EUROPEAN CHEMICALS AGENCY

Helsinki, 20 August 2020

Addressees
Registrants of JS_701-25-9 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
28/01/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Fatty acids, C16 and C18-20 (even numbered, unsaturated), 2-ethylhexyl esters
EC number: 701-259-9
CAS number: NS

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***29 August 2022***.

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the Substance

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. 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)

2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490)

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

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

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

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route

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

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

Conditions to comply with the requested information

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation. Therefore you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must also update the chemical safety report, where relevant, including any changes to classification and labelling based on the newly generated information. The timeline has been set to allow for sequential testing.

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

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on general considerations

(i) Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

In your category justification documentation you state the following:

"The REACH Registration dossier for the UVCB substance [Fatty acids, C12-20 and C12-20-unsatd., 2-ethylhexyl esters]; CAS 91001-42-2, EC 292-811-3 relies on read-across to the comparable UVCB substances ETP [Fatty acids, tall-oil, epoxidised, 2-ethylhexyl esters]; CAS 61789-1-3, EC 263-024-2 and ESBO [Soybean oil, epoxidised]; CAS 8013-07-8, EC 232-391-0 for a number of toxicological endpoints. This document describes the structural, toxicokinetic and toxicological similarities between the substances which allow the read-across of data".

However, as per ECHA's communication on change of substance identification (communication number: SUB-C-2114431346-54-01/F; Communication date: 15 June 2018), the identifiers of your registration has been changed in REACH-IT from **292-811-3** to **701-259-9**. Your substance name has been changed from **fatty acids, C12-20 and c12-20-unsatd., 2-ethylhexyl esters** to **fatty acids, c16 and c18-20 (even numbered, unsaturated), 2-ethylhexyl esters**. You have not modified your category justification documentation after this change of the identifiers of the Substance.

On that basis, ECHA understands that you maintain your adaptation for the Substance, with the new identifiers.

You seek to adapt the following standard information requirements by applying read-across approaches 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 cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you have formed a group of "Epoxidised Oils and Derivatives". You have provided a read-across justification document in IUCLID Section 13.

You identified the following category members:
[1] Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP), EC No. 263-024-4, (CAS No. 61789-01-3)
[2] Epoxidised Soybean oil (ESBO), EC No. 232-391-0, (CAS No. 8013-07-8)
[3] The Substance

You have provided information on the main constituents of the target and source substances, as well as a comparison of their composition (see below chapter "Characterisation of the composition of the group members").

One of the source substances is 2 Ethylhexyl stearate, which is a constituent of the (target) Substance Fatty acids, C16 and C18-20 (even numbered, unsaturated), 2-ethylhexyl esters, EC No 701-259-9, (CAS No NS) with the percentage of 1-6.

Further than that, you have not defined the structural basis for the grouping.

You provide the following reasoning for grouping the substances: "*There are structural, toxicokinetic and toxicological similarities between the substances which allow the read-across of data.*"

In your comments to the draft decision you admit that the read-across justification in your dossier was "*weak*" and that "there is *many data gaps in the dossiers for these fatty acid derivatives*". You suggest to use data on a new read-across source substance 2-ethylhexyl palmitate (EHP). In order to strengthen your read-across documentation and justification and also in terms of animal welfare and the avoidance of unnecessary and redundant vertebrate testing, you suggest a tiered testing programme in your comments, which involves data on some physical-chemical properties, hydrolysis, bridging information on bacterial gene mutation assays, Daphnia and algal tests as well as literature data on metabolism.

However, you have still not defined the structural basis for the grouping and you have not provided any supporting documentation, nor new hypothesis to support the adaptation with the new substance. Without supporting information your read-across claim cannot be assessed.

ii. Assessment of the grouping

ECHA notes the following shortcomings with regards to your grouping approach.

Characterisation of the composition of the group members

Annex XI, Section 1.5 of the REACH Regulation provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of chemical similarity may be considered as group.*"

According to the ECHA Guidance, "*in identifying a category, it is important that all potential category members are described as comprehensively as possible*", because the purity profile and composition can influence the overall toxicity/properties of the potential category

members.[2] Therefore, qualitative and quantitative information on the **compositions** of the category members, also including considerations of differences, when applicable, should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities, and hence to confirm the category membership.

Furthermore, the provided information for categories consisting of UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances needs to include qualitative compositional information of the individual constituents of the category members; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable.[3]

Your read-across justification document contains some compositional information for the members of your category. You have not provided information on other than the main constituents of the target and source substances. The source substances are formed via epoxidation and include constituents (e.g. epoxidised linolein), which are not found in the target substance. The source substances (ESBO and ETP) lack most of the fatty acids in the range of C12-C16, whereas the target substances include [redacted] of those. Furthermore, the target substance contains ethylhexyl oleates, ethylhexyl stearates etc., which according to the justification document are not constituents of the two source substances.

You claim that in OECD SIDS Initial Assessment Report for SIAM 22, "the essential similarity of two epoxidies oils and two ester derivatives" has been confirmed.

Considering the composition and the UVCB nature of these substances the information given in the justification document is considered incomplete, because the full composition of two source substances is not covered.

Without consideration of e.g. the differences as specified above (e.g. fatty acid composition and difference between ethyl hexyl esters and epoxidised fatty acids), qualitative or quantitative comparative assessment of the compositions of the different category members cannot be completed.

Furthermore, you have not documented that the (target) Substance was addressed in the OECD assessment.

In your comments to the draft decision, you admit that "*time relating to the composition of the respective fatty acid sources was not conclusive and it is accepted that faced with the evidence available to those following ECHA guidance, it is possible to conclude that there was insufficient analytical evidence*".

In your comments to the draft decision, you indicated that you would possibly use a read-across approach to meet this information requirement, using 2-ethylhexyl palmitate (EHP) as source substance. EHP is made of C16 saturated chains whereas the Substance consists of C12 - C20 chains, mainly unsaturated. The constituents of the Substance with shorter carbon chains (e.g. C12) can be expected to be more bioavailable and as a result more toxic than EHP which is made of C16 chains. Furthermore, the unsaturated constituents of the Substance have the potential to be more reactive and therefore more toxic than the saturated chains of which EHP consists. Therefore, a read-across from EHP to the Substance could not be accepted.

[2] Guidance on information requirements and chemical safety assessment Chapter R.6, Section R.6.2.4.1
[3] Guidance on information requirements and chemical safety assessment Chapter R.6, Section R.6.2.5.5

Therefore, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the different composition of the category members and consequently it has not been confirmed that the target substance belongs to the same category as the source substances.

A. Predictions for properties

a. Prediction for toxicological properties

You have provided the following reasoning for the prediction of toxicological properties: *"There are structural, toxicokinetic and toxicological similarities between the substances which allow the read-across of data"*. You have also suggested a worst case approach for the purpose of read-across. A further element of your hypothesis is the claim that source and target substances are metabolised to similar break-down products.

ECHA understands that you predict the properties of the (target) Substance using a read-across hypothesis, which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be qualitatively and quantitatively equal to those of the source substance.

Missing supporting information to compare properties of the substances

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.*

According to the ECHA Guidance, one of the factors in determining the robustness of a category is the density and distribution of the available data across the category.[4] 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.

Concerning the two source substances**,** one of these substance has been studied for the following endpoints, skin and eye irritation, skin sensitisation, repeated dose toxicity, carcinogenicity and pre-natal developmental toxicity. The two source substances have been studied for genetic toxicity and reproductive toxicity.

No study has been provided for the (target) Substance, although some studies are available for individual, but not all constituents of the (target) Substance, e.g. for ethylhexyl palmitate and for octyl stearate.

In the absence of toxicological data on the (target) Substance for the relevant endpoints, or at least on the very limited toxicity data on some of its constituents, the similarity with the source substances cannot be confirmed. Hence, you have not established that a reliable prediction of the properties under consideration of the target substance can be derived on the basis of your read-across hypothesis.

Therefore, the information provided is not sufficient to conclude that toxicological properties are likely to follow a regular pattern.

In your comments to the draft decision, you indicate that you plan to use data on a new read-across source substance 2-ethylhexyl palmitate (EHP) with a tiered testing programme, which intends to support "equivalent properties". This testing program involves data on some

[4] Guidance on information requirements and chemical safety assessment Chapter R.6, Section R.6.2.1.5.

physical-chemical properties, hydrolysis, bridging information on bacterial gene mutation assays, Daphnia and algal tests as well as literature data on metabolism. At present no data on this new source substance is provided in the dossier. Without supporting information on all the source substances the read-across approach cannot be assessed.

Additionaly, concerning the human health effects, no testing is proposed in the testing strategy given in your comment, except two genotoxicity tests.

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[1]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on other category members. Supporting information must include bridging studies to compare properties of the category members.

There is currently no information allowing a comparison the sub-chronic and the developmental toxicity properties of the new source and the target substance and to confirm that source and target substance cause the same type of effects. Data on similarity of genotoxicity (which is suggested in the testing strategy) is not relevant in this regard, since it does not concern the observations and endpoints that are addressed in the sub-chronic and developmental toxicity studies.

Furthermore, you suggest to use data on a new read-across source substance 2-ethylhexyl palmitate (EHP). At present no data on that source substances is provided in the dossier. The studies potentially provided on EHP, and the respective revisions in the read-across justificaion will be evaluated in the stage of follow-up evaluation.

Missing information on the formation of common compound

Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". The ECHA Guidance[5] state that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

"*Adequate and reliable documentation*" must include toxicokinetic information on the formation of the common compound target and source substances, information on the target Substance, and information on the worst-case consideration.

Your read-across hypothesis is partly based on the (bio)transformation of the target and source substances to a common compound(s).

In this context, information characterising the rate and extent of the metabolism of the target substance and of the source substance is necessary to confirm the formation of the proposed common hydrolysis product and to assess the impact of the exposure to the parent compounds.

You claim that two of the source substances are metabolised to **epoxidised fatty acids** and 2-ethylhexanol, whereas the (target) Substance is metabolised to **fatty acids** and to and 2-ethylhexanol.

[5] Guidance on information requirements and chemical safety assessment Chapter R.6, Section R.6.2.2.1.

You have not, however, provided any *experimental* data or other adequate and reliable information to document that these metabolic pathways/steps take place, and you have not addressed the difference between fatty acids and epoxidised fatty acids. Furthermore, the uncertainty of the metabolites/metabolism, which is due to the UVCB nature of these substances has not been covered in your justification document.

In light of your comments to the draft decision, your read-across hypothesis seems to be that the substances hydrolyse to similar products. According to your comments you assume that metabolic processes are equivalent for target and sources, and you plan to provide public information on fatty acids / alcohols and their metabolic products to support your case. Concerning your claim on common metabolites, at present you have not provided relevant experimental information on the Substance and on the source substances, neither have your shown that the rate of the metabolism is such that it prevents exposure to the parent substances. Without that documentation your hypothesis of similar hydrolysis products cannot be verified, and consequently your read-across adaptation is not acceptable.

In the absence of this information, you have not demonstrated that there is common metabolism as assumed/claimed in your read-across hypothesis.

Missing supporting information to substantiate worst-case consideration

As indicated above, your read-across hypothesis is partly based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of the target substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substance is necessary to confirm a conservative prediction of the properties of the target substance from the data on the source substance. Such information can be obtained, for example, from bridging studies of comparable design and duration for the target and the source substances.

You claim that "*epoxidised fatty acids may (theoretically) be more toxic than fatty acids*" and therefore, "*the use of epoxidised substances as source data can be considered to represent a worse case*". This difference between target and sources substances has not been documented with toxicological data on the target substance.

In the absence of such information, you have not established that the source substance constitutes a worst-case for the prediction of the property under consideration of the target substance. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

B. Conclusions on the read-across approach

As explained above, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation is it is rejected and it is necessary to perform testing on your Substance.

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

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

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 in Annex VII to REACH.

You have provided three studies in your dossier:

i. Ames test OECD 471 with the source substance Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP), EC No 263-024-4, (CAS No 61789-01-3), according to GLP, [redacted] 2005,
ii. Ames test OECD 471 with the source substance Soybean oil, epoxidised (ESBO), EC No 232-391-0, (CAS No 8013-07-8), according to GLP, in [redacted], made in 1992.
iii. Ames test OECD 471 with the source substance Soybean oil, epoxidised (ESBO), EC No 232-391-0, (CAS No 8013-07-8), according to GLP, in [redacted], made in 1981.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations above, your adaptation is rejected. Therefore, the information requirement is not fulfilled.

In your comment to the draft decision, you have indicated that you agree to perform this study.

Consequently, you are required to provide information according to OECD TG 471 on the Substance for this endpoint.

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study on aquatic plants is a standard information requirement of Annex VII of REACH.

You have sought to adapt this information requirement by stating that the Substance is highly insoluble.

Column 2 of Annex VII 9.1.2. of REACH indicates that "*the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes*".

No experimental data is available for water solubility but only QSAR predictions. The water solubility values predicted for the main constituents of the Substance are very low.

However, in this case, this information does not amount, on its own, to mitigating factors indicating that aquatic toxicity is unlikely to occur.

In particular, fatty acids have been widely reported to have allelopathic activity on microalgae (Borowitzka MA, 2016)[6]. Similar effects cannot be reasonably ruled out from the Substance since it is made of fatty acid derivatives. While the mode of action for this allelopathic activity is yet uncertain, it may be caused by characteristics common to fatty acid and their derivatives.

Therefore, your adaptation is rejected. You must perform a growth inhibition study on algae with the Substance.

In your comments to the draft decision, you indicated that you agreed to perform this study.

[6] Borowitzka MA (2016). Chemically-Mediated Interactions in Microalgae. In "*The Physiology of Microalgae - Developments in Applied Phycology 6*", Springer International Publishing Switzerland 2016. ISBN: 978-3-319-24943-8.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

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

1. ***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 in Annex VIII to REACH.

You have provided two studies in your dossier:

i. Cytogenicity assay according to OECD TG 473, in GLP, with source substance Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP), EC No 263-024-4, (CAS No 61789-01-3), [redacted] 2005;
ii. Cytogenicity assay according to OECD TG 473, in GLP, with source substance Soybean oil, epoxidised (ESBO), EC No 232-391-0, (CAS No 8013-07-8), [redacted] 2005.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.

In your comment to the draft decision, you have indicated that you agree to perform this study.

To fulfil the information requirement for the Substance, both *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered appropriate/ adequate.

2. ***Only if both studies under sections A.1 and B.1 have negative results, In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

You have provided two studies in your dossier:

i. In vitro gene mutation study in mammalian cells according to OECD TG 476, with source substance Soybean oil, epoxidised (ESBO), EC No 232-391-0, (CAS No 8013-07-8), according to GLP, [redacted] 1992;
ii. In vitro gene mutation study in mammalian cells according to OECD TG 476, with source substance Soybean oil, epoxidised (ESBO), EC No 232-391-0, (CAS No 8013-07-8), according to GLP, [redacted] 1986.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are

described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.

In your comment to the draft decision, you have indicated that you will use grouping approach to meet this information requirement. Your comments related to read-across have been addressed above in the "Appendix on general considerations", where it is concluded that your read-across is not acceptable.

Consequently, you are required to provide information on the (target) Substances for this endpoint, if the in vitro gene mutation study in bacteria and the in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study provide a negative result

To fulfil the information requirement for the Substance, both the in vitro mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable.

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

A Screening for reproductive/developmental toxicity study (OECD TG 421 or 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.
You have provided two studies for this endpoint in your dossier:

i. OECD TG 422 combined repeated dose toxicity study with the reproduction/developmental toxicity study provided with source substance substance Fatty acids, tall-oil, epoxidized,2-ethylhexylesters (ETP), EC No 263-024-4, (CAS No 61789-01-3), according to GLP, [redacted] 2005;
ii. OECD TG 415 One-Generation Reproduction Toxicity Study with the source substance Epoxidised Soybean oil (ESBO), EC No 232-391-0, (CAS No 8013-07-8), according to GLP, [redacted] 1993.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. Therefore, the information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint.

A study according to the test method OECD TG 421/422 should be performed in rats with oral[7] administration of the Substance.

[7] ECHA Guidance R.7a, Section R.7.6.2.3.2.

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

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

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

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. An additional endpoint-specific deficiency has been identified in your read-across adaptation.

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408.

You have provided a study for this endpoint in your dossier:

i. OECD TG 422 combined repeated dose toxicity study with the reproduction/developmental toxicity study with source substance Fatty acids, tall-oil, epoxidized,2-ethylhexylesters (ETP), EC No 263-024-4, (CAS No 61789-01-3), according to GLP, [redacted] 2005.

The Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) you have submitted does not have the required exposure duration of 90 days as required in OECD TG 408, because according to the study record, the exposure duration of that screening test was 42 days (for females). Furthermore, the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than required by the OECD TG 408 leading to lower statistical power.

In your comment to the draft decision, you have indicated that you will use grouping approach to meet this information requirement. Your comments related to read-across have been addressed above in the "Appendix on general considerations", where it is concluded that your read-across is not acceptable.

Based on the above, the information you provided do not fulfil the information requirement.

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity[8]. The sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance, because the Substance is a liquid of very low vapour pressure (2.5E-4 Pa at 25°C) and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.

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

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

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided two studies in your dossier:

i. OECD TG 414 made in 1999, with source substance 2 Ethylhexyl stearate, (which is a constituent of the (target) Substance Fatty acids, C16 and C18-20 (even numbered, unsaturated), 2-ethylhexyl esters, EC No 701-259-9, (CAS No NS) with the percentage of 1-6), not according to GLP, [redacted] 1999;
ii. PNDT study according to OECD TG 414, with source substance 2 Soybean oil, epoxidised (ESBO), EC No 232-391-0, (CAS No 8013-07-8), according to GLP, [redacted] 1993.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The requirements for such an adaptation are described in Appendix on general considerations above.

As explained in the Appendix on general considerations, your read-across adaptation is rejected. An additional endpoint-specific deficiency has been identified in your read-across adaptation.

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[9]

For this endpoint, your other source substance of the read-across is 2 Ethylhexyl stearate, which is a constituent of the (target) Substance with the percentage of [redacted] You have not provided toxicological information on the other contituents of the Substance, neither have you addressed the structural and toxicological difference between this constituent and the Substance. Furthermore, you have not justified how the prediction of this toxicity endpoint could be derived from the information provided of this source substance.

Therefore, you have not provided documentation as to why this information is relevant for your Substance as a whole.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s). Therefore, the information requirement is not fulfilled.

In your comment to the draft decision, you have indicated that you will use grouping approach to meet this information requirement. Your comments related to read-across have been addressed above in the "Appendix on general considerations", where it is concluded that your read-across is not acceptable.

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[10] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

[9] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1
[10] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Long-term toxicity testing on aquatic invertebrates is a standard information requirement of Annex IX of REACH.

You have sought to adapt this information requirement by stating that the substance is highly insoluble and is unlikely to be bioavailable to aquatic organisms.

Under Annex IX, Section 9.1, Column 2 of REACH, you must perform long-term toxicity testing on aquatic organisms if your Chemical Safety Assessment (CSA) indicates the need to investigate further the effects on aquatic organisms.

Under Annex I, section 0.1 of REACH, you must demonstrate in your CSA that risks arising from the use of the Substance are controlled.

For the environmental hazard assessment (Annex I, section 3.0 of REACH), the available toxicity information should at least cover species of three trophic levels for aquatic organisms: algae/aquatic plants, invertebrates (*Daphnia* preferred) and fish.

For hydrophobic or poorly water soluble (e.g. water solubility below 1 mg/L or below the detection limit of the analytical method of the test substance), long-term tests must be considered (see, by analogy, REACH Annex VII , Section 9.1.1, Column 2 and REACH Annex VIII , Section 9.1.3, Column 2).

The Substance is hydrophobic (Log Kow> 5.7) and, based on QSAR results, predicted to be poorly water soluble.

You have claimed that the Substance is so hydrophobic that it would not be bioavailable to aquatic organisms. You have made reference to the OECD SIDS Initial Assessment Report for Epoxidized Oils and Derivatives (SIAM 22, 18 -21 April 2006). In that report, it is indicated that it was not possible to detect EODA (9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (CAS: 68609-92-7)) from a Water Accommodated Fraction (WAF) prepared from a loading of 100 mg/L.

However, you have not provided experimental information on the bioavailability of the Substance itself.

The substances addressed in the OECD SIDS assessment, and in particular EODA, are C18 epoxidised acid derivatives whereas the Substance consists of C12 - C20 acid esters. As explained above in the 'Appendix on general considerations' of the present decision, you have not provided sufficient information to support a read-across between your Substance and the C18 epoxidised acid derivatives assessed in the OECD report. In particular, the constituents of your Substance with shorter carbon chains (e.g. C12) can be expected to be more bioavailable than C18 substances.

The same reasoning applies to long-term aquatic toxicity in fish (Appendix C4 below).

In your comments to the draft decision, you indicated that you would possibly use a read-across approach to meet this information requirement, using 2-ethylhexyl palmitate (EHP) as source substance. EHP is made of C16 saturated chains whereas the Substance consists of C12 - C20 chains, mainly unsaturated. As explained above, the constituents of the Substance with shorter carbon chains (e.g. C12) can be expected to be more bioavailable and as a result more toxic than EHP which is made of C16 chains. Furthermore, the unsaturated constituents of the Substance have the potential to be more reactive and therefore more toxic than the saturated chains of which EHP consists. Therefore, a read-across from EHP to the Substance could not be accepted.

Therefore,

- you have not demonstrated that the Substance is not bioavailable;
- you cannot demonstrate that risks towards aquatic organisms are controlled;
- you need to investigate further the effects on aquatic organisms;
- your adaptation is rejected;
- you must perform a long-term toxicity study on aquatic invertebrates with the Substance.

In your comments to the draft decision, you also indicated that you were willing to perform a short-term study on *Daphnia* (immobilisation test). However, as explained above, short-term aquatic tests are not appropriate to assess the ecotoxicity of poorly soluble substances and long-term tests must be performed instead.

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

Long-term toxicity testing on fish is a standard information requirement of Annex IX of REACH.

You have sought to adapt this information requirement by stating that the substance is highly insoluble and is unlikely to be bioavailable to aquatic organisms.

As explained in Appendix C.3 above, your adaptation is rejected.

In your comments to the draft decision, you indicated that you would consider performing long-term toxicity testing on fish only if biological effects would be observed in other environmental tests. However, for the environmental hazard assessment (Annex I, section 3.0 of REACH), the available toxicity information should at least cover species of three trophic levels for aquatic organisms: algae/aquatic plants, invertebrates (*Daphnia* preferred) and fish. No appropriate data is currently available to assess the toxicity to fish.

Therefore, you must perform a long-term toxicity study on fish with the Substance.

Appendix D: Procedural history

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

The compliance check was initiated on 14 January 2019.

The decision making followed the procedure of Articles 50 and 51 of REACH, 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) and/or 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 E: Observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

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

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

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

4. Test material

Selection of the test material(s)

The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity. In particular, the constituents of your Substance with shorter carbon chains (e.g. C12) can be expected to be more bioavailable than constituents of your Substance with longer carbon chains (e.g. C18), and therefore the test material should contain the maximum feasible concentration of C12 fatty acids present in the registered substance.

Technical reporting of the test material

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

[11] https://echa.europa.eu/practical-guides

Considering the specific characteristics of the registered substance, in identifying each constituent, the following characteristics must be reported:

- The type of fatty acid, indicating carbon chain length and whether unsaturation and/or branching exists, and whether the fatty acid is esterified (e.g. 'C20 fatty acids, mono- di- and tri-unsaturated, 2-ethylhexyl esters'). The exact positions of the unsaturation and/or branching must be specified if known (e.g. '2-ethylhexyl (9E)-octadec-9-enoate').

5. Environmental testing with UVCBs

Before conducting the requested ecotoxicity tests above (Appendices A.2 and C.3 – C.4) you are advised to consult ECHA Guidance R.11 (Section R.11.4.2.2) and R7b (Table R.7.8-3 and Appendix R.7.9-4). It provides advice on choosing the design of the requested aquatic ecotoxicity test(s) for difficult to test substances and on calculation and expression of the result of the test(s).

If you decide to use the Water Accommodated Fraction (WAF) approach in your ecotoxicity tests, please note that this approach may not be adequate to determine the toxicity of multi-component substances where its poorly soluble components are of concern, as in the case of your Substance. In general, it is critical that a robust chemical analysis is carried out before the test, to identify those constituents present in the water to which the test organisms are exposed. Additionally, chemical analysis to demonstrate attainment of equilibrium in WAF preparation and stability during the conduct of the test is required. Methods capable of identifying gross changes in the composition of WAFs with time, such as e.g. ultra-violet spectroscopy or total peak area, are required for this purpose. The method used to prepare the WAF should be fully described in the test report and evidence of the compositional stability of the test substance over time should be provided.

You should express all test results in terms of measured concentrations as far as possible. If you use the "loading rate" for expressing exposures of mixtures that neither fully dissolve nor completely form a stable dispersion or emulsion over the required test range, WAFs can be considered analogous to the term "nominal concentration". As indicated in the OECD test guidelines 201, 221 and 210, and in OECD GD 23, when the measured concentrations do not remain within 80-120% of the nominal concentration, the effect concentrations need to be analytically determined and expressed relative to the arithmetic or geometric mean of the measured concentrations. Therefore, it is recommended that before applying a WAF method, you should first consider conducting a preliminary stability test as per OECD GD 23. If based on that test you consider that the WAF is the only option to prepare the test solution, you should report the potential effect concentrations from the WAF test based on mean measured concentrations.

4. List of references of the ECHA Guidance and other guidance/ reference documents[12]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping

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

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

ECHA Read-across assessment framework (RAAF, March 2017)[13]

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

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

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

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

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

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

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

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

OECD Guidance documents[14]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[13] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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Appendix F: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.