EUROPEAN CHEMICALS AGENCY

Helsinki, 14 November 2019

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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. ***In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

2. ***In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

3. ***In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that both studies requested under 1. and 2. have negative results;**

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

You are required to submit the requested information in an updated registration dossier by ***23 November 2020***. You shall also update the chemical safety report, where relevant. The deadlines have 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

I. Grouping and read-across approach for (eco)toxicological information

0. Grouping of substances and read-across approach

Your registration dossier contains 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 group (category) of 'di-ester sulphosuccinates' to predict from data for reference substance(s) missing (eco)toxicological properties for other substances within this group (read-across approach).

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.);
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.);
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.2.);
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- 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 invertebrates (Annex IX, Section 9.1.5).

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach in general before assessing the individual properties of the substance in section II of this appendix.

ECHA notes that 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 category. Secondly, it is required that the relevant properties of a substance within the category may be predicted from data for reference substance(s) within this category (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to the information generated by prescribed tests or test methods.

Based on the above, a grouping and read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a specific (eco)toxicological 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 (eco)toxicological 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 grouping and 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.

0.1. Scope of the category

You have provided two read-across documents in Section 13 of IUCLUD. In the first document ('Read across argumentation for the sulfosuccinates') the 'sulfosuccinates' are divided into five sub-categories. The second document ('Read across justification di-esters') is a detailed read-across argumentation for the sub-category 'di-ester sulfosuccinates'.

The structural basis for the grouping, including its boundaries and applicability domain are defined as:
'*The basic structure of di-ester sulfosuccinate is succinic acid which is sulfonated and where both carbon acid groups are esterified with alkyl alcohols of different chain length or cyclic C6 rings. In the di-ester group, both carboxylic acids groups are esterified [...] The current group contains linear, branched and cyclic sulfoscuccinic acid di-ester sulfosuccinates with C- chain length from C4 to C13, sharing same functional groups (same general basic structure). [...]*'

You have identified the following substances as 'di-ester sulfosuccinates' category members:

[1] Butanedioic acid, sulfo-, 1,4-bis(2-methylpropyl) ester, sodium salt (CAS No 127-39-9; EC No 204-839-5);
[2] Reaction mass of sodium (methylbutyl and pentyl) sulfonate and sodium 1,2-bis(pentyloxycarbonyl)ethanesulphonate (CAS No: not provided; EC No 941-224-7);
[3] Butanedioic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl) ester, sodium salt (CAS No 2373-38-8; EC No 219-147-9);
[4] Butanedioic acid, sulfo-, 1,4-dicyclohexyl ester, sodium salt (CAS No 23386-52-9; EC No 245-629-3);
[5] Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (CAS No 577-11-7; EC No 209-406-4);
[6] Butanedioic acid, sulfo-, 1,4-diisodecyl, ester, sodium salt (CAS No 29857-13-4; EC No 249-894-6);
[7] Butanedioic acid, sulfo-, 1,4-diisotridecyl ester, sodium salt (CAS No 55184-72-0; EC No 259-515-6); and
[8] Butanedioic acid, 2-sulfo-, 1, 4-di-C11-14-isoalkyl esters, C13-rich, sodium salts

[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

(CAS No 848588-96-5; EC No: not applicable.

These substances are hereafter indicated as substances [1] to [8].

With regard to the proposed grouping ECHA has the following observations:

0.1.1. Applicability domain of the category

The applicability domain of a category is defined by the set of inclusion and/or exclusion criteria that identify the range of values within which reliable predictions can be made for category members.

In section 1.1.b of your read-across justification document, the applicability domain of your category is defined by the basic structure of the category members as "*succinic acid which is sulfonated and where both carbon acid groups are esterified with alkyl alcohols of different chain length or cyclic C6 rings*". You also refer to the type of alkyl alcohols used to form the di-esters to characterise the applicability domain: "*the current group contains linear, branched and cyclic sulfoscuccinic acid di-ester sulfosuccinates with C- chain length from C4 to C13, sharing same functional groups*". Moreover, ECHA notes that in the section *3. Composition* of the 'Read across justification di-esters' document you indicate sodium (2+) to be the only relevant cation for the members of this 'di-ester sulfosuccinates' category.

Based on this information, ECHA understands that the length and the linear, branched or cyclic nature of the carbon chain constitute the main structural differences among the members of the category. The range of the linear carbon chain length allowed within the category is well defined, ranging from C4 to C13, and the only cation applicable for the category members is sodium. However, ECHA observes that you have not provided inclusion/exclusion criteria defining the allowed structural and positioning variations in relation with the branching and cyclic aspects of the structure of the category members. In particular no information on the distribution of the carbon chain length between the linear and the branched alkyl rests i.e. the carbon chain length of the linear and the carbon chain length and positioning of the alkyl branching, or the cyclic alkyl rests is provided other than referring to an overall range of C4 to C13. Refined inclusion and exclusion criteria addressing this aspect are necessary to unambiguously establish the boundaries of the applicability domain of the category. In the absence of this information, ECHA considers that you have failed to adequately characterise the boundaries of the applicability domain of the category and that the range of substances for which the properties can be predicted within this category cannot be determined.

0.1.2. Characterisation of the composition of the category members

The characterisation of the substances identified as members of a category needs to be as detailed as possible in order to confirm category membership and to assess whether the attempted predictions are not compromised by the composition and/or impurities. The information provided on the substance characterisation of the category members must establish a clear picture of the chemical structures of their constituents to establish the extent of qualitative and quantitative differences and similarities in the structure and in the composition of these substances. ECHA recommends to follow its *Guidance for identification and naming of substances under REACH and CLP* for all source substances within the category.[4]

[4] Guidance for identification and naming of substances under REACH and CLP (version 2.1, May 2017). ECHA, Helsinki. 127 pp. Available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Under section 1.1.a. of the read-across justification document, you address the composition of the members of the category, specifying that the "*mono-constituent di-ester sulfosuccinate substances all have the same basic structure and differ only in the alkyl chain R which includes C4-C13 groups or a saturated cyclic C6 group which only varies in the amount and linearity of the different C-chains or the presence a ring structure*". On that basis, ECHA understands that qualitative and quantitative similarity in the constituents of the members of the category (i.e. composition) is an important aspect in the formation of this category. On page 6 of the read-across justification document, you provide further information on the composition of the category members as part of a data matrix for the category. In particular, under section "*active ingredient composition*" you reported that the carbon chain length of the main constituents of the category members varies from C4 to C14. You also reported a minimal percentage of alkyl derivatives of one defined carbon chain length for each category member.

You indicated that the members of this category differ based on the "*the amount and linearity of the different C-chains or the presence a ring structure*". ECHA understands from this information that quantitative and qualitative differences with regard to the alkyl chains exist in the composition of the members of this category. You have provided, for each category member, information on the amount of one alcohol of defined carbon chain length used in the respective manufacturing process. No other quantitative and qualitative information detailing the linear, branched or cyclic nature of this specific alcohol is provided in the read-across justification document. Therefore ECHA considers that the level of information provided on the composition of the different category members in the read-across justification document is not adequate to establish the extent of the similarity and of the differences in the structure and in the composition of these substances.

0.2. Assessment of predictions within the category

0.2.1. Description of your predictions of toxicological and ecotoxicological properties

Your read-across justification document for the proposed 'di-ester sulfosuccinates' category ("Read across justification di-esters") covers:

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

You use the following arguments to support the prediction of properties within the category:
"*The subgroup [...] is built on the following characteristics:*
- similarities in the chemical process
- similar functional groups
- similar general composition [...]
The assumption that the properties of the subgroup members are similar can be shown by a comparison of the physical-chemical and toxicological data [...]"

You have provided the following hypothesis for the prediction of toxicological properties: "*no trend with the subgroup could be observed*" and "*it is clear that irrespective of the trend in carbon chain length, the Log Kow or the water solubility, the toxicological properties are similar [...]*". In order to support your hypothesis, you further referred to similarities in the acute toxicity, skin irritation, eye irritation, skin sensitisation properties of the category

members. You also pointed at the outcome of bacterial mutagenicity assays and sub-acute and sub-chronic repeated dose toxicity studies conducted with the category members.

You have provided the following hypothesis for the prediction of ecotoxicological properties: "*There is a tendency of increasing ecotoxicity with increasing chain length*" and "*In general, the ecotoxicity increases with increasing chain length.'* Substance [4] *'is an exception of this trend since apparently this molecule is less toxic than expected based on the C-chain length which might be due to the cyclic structure [...]*". In order to support your hypothesis, you further refer to the trend in the acute aquatic toxicity results of the category members in particular for daphnids and fish.

ECHA understands that on the basis of structural similarity and similarity or regular pattern in (eco)toxicological properties for some members of the category, you consider it possible to predict the human health and environmental toxicity properties of the registered substance from the other members of the proposed 'di-ester sulfosuccinates' category. As an integral part of this prediction, you propose that the source and registered substances have properties that are similar or follow a regular pattern for the above-mentioned information requirements under section 0.1. ECHA considers that this information is your read-across hypothesis.

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

Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health and environmental properties. You have not established why the predictions for human health and environmental properties are reliable, as explained below. Thus structural similarity *per se* is not sufficient to enable the prediction of human health or environmental properties of a substance.

In the read-across justification document you address elements of structural similarity among the category members. However, no considerations on the structural differences and particularly regarding the nature and length of the alkyl chains, i.e. linear, branched (including position of branching) or cyclic, are provided. Specifically, you do not address the reasons why and how a specific property for the registered substance may be predicted on the basis of the results obtained with the proposed category members despite the structural differences. Therefore, ECHA considers that there is insufficient information to support your read-across hypothesis and above listed in this paragraph information should be provided.

A prerequisite for a prediction based on read-across is that the substances involved are structurally similar and are likely to have similar properties or follow a regular pattern. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

The read-across justification document includes a data matrix for physico-chemical, environmental fate and (eco)toxicological properties, allowing a comparison of these properties between the category members.

In regard to physico-chemical properties, the intrinsic surfactant properties of the category members interfere with the determination of physico-chemical properties. In particular, the methods used to measure values for water solubility and Log Kow are not adequate for surfactants if they are not based on critical micelle concentration. As a consequence, ECHA considers that the information obtained from these methods do not constitute an adequate basis to support this read-across approach.

In regard to toxicological and ecotoxicological properties, ECHA has addressed separately below whether the data support the hypothesis for prediction.

The read-across justification shall address the reasons why and how a specific property for the registered substance may be predicted on the basis of the results obtained with the proposed category members despite the structural differences.

0.2.2.1. Toxicological properties

As indicated above, ECHA considers that your read-across hypothesis is based upon similarity in physico-chemical properties and the observation of "*no trend within the subgroup*". You have further stated that the absence of trend is explained by low toxicity in the whole subgroup. To support this claim you have indicated that the substances in the subgroup have (1) low acute toxicity; (2) low systemic toxicity as the NOAEL from the repeated dose toxicity studies are above 750 mg/kg bw; (3) similar pattern with regard to skin irritation (Skin Irrit. 2), eye irritation (Eye Damage 1), and skin sensitisation; and (4) negative gene mutation in bacteria. On page 9 and 10 of the read-across justification document, you have provided further information on the toxicological properties of the category members as part of a data matrix for the category.

With this consideration, you have used read-across to predict properties of category members for the endpoints genotoxicity, reproductive toxicity, and developmental toxicity and hereafter called 'endpoints under consideration'.

ECHA has evaluated your read-across hypothesis and considered whether the justification you have provided to support your hypothesis are relevant and adequate to allow prediction of toxicological properties for the endpoints under consideration. In this regard, a number of deficiencies are identified in the justification used to support the read-across hypothesis and these are listed below.

i) Relevance of the supporting information for the predictions of all the endpoints under consideration:

According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.2.1.f, (version 1.0, May 2008) "*it is important to provide supporting information to strengthen the rationale for the read-across. 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 the substances included in the category have similar properties for the endpoints under consideration in the read-across approach, you refer to the acute toxicity, skin irritation, eye irritation, skin sensitisation properties of the category members. Whilst this data set suggests that the substances may have similar properties for acute toxicity, skin and eye irritation, and skin sensitisation, these studies do not inform on the mutagenicity, developmental and reproductive toxicity properties of the category members. Accordingly, these information are not considered as relevant to support prediction of all the endpoints under consideration.

ii) Acceptance of the source studies for the repeated dose toxicity endpoints:

You have referred to the outcome of sub-acute and sub-chronic repeated dose toxicity studies conducted with category members to show similar toxicological properties between the category members after systemic exposure. ECHA has evaluated the source

studies provided in the technical dossier of the category members and also referred to in your read-across approach. Following this assessment, ECHA has identified several deficiencies.

1) the "*OECD Manual for Investigation of HPV Chemicals, Chapter 3: Data Evaluation, 2005*" reported that the [redacted] studies conducted during the 1960's and until 1978 have "*numerous discrepancies between raw data and study reports, and gross deficiencies*" and these studies are potentially invalid and findings are unreliable unless a study has been formally audited by a regulatory authority and the audit did not uncover any problems. However, ECHA notes that the studies conducted by [redacted] were from year 1969. There is no indication that the provided [redacted] source studies were audited.
2) Article 13 paragraph 2 and 3 requires that toxicological test and analyses are carried out in compliance respectively with international test methods recognised as appropriate and with the principles of Good Laboratory Practices (GLP). However, the sub-acute repeated dose toxicity studies submitted do not comply with GLP and with the applicable test guideline. More particularly, they have shorter exposure duration, investigated limited parameters, and tested only single sex in comparison to a sub-chronic study according to OECD TG 408.

Therefore, ECHA considers that this information does not constitute relevant supporting information in the context of a read-across approach intended to predict the toxicological properties for the endpoints under consideration.

iii) Data density for endpoints under consideration:

Annex XI, Section 1.5 of the REACH Regulation requires 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 a group, or "category" of substances*". A number of factors contribute to the robustness of a category. According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.1.5.f, (version 1.0, May 2008), one of these factors is the density and distribution of the available data across the category. In order to identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available. However, you have referred to the available source information for the endpoints under consideration and concluded that the category members are "*not genotoxic (nor carcinogenic) and not toxic to reproductive and developmental toxicity*". However, ECHA observes that the data density across the category is limited based on the information provided in the read-across justification document and technical dossier of category members. Specifically, information on gene mutation in bacteria is available for 4 out of 8 members of the category, i.e. substances [3], [5], [6], and [8]. *In vitro* cytogenicity data is available for category members [3], [5], and [8] whereas *in vitro* gene mutation in mammalian cells has been investigated only in 2 category members, i.e. substance [3] and [8]. ECHA considers that the provided tests do not cover the structural differences within the category domain. For reproductive toxicity and developmental toxicity, information is only available for one member of the category, substance [5]. ECHA considers that with only one data points, no quantitative trend between the category members can be established for this endpoint. Accordingly, the data do not allow to have overall conclusion on the endpoint under consideration.

iv) Consistency of results on mutagenicity studies:

Annex XI, Section 1.5 of the REACH Regulation requires 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 a group". According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.2.2, (version 1.0, May 2008) "*a demonstration of consistent trends in the behaviour of a group of chemicals is one of the desirable attributes of a chemical category and one of the indicators that a common mechanism for all chemicals is involved*". The observation of a deviation in a trend among some members of a category is a warning sign. An explanation for this deviation in the trend resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence. You have stated that "*no effects were seen in any of the mutagenicity study*" performed with the category members. However, ECHA notes difference in the results of the provided mutagenicity information among the category member. Specifically, positive results[5] are observed in the *in vitro* chromosomal aberration study conducted with the category member [5] and ECHA has requested an *in vivo* follow-up of the positive findings on this test for substance Potassium 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate (CAS No 7491-09-0; EC No 231-308-5), while negative results are reported for equivalent studies conducted for category members [3] and [8]. In view of this difference, the information provided in the dossier contradicts your claim that the mutagenicity properties of the category members are similar. Accordingly, you have not demonstrated of 'no trend' among the category members.

Based on all the deficiencies explained above, ECHA considers that the read-across justification provided in the category justification document does not support the claim of 'no trend' within the category members. Hence, the read-across justification lacks scientific evidence substantiated by adequate and reliable data.

In addition, there are specific considerations relating to the quality of the source studies for the endpoint repeated dose toxicity and reproductive toxicity, which also result in a failure to meet the requirement of Annex XI, 1.5. These further deficiencies are addressed under the endpoints concerned.

0.2.2.2. Aquatic toxicity

As indicated above, ECHA understands that your read-across hypothesis is based upon a trend in aquatic toxicity properties. You have further stated that the ecotoxicity generally increases with increasing C-chain length with the exception of substance [4] due to the cyclic structure. To support this claim you have indicated that for the substances in the subgroup a higher toxicity to daphnids and fish was generally associated with longer C-chain length.

With this consideration, you have used read-across to predict properties of category members for the endpoints algae growth inhibition, short-term toxicity testing on aquatic invertebrates, short-term toxicity testing on fish and long-term toxicity testing on aquatic invertebrates.

ECHA has evaluated your read-across hypothesis and considered whether the justification you have provided to support your hypothesis are relevant and adequate to allow prediction of aquatic toxicity properties for the endpoints under consideration. In this regard, a number of deficiencies are identified in the justification used to support the read-across hypothesis and these are listed below.

[5] ECHA has consider that the study should be interpreted as positive using the following criteria:
1) Statistical significant increase in the proportion of cells with structural aberrations (excluding gaps) occurred at one or more concentrations;
2) The proportion of aberrant cells at such data points exceeded the normal range;
3) The results were confirmed in a second experiment.

i) No data on substances at the border of the category:

According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6. Section R.6.2.4.1 – step 6, (version 1.0, May 2008) "*if toxicity is expected to vary in a regular pattern from one end of the range of category members to the other end (e.g. high toxicity to low toxicity), samples chosen for testing should bracket both ends of toxicity. If the category is large, testing also needs to be performed and/or data should be available for one or more members in the middle of the range of toxicity.*" However, ECHA observes that for the aquatic toxicity endpoints under consideration there is no data available for the two substances at the border of the category with the shortest alkyl C-chain length, i.e. Substances [1] and [2]. In addition, you have not provided a justification supported by scientific evidence on how and why reliable predictions can be established, i.e. why and how lower aquatic toxicity is expected for these two substances at the border of the category, in agreement with the proposed trend. In the absence of data for substances at the borders of the category, ECHA considers that the information provided in your dossier is not sufficient to support your read-across hypothesis that the proposed trend would cover all category members.

ii) Data density for long-term toxicity testing on aquatic invertebrates

Annex XI, Section 1.5 of the REACH Regulation requires 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 a group, or "category" of substances*". A number of factors contribute to the robustness of a category. According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.1.5.f, (version 1.0, May 2008), one of these factors is the density and distribution of the available data across the category. There needs to be sufficient experimental data in order to identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category. However, based on the information provided in the read-across justification document and the data included in the technical dossier, ECHA observes that the data density across the category is limited for the endpoint long-term toxicity testing on aquatic invertebrates since data are available only for two substances (i.e. Substances [5] and [6]). ECHA considers that with only two data points, no quantitative trend between the category members can be established for this endpoint. Consequently, the information provided in your dossier is not sufficient to support your read-across hypothesis that there is a trend of increasing aquatic toxicity with increasing chain length for this endpoint.

iii) Lack of justification for long-term toxicity testing on aquatic invertebrates

A read-across justification must be specific to the endpoint or property under consideration due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key test design parameters, biological targets), as indicated in ECHA's Read-Across Assessment Framework (RAAF, March 2017). However, you claim that based on the proposed trend for the short-term aquatic toxicity "*higher ecotoxicity associated with longer C-chains*" for the endpoint of long-term toxicity testing on aquatic invertebrates you use the results obtained with Substance [5] to predict the long-term toxicity for Substances [1], [2] and [3]. You claim that this prediction is justified by the fact that it is based on a substance with longer C-chain length. However, since you provide no justification supported by scientific evidence on why and how the results of the acute studies would support the predictions for this

chronic endpoint, ECHA considers that your read-across justification is lacking the relevant reasoning specific to the endpoint of long-term toxicity testing on aquatic invertebrates.

iv) Consistency of results for short-term aquatic toxicity endpoints

Annex XI, Section 1.5 of the REACH Regulation requires 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 a group*". According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.2.2, (version 1.0, May 2008) "*a demonstration of consistent trends in the behaviour of a group of chemicals is one of the desirable attributes of a chemical category and one of the indicators that a common mechanism for all chemicals is involved*". The observation of a deviation in a trend among some members of a category is a warning sign. An explanation for this deviation in the trend resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence. However, based on the information provided in the read-across justification document and on the data included in the technical dossier, ECHA observes that the data available for the short-term aquatic toxicity endpoints do not support your read-across hypothesis of ecotoxicity trend across the category and deviations are not explained in your category justification. First, ECHA notes that your proposed trend of increasing ecotoxicity with increasing chain length is not observed for the endpoint algae growth inhibition, for which available short-term results indicate that the substances "*showed little to no toxicity*". You have not provided a justification supported by scientific evidence on how and why reliable predictions can be established for this endpoint. More specifically, your hypothesis is based on a general trend of increasing ecotoxicity with increasing chain length. However, the proposed trend is not observed for the endpoint algae growth inhibition. Second, ECHA notes that, for the endpoints of short-term toxicity testing on fish and short-term toxicity testing on aquatic invertebrates, effect values decrease only for the substances with alkyl C-chain length varying from C6 to C11, in sequence Substances [3], [5] and [6]. However, effect values for Substance [8] with the longest C-chain length (C13) are similar (and even slightly higher) than those for C11 (Substance [6]), which has the "*highest acute aquatic toxicity of all di-esters*" as acknowledged by you. Finally, you note in the read-across justification that the ecotoxicity trend is not applicable to Substance [4] due to the cyclic structures present in the molecule of the substance. Consequently, the information provided in your dossier contradicts your claim that there is a trend of increasing aquatic toxicity with increasing chain length for these endpoints across all category members.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have noted that:

- Will reinvestigate/re-arrange the data matrix from the additional aquatic ecotoxicity data that will be generated.
- Will perform the acute aquatic tests requested for that group/category; hence further data will be available in future so that no grouping approach will be used anymore to provide the acute aquatic ecotoxicity information.
- Consider the minor "decrease" of the ecotoxicity from [6] CAS 29857-13-4 and [8] CAS 848588-96-5 (source substance for [7] EC 259-515-6 (CAS "55184-72-0)) to be within the normal range of variation for such tests investigating biological responses (factor of about 2). Otherwise, once all data (incl. analytical data) are available you will evaluate the data matrix and will decide if sub-categories are needed.
- Will support the category approach and the read-across argumentation by additional

and/or supporting biodegradation testing of all diester group substances. Testing will be according to OECD TGs 301/310 and/or 302 in order to assess ready, enhanced and/or inherent biodegradability..

Based on all the deficiencies explained above, ECHA considers that there is not sufficient supporting or there is contradicting information to confirm your hypothesis that the category members have increasing aquatic toxicity with increasing C-chain length. Accordingly your hypothesis based upon trend within the proposed 'di-ester sulfosuccinates' category is not substantiated on scientific evidence.

0.2.3. Conclusion on the read-across approach for toxicological and ecotoxicological properties

The adaptation of the standard information requirements in the technical dossier is based on the read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, Section 1.5.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have noted that agree with ECHA's observations and will provide more (detailed) information on:

- Applicability domain of the category;
- Characterisation of the composition of the category members;
- the structural differences of the category members and on the reasons why and how a specific property for the registered substance may be predicted on the basis of the results obtained with the proposed category members despite the structural differences.

You also request prolongation of the decision deadline in line with your testing plan. ECHA has assessed and responded to your request to prolong the decision deadline below. ECHA notes your intention to further justify category and awaits for further information to be submitted in the registration dossier by the deadline indicated in the decision.

II. Specific considerations on the information requirements

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.

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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 REACH regulation by providing GLP compliant negative *in vitro* gene mutation studies in bacteria performed with category member [8] according to OECD TG 471 ([redacted], 2013). However, your adaptation of the information requirement according to Annex XI, Section 1.5.,

is rejected for the reasons explained above in section "*I. Grouping of substances and read-across approach*".

Thus, 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 considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

In your comments to the draft decision you indicate your agreement to conduct the requested testing, and request prolongation of the decision deadline in line with your testing plan. ECHA has assessed and responded to your request to prolong the decision deadline below.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) .

2. *In vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An "*In vitro cytogenicity study in mammalian cells or an in vitro micronucleus study*" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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 REACH regulation in a category approach by providing GLP compliant negative *in vitro* micronucleus test in human peripheral lymphocytes performed with category member [8] according to OECD TG 487 ([redacted] 2013). However, your adaptation of the information requirement according to Annex XI, Section 1.5., is rejected for the reasons explained above in section "*I. Grouping of substances and read-across approach*".

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

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments to the draft decision you indicate your intention to adapt the information requirement using grouping and read-across approach (source substance [8]). ECHA awaits the improved read-across supporting documentation in line with observations of Section I. Grouping and read-across approach for (eco)toxicological informationto and Annex XI 1.5. to be submitted by the deadline indicated in the decision. Concerning your request to prolong the decision deadline, ECHA has assessed and responded to it below.

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: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

3. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "*if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2.*" is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5., of the REACH Regulation in a category approach by providing GLP compliant negative *in vitro* gene mutation study in mammalian cells performed with category member [8] according to OECD TG 476 ([redacted] 2013). However, your adaptation of the information requirement according to Annex XI, Section 1.5., is rejected for the reasons explained above in section "*I. Grouping of substances and read-across approach*".

Thus, 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 provided that both studies requested under 1 and 2 have negative results.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision you indicate your intention to adapt the information requirement using grouping and read-across approach (source substance [8]). ECHA awaits the improved read-across supporting documentation in line with observations of Section I. Grouping and read-across approach for (eco)toxicological informationto and Annex XI 1.5. to be submitted by the deadline indicated in the decision. Concerning your request to prolong the decision deadline, ECHA has assessed and responded to it below.

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 1 and 2 have negative results.

4. 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 provided a GLP compliant "*three-generation reproductive toxicity*" ([redacted] 1986), and a non-GLP compliant "*two-generation reproductive toxicity*" ([redacted] 1970) in rats that were performed with category member [5]. However, your adaptation of the information requirement according to Annex XI, 1.5 is rejected for the

reasons explained above in section "*I. Grouping of substances and read-across approach*".

In addition, these studies do not cover all the key parameters foreseen to be investigated in a Reproduction/ developmental toxicity screening test (OECD TG 421/422). The main missing parameters from the Parental (P) generation are histopathology and weight of reproductive organs, histopathology and weight of major non-reproductive organs (OECD TG 422 only); and from the offspring (F1) are certain parameters for endocrine modes of action.

Thus, 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.

In your comments to the draft decision you indicate your agreement to conduct the requested testing, and request prolongation of the decision deadline in line with your testing plan. ECHA has assessed and responded to your request to prolong the decision deadline below.

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."

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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. However, following your comments on the draft decision indicating a tonnage band downgrade, only, ECHA has taken into account the updated tonnage band (submission number [redacted] submission date 27 June 2019 and tonnage band 10-100 tpa), only. No assessment of the updated registration has occurred. Based on the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band as basis for the draft decision from 100 - 1000 tonnes per year (submission number: Submission number: [redacted] Submission date: 25 June 2018) to 10 – 100 tonnes per year (submission number: [redacted]).

The compliance check was initiated on 2 May 2018.

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 your information about tonnage band downgrade. This has resulted in the removal of the following decision requests:

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

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;

5. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: Aerobic mineralisation in surface water – simulation biodegradation test, EU C.25./OECD TG 309) at a temperature of 12 °C with the registered substance;

6. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: Aerobic and anaerobic transformation in soil, EU C.23./OECD TG 307) at a temperature of 12 °C with the registered substance;

7. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24./OECD TG 308) at a temperature of 12 °C with the registered substance;

8. Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method;

9. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305, aqueous

exposure) with the registered substance.

The deadline is amended from 57 months to 12 months. With this removal of the requests, there is no need to consider the prolongation of the deadline.

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.

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Appendix 3: Further information, observations and technical guidance

1. You submitted an updated registration dossier to ECHA on 25 June 2018 (submission number [redacted]) following an informal call held between you and ECHA on 14 September 2017 concerning some aspects of the substance identity information in your dossier. In the updated dossier, you acknowledged that '*the EC number 259-515-6 currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons*' and provided a revised IUPAC name "sodium bis[C12-14 (branched) alkyl] sulfosuccinate" in section 1.1. You will be contacted by ECHA once the evaluation is complete to start the identifiers change process.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of your Member State.

4. 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.