EUROPEAN CHEMICALS AGENCY

Helsinki, 20 August 2020

Addressees
Registrants of JS_C14-22 2EH ester epoxidized listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
13/09/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Fatty acids, C14-22, 2-ethylhexyl esters, epoxidized
EC number: 305-962-8
CAS number: 95370-96-0

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 deadlines provided.

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

3. The long-term toxicity testing on aquatic invertebrates also requested at C.3. below (triggered by Annex VII, Section 9.1.5., column 2)

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 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.; test method OECD TG 476 or TG 490)

3. Justification for an adaptation of the Short-term repeated dose toxicity study (28-day) (Annex VIII, Section 8.6.1.)

4. The long-term toxicity testing on fish also requested at C.4. below (triggered by Annex VIII, Section 9.1.3., column 2)

C. Requirements applicable to all the Registrants subject to Annex IX of REACH[1]

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

D. Requirements applicable to all the Registrants subject to Annex X of REACH[1]

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rat or rabbit), oral route with the Substance

Conditions to comply with the requested information

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- 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;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

When a study is required under several Annexes of REACH, the reasons are provided in the corresponding appendices of this decision. The registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants in accordance with Article 53 of REACH.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

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

[1] Testing required under this Annex can only be started or performed after the decision has been adopted according to Article 51.

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

You are required to submit the requested information in an updated registration dossier by ***25 November 2022*** except for the information requested under Appendix C.1 which shall be submitted in an updated registration dossier by ***25 November 2021***. For each deadline, you shall also update the chemical safety report, where relevant. The deadlines have been set to allow for sequential testing where relevant.

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

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

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix on general considerations

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

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) 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 8.4.3.) if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained.
- Short-term repeated dose toxicity study (28-day)
- Sub-chronic toxicity study (90-day)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

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.

Grouping of substances and read-across approach

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

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4, 5].

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you have formed a group of "Epoxidised Oils". You have provided a read-across justification document in IUCLID Section 13. You claim that in OECD SIDS Initial Assessment Report for SIAM 22, *"the essential similarity of three epoxidised oils and their derivatives"* has been confirmed. The group is called Epoxidised Oils and Derivatives Category, EODs.

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

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. Epoxidiced indseed oil (**ELO**), EC No. 232-401-3, (CAS No. 8016-11-3), and

4. The Substance.

You provide the following reasoning for the grouping the substances: "*...read-across is based on the structural and functional similarities within the EOD group, and the similar toxicological profile built up from various study results*", and "*Read-across bridges are used for members of the EOD group where appropriate, is justified based on similar toxicity profiles and structural and functional similarities.*"

You have not defined the structural basis for the grouping. Neither have you defined the applicability domain of the grouping.

In order to strengthen your read-across documentation and justification, also in terms of animal welfare and the avoidance of unnecessary and redundant vertebrate testing, you suggest a tiered testing programme in your comments to the draft decision. You indicated that you plan to provide 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. ECHA notes that you plan to enhance your read-across adaptation however, withouth supporting information it 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.[6] 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.[7]

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

First you have stated that *"UVCB's are of variable composition and consequently it is not possible to look for directly related structural analogues or analogous series."* You have provided the Iodine values of these four substance, which "depict the number of double bonds left in the oil and therefore the degree of epoxidisation that has been achieved". Furthermore you indicated Oxirane oxygen percentage, which "depict the number of epoxy groups present in the oil and therefore the degree of epoxidisation that has been achieved." Similar values are given for four substances addressed.

Your read-across justification document contains basic compositional information for the members of your "category", ie generic description of main constituents. The composition of these three substances differs, since the source substances (ESBO, ELO and ETP) lack most of the fatty acids in the range of C12-C16, whereas the target substances include [redacted] of those. Furthermore, ESBO and ETP contain triglycerides, while the target substance doesn't. The target substance contains 2-ethylhexyl palmitate and 2-ethylhexyl stearate, which according to the justification document are not constituents of the source substances.

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

Without consideration of e.g. the differences aspecified above, qualitative or quantitative comparative assessment of the compositions of the different category members cannot be completed.

The tiered testing programme that you suggest in your comments to the draft decision 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 not provided additional information on comosition of the target and the source substances. Therefore, comparative assessment of the compositions of the different category members cannot be completed, and therefore the basic requirement of a read-across adaptation is not met. The attempted prediction, when based on the additional information listed above, is hence compromised by the different composition of the category members and therefore, your read-across is not acceptable.

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: " *"...read-across is based on the structural and functional similarities within the EOD group, and the **similar toxicological profile** built up from various study results."*

ECHA understands that you predict the properties of the 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.*

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substance is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the target and the source substances.

The data set reported in the technical dossier does not include any toxicological studies for the target substance to support your read-across hypothesis.

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

The tiered testing programme suggested in your comments, which intends to support "equivalent properties", 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.

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 adequate information allowing a comparison the sub-chronic and the developmental toxicity properties 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.

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[8] 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.*

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

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 (on a *theoretical/general basis*) claim that two of the source substances are metabolised to **epoxidised fatty acids** and glycerol, whereas the (target) Substance is metabolised to epoxidised **fatty acids** and to 2-ethylhexanol. You have not provided any *experimental* data or other adequate and reliable information to document that these metabolic pathways/steps take place. 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 the absence of this information, you have not demonstrated that there is common metabolism as assumed/claimed in your read-across hypothesis.

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 adaptation. Concerning your claim on common metabolites, at present you have not provided any additional relevant experimental information on the Substance and on the source substances, neither have you 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.

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.

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 a key study and a supporting study in your dossier:

i. Ames test OECD 471 with the source substance ESBO; EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 1992;
ii. Ames test OECD 471 with the source substance ESBO; EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 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.

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

Consequently, you are required to provide information on the target (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 and oxylipins have been widely reported to have allelopathic activity on microalgae (Borowitzka MA, 2016)[9]. 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

[9] 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.

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.

3. The long-term toxicity testing on aquatic invertebrates also requested at C.3. below (triggered by Annex VII, Section 9.1.1., column 2)

Short-term toxicity testing on aquatic invertebrates is a standard information requirement of Annex VII of REACH. However, according to Annex VII, section 9.1.1, column 2, for poorly water soluble substances (e.g. water solubility below 1 mg/L) long-term toxicity study on aquatic invertebrates (Annex IX, Section 9.1.5) must be considered instead of an acute test. Hydrophobic and poorly water soluble substances require longer time to reach steady-state conditions and the short-term tests may not give a true measure of toxicity for this type of substances.

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

Therefore, long-term toxicity testing is needed to accurately define the hazard of the Substance.

The examination of the information provided in the Lead dossier for this endpoint, as well as the selection of the requested test and the test design are addressed in Appendix C, section 3.

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, with source substance ESBO, EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 1992.

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 comments 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 a two studies in your dossier:

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

We have assessed this information and identified the following issue(s):

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. Justification for an adaptation of the Short-term repeated dose toxicity study (28-day) (Annex VIII, Section 8.6.1.)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

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.

You have provided the following studies for this endpoint in your dossier:

i. Combined repeated dose toxicity study, OECD TG 422 with the reproduction/developmental toxicity study provided with source substance ETP, EC No. 263-024-4, (CAS No. 61789-01-3), according to GLP, [redacted] 2005;
ii. Combined Chronic Toxicity/Carcinogenicity Study OECD TG 453 made with source substance ESBO, EC No. 232-391-0, (CAS No. 8013-07-8), not according to GLP, [redacted] 1986;
iii. Non-guideline chronic toxicity oral study, with source substance ESBO, EC No. 232-391-0, (CAS No. 8013-07-8), not according to GLP, [redacted] 1960

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

In your comments 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.

Column 2 of Annex VIII, Section 8.6.1., provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section C.1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

Because you still must comply with the information requirement in Annex VIII, Section 8.6.1.,

you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

4. The long term toxicity testing on fish also requested at C.4. below (triggered by Annex VIII, Section 9.1.3., column 2)

Short-term toxicity testing on fish is a standard information requirement of Annex VIII of REACH. However, according to Annex VIII, section 9.1.3, column 2, for poorly water soluble substances (e.g. water solubility below 1 mg/L) long-term toxicity study on fish (Annex IX, Section 9.1.6) must be considered instead of an acute test. Hydrophobic and poorly water soluble substances require longer time to reach steady-state conditions and the short-term tests may not give a true measure of toxicity for this type of substances.

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

Therefore, long-term toxicity testing is needed to accurately define the hazard of the Substance.

The examination of the information provided in the Lead dossier for this endpoint, as well as the selection of the requested test and the test design are addressed in Appendix C, section 4.

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 days) is a standard information requirement listed in Annex IX, Section 8.6.2. of REACH.

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.

You have provided three studies for this endpoint in your dossier:

i. Combined repeated dose toxicity study, OECD TG 422 with the reproduction/developmental toxicity study provided with source substance ETP, EC No. 263-024-4, (CAS No. 61789-01-3) according to GLP, [redacted] 2005;
ii. Combined Chronic Toxicity/Carcinogenicity Study OECD TG 453 made with source substance ESBO; EC No. 232-391-0, (CAS No. 8013-07-8),not according to GLP, [redacted] 1986;
iii. Non-guideline chronic toxicity oral study, with source substance ESBO; EC No. 232-391-0, (CAS No. 8013-07-8), not according to GLP, [redacted] 1960

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, there is a data gap and you need to generate the missing information on your Substance.

For an oral Sub-chronic toxicity study, the OECD TG 408 is the appropriate test method. According to the ECHA Guidance[10] and the OECD TG 408, the rat is the preferred species for the study.

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[11]. As the substance is a liquid 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

[11] 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 a two studies in your dossier:

i. PNDT study according to OECD TG 414, with source substance ESBO, EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 1993.
ii. OECD TG 415 One-Generation Reproduction Toxicity Study with the source substance ESBO; EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 1993.

We have assessed this information and identified the following issue(s):

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 comments 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[12] administration of the Substance.

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

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 for (REACH Annex VII , Section 9.1.1, Column 2 and REACH Annex VIII , Section 9.1.3, Column 2).

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

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 derivatives whereas the Substance consists of C12 - C20 derivatives. 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 perform a long-term toxicity study on *Daphnia* depending on the outcome of 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.

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.

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: Reasons for the requests to comply with Annex X of REACH

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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

In addition, you have adapted this information requirement by referring to the 3th indent of Column 2 of Annex X, Section 8.7.

You have provided a two studies in your dossier:

i. PNDT study according to OECD TG 414 made in 1993, with source substance ESBO, EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 1993.
ii. OECD TG 415 One-Generation Reproduction Toxicity Study with the source substance ESBO; EC No. 232-391-0, (CAS No. 8013-07-8), according to GLP, [redacted] 1993.

We have assessed this information and identified the following issue(s):

1. You have not provided a PNDT study with second species.

2. 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.

3. The 3th indent of Column 2 in Annex IX, Section 8.7., allows you to adapt this information requirement if <u>all</u> of the following conditions are met: the substance is of low toxicological activity, it can be proven from the toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and there is no or no significant human exposure.

   You have alleged that no systemic absorption occurs but you have not provided any supporting evidence. Further, judging from the uses which you have reported (PROCs 4, 5,7 , 8a, 9, 14 showing consumer uses and uses by professional workers outside of the closed processes) it is considered likely that there is significant human exposure.

   Two of the conditions in the Column 2 criteria are not met. Therefore, your adaptation is rejected.

Consequently, there is a data gap and you need to generate the missing information on your Substance.

A PNDT study according to the OECD TG 414 study should be performed in rabbit or rat as the preferred second species, depending on the choice of species in the PNDT study in the first species (request C.2 in this decision).

The study shall be performed with oral[13] administration of the Substance.

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

Appendix E: 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.

ECHA notified you of the draft decision and invited you to provide comments.

In your comments, you consider that 12 months deadline is too short for providing the 90-day study and point to a decision on another case (EC No 701-259-9), where 24 months deadline was given. Please note, that in that case 24 month was given to provide all the requested information and not only to provide the 90-day study. Additionally, the present case concerns an Annex X registration. The deadline of 12 months for 90 day study is set to enable an assessment of the potentially triggered cohorts of the EOGRT study, as explained below in Appendix F. The case you refer to (EC No 701-259-9) concerns an Annex IX registration, where EOGRTS is not a standard information requirement. Therefore, a separate 12 months deadline for the 90 day study was not given in that case.

ECHA did not amend the requests 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.

EUROPEAN CHEMICALS AGENCY

Appendix F: Observations and technical guidance

1. The information requirement under Section 8.7.3. of Annex X to REACH (Extended one-generation reproductive toxicity study, EOGRTS) is not addressed in this decision, because the information from the Sub-chronic toxicity study (90-day), requested in the present this decision, is relevant for the design of the EOGRTS.

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

3. 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.

4. 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'[14].

5. 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 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

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

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.

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 branching, unsaturation, and/or epoxy-groups exists, and whether the fatty acid is esterified (e.g. 'C18 fatty acid, dioxirane, 2-ethylhexyl ester'). The exact positions of branching, unsaturation, and epoxy-groups must be specified if known.

- Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website15.

6. 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).

In case 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 prior 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.

7. List of references of the ECHA Guidance and other guidance/ reference documents[16]

Evaluation of available information

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

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
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)[17]

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[18]
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.

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

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

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

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