolic similarity between substances. However, ECHA notes that this statement is not substantiated by sufficient data: toxicokinetic data are available only for CAS No. 577-11-7 from the di-ester subgroup but not for any other subgroup to enable a comparison, and the impact of the structural differences on metabolism was not discussed. So it is not possible to conclude whether there is kinetic/ metabolic similarity in the absence of comparable data. Therefore, it is not possible to conclude that the toxicological properties of the target could be predicted from the data obtained with this source substance on the basis of kinetic/ metabolic similarity.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Following the notification of the draft decision you submitted comments regarding the read-across strategy. You proposed an analogue approach between the target and the source substance EC 939-654-5 instead of the grouping approach used originally in the dossier, although the read-across justification still make reference to the N2 subgroup properties. You identified the proposed source substance as a worst case scenario and proposed a testing strategy aiming to substantiate the read-across justification with regard to toxicological data. In the draft decision it was pointed out that the only higher tier test available for N2 subgroup was the OECD 422 study with the registered substance EC 939-637-2. To demonstrate a similar potency in toxicological properties of the target and source, you proposed to perform another OECD 422 with the source substance EC 939-654-5, subject to the requests in the another decision, and perform the requested EC 939-654-5 tests only after the results from the OECD 422 are available.

You did not specifically request a time extension of the deadline provided in the draft decision in association to the postponment of the other tests. However, you indicated that you would like to perform a stepwise sequential testing programme where first you would like to perform the screening study with the analogue substance Reaction products of ricinoleic acid with 2-aminoethanol and maleic acid and sodium hydrogensulfite (EC 939-654-5) to determine whether to continue with the OECD TG 408 and OECD TG 414 with the registered substance or with the analogue substance (EC 939-654-5).

ECHA-S notes that the 24 months deadline indicated in the draft decision allows for sequential testing for the studies requested in the decision (OECD TG 408 and OECD TG 414).

With regard to the proposed strategy it is not possible at this step to take into account information that would be provided in the future. Nevertheless, you can make a read-across adaptation using the newly generated data to improve the read-across justification. However, ECHA-S notes that there is no guarantee that the improved read-across would be considered sufficient. ECHA-S notes that any dossier update(s) will be evaluated after the deadline specified in the final decision, during the follow up process.

With regards to the performance of the OECD 422 for the purpose of read-across substantiation ECHA-S also notes that the data from this study might still not be sufficient for the read-across justification. All the available data need to be taken together and a rationale for the read-across has to be provided. However, since the study is not yet available no further conclusion can be taken at this moment in the decision making process with regard to the proposed read-across.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5., and these are set out under the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

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

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.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

In the technical dossier you have provided the following study records:

i. Key study: Combined repeated dose and reproduction / development screening study ([redacted] 2013) with the registered substance in rats, via oral route (gavage), rel. 1, according to OECD TG 422, GLP compliant;
ii. Key study: Sub-chronic (90-day) study ([redacted] 1976) in rats, via the oral route with the analogue substance, Aspartic acid, N-(3- carboxy-1-oxosulfopropyl)-N- (C16-C18 (even numbered), C18unsaturated alkyl) tetrasodium salts (EC 939-704-6), equivalent to OECD TG 408, non-GLP, rel. 2;
iii. Supporting study: Sub-chronic (90-day) study ([redacted] 1976) in dogs, via the oral route with the analogue substance, Aspartic acid, N-(3- carboxy-1-oxosulfopropyl)-N- (C16-C18 (even numbered), C18unsaturated alkyl) tetrasodium salts (EC 939-704-6), equivalent to OECD TG 409, non-GLP, rel. 3;
iv. Supporting study: 14-day dose range-finding study ([redacted], 2013) with the analogue substance, Aspartic acid, N-(3- carboxy-1-oxosulfopropyl)-N- (C16-C18 (even numbered), C18unsaturated alkyl) tetrasodium salts (EC 939-704-6) in rats, via oral route (gavage), rel. 2, equivalent to OECD TG 422, GLP compliant; and
v. Supporting study: 14-day dose range-finding study ([redacted], 2013), via the oral route with the registered substance, according to OECD TG 422, GLP complaint, rel. 1.

However, these studies do not provide the information required by Annex IX, Section 8.6.2., as explained hereunder.

ECHA notes that you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing three study records, ((ii.), (iii.) and (iv.) above), with the analogue substance Aspartic acid, N-(3- carboxy-1-oxosulfopropyl)-N- (C16-C18 (even numbered), C18unsaturated alkyl) tetrasodium salts (EC 939-704-6).

However, as explained above in "Grouping of substances and read-across approach" section of this decision, your adaptation of the information requirement is rejected. Moreover, ECHA notes that there are shortcomings on the individual studies with the analogue substance, such as poor quality (Klimisch reliability 3 for study iii.) (failure to list organs subject to histopathological examination and hence a failure to produce adequate and reliable documentation for study ii.) and shorter exposure duration for study iv. (i.e. failure to cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter).

You have also provided the screening study (study i. above) and the 14-day dose range-finding study (study v. above), with the registered substance, as key and supporting studies, respectively. However, ECHA notes that these studies do not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408).

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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is reported to occur as a water soluble solid with no significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm). There are spray applications. However, the substance has a low vapour pressure (0.04 Pa) and you stated that "*The substance is produced, formulated and used as a sodium salt in aqueous solution. Hence, the substance is considered not volatile during production, formulation and use.*" Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

In your comments on the draft decision you agree to perform the repeated dose 90-day oral toxicity study (OECD TG 408) either with the registered substance or with the analogue substance Reaction products of ricinoleic acid with 2-aminoethanol and maleic acid and sodium hydrogensulfite (EC 939-654-5). As already mentioned under the *Grouping and read-across approach for toxicological information* currently ECHA cannot accept the read-across approach, hence the study requested should be provided with the registered substance. ECHA reminds that all the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

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

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.

A "pre-natal developmental toxicity study" (test method EU B.31./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 the following study records:

i. Key study: Pre-natal developmental toxicity study in rats via the oral route (feed) (equivalent to OECD TG 414; non-GLP; rel. 2) with the analogue substance Butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate (CAS no. 577-11-7);
ii. Supporting study: Pre-natal developmental toxicity study in rats via the oral route (feed) (equivalent to OECD TG 414; non-GLP; rel. 2) with the analogue substance calcium bis{1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate} (CAS no. 128-49-4); and

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

Additionally, ECHA notes that both studies (i. and ii above) fail to provide adequate and reliable documentation (as required by Annex XI, 1.5) and have important shortcomings. More specifically, in study (i.) there is missing information on the study design, including details on the analytical verification of the doses, details on mating procedure and frequency of treatment. Moreover, only two dose levels were tested. There is also a lack of information on the results concerning the general toxicity of the maternal animals, including data on clinical signs, mortality, body weight and weight changes, ophthalmological findings (if tested), haematology, histopathology, and organ weight findings including organ / body weight ratios. As regards, study (ii.) there is missing data concerning the study design and the results on the general toxicity of the maternal animals. Hence, the data provided from these two studies cannot be considered to be equivalent to the data generated by the corresponding test methods referred to in Article 13(3) (Annex XI, section 1.1.2.(4)).

In the technical dossier, as another supporting study, you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with the registered substance (study report, [redacted] 2013). However, this study 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. Therefore, your adaptation of the information requirement is rejected.

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 EU B.31./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 water soluble 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: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

In your comments on the draft decision you agree to perform the pre-natal developmental toxicity study (OECD TG 414) either with the registered substance or with the analogue substance Reaction products of ricinoleic acid with 2-aminoethanol and maleic acid and sodium hydrogensulfite (EC 939-654-5). As already mentioned under the *Grouping and read-across approach for toxicological information* currently ECHA cannot accept the read-across approach, hence the study requested should be provided with the registered substance. ECHA reminds that all the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 414 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

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 13 September 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.

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.