EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 1 June 2021

Addressees
Registrant(s) of JS_1034820-43-3_ as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
30/03/2018

Registered substance subject to this decision ("the Substance")
Substance name: Propanoic acid, 3,3'-thiobis-, di-C11-14-isoalkyl esters, C13-rich
EC number: 823-780-1
CAS number: 1034820-43-3

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed in A.1., A2. below by ***8 June 2022*** and all other information listed below by ***8 September 2023***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. Skin sensitisation (Annex VII, Section 8.3.):

   - i) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.) with the Substance; and
   - ii) *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429) with the Substance, in case the *in vitro/in chemico* test methods specified under point i) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment

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

3. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201).

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annex VII of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa).

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

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 Reasons common to several requests

1. Assessment of your 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:

- Skin sensitisation (Annex VII, Section 8.3.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

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[2] and related documents[3, 4].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.

You read-across between dilauryl thiodipropionate, EC No. 204-614-1 (CAS No. 123-28-4) (also in IUCLID referred to as didodecyl 3,3'-thiodipropionate), and distearyl thiodipropionate, EC No. 211-750-5 (CAS No. 693-36-7), as source substances and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: "*The substances are expected to have a similar metabolic pathway due to the structural similarity and comparable physicochemical properties. They are therefore deemed to have a similar toxicological profile".*

In your comments to the draft decision, you indicate that the main argument for your read-across hypothesis is that the source and target substances present a biological equivalence because of the structural similarity and comparable physicochemical properties. You further consider that no new experimental tests on the Substance are necessary due to the high

[2] 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

[3] 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)

[4] 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

structural similarity and comparable physicochemical properties between the Substance and the source substances, and the already available studies on the analogue substances.

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 quantitatively equal to those of the source substances.

ECHA notes the following shortcoming(s) with regards to prediction(s) of toxicological properties as submitted in the dossier and with your comments on the draft decision.

Supporting information

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*"[5]. 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).

Supporting information must include supporting information such as bridging studies to compare properties of the Substance and source substances.

1. Missing supporting information to compare properties of the substances

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) 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 Substance and of the source substance(s).

In your read-across justification, you claim that the Substance and the source substances are comparable regarding toxicological hazard based on a summary of available toxicity data in table 6 named "*Toxicological information*", which covers acute toxicity, irritation, sensitisation, genetic toxicity, repeated dose toxicity and/or for toxicity to reproduction and development and *in vitro* chromosomal aberration.

In your comments to the draft decision, you agree that no bridging studies are provided in your dossier to compare the properties of the substances. You provide toxicity alerts ("profiles") for the constituents of the Substance and for the source substance dilauryl thiodipropionate (EC No. 204-614-1) as predicted by the QSAR Toolbox and VEGA to support your hypothesis of absence of differences in their toxicological properties.

In your comments to the draft decision, you acknowledge the fact that no experimental study is available on dermal or oral absorption and metabolism of the source and target substances and that there are uncertainties related to the predictions you provided for these properties.

The data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and of the source substance(s) to support your read-across

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

hypothesis. In particular, you did not provide any information on the properties of the Substance regarding the above-mentioned endpoints, which would allow a comparison with the properties of the source substances. You have not demonstrated that the QSAR predictions provided with your comments cover the endpoints considered in their entirety, with their complexity and uncertainties, and that these predictions can be seen, on their own, as evidence of similarity in the properties of the Substance and the source substances. Furthermore, ECHA notes some reliability issues with these predictions, which are addressed under the endpoint specific sections of this draft decision.

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

2. Relevance of the supporting information

According to the ECHA Guidance[6] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In your comments to the draft decision, and in order to support your claim that your Substance and source substances have similar properties for the endpoints under consideration in the read-across approach, you refer to predictions of their absorption and metabolic properties using EpiSuite 4.1 – Dermwin v.2.02 and QSAR Toolbox v.4.4, respectively, as well as to predictions of toxicity alerts ("profiles") using QSAR Toolbox v.4.4, VEGA v.1.1.4 and Derek Nexus v6.0.1.

Whilst you claim that the data set you provided in your comments to this draft decision suggests that the substances may have comparable properties for absorption and metabolism, these predictions do not directly inform on the sensitisation or mutagenicity properties of the target and source substances.

Similarly, the toxicity alerts you provided to support your hypothesis contain predictions for endpoints not related to sensitisation or mutagenicity properties of the target and source substances, such as repeated dose toxicity, toxicity to reproduction and development, carcinogenicity, estrogen receptor relative binding affinity, respiratory irritation, eye or skin irritation.

Regarding mutagenicity, you acknowledge the fact that the expected similar metabolic pathway between the source and target substances is only an assumption, which is not supported by experimental evidence but only by predictions of metabolites from the QSAR Toolbox v.4.4.

Accordingly, these pieces of information are not considered as relevant to support prediction of all the endpoints under consideration.

3. Read-across hypothesis contradicted by existing data

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

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[7] indicates 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). The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence. 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).

Regarding skin sensitisation, you indicate that the source substance dilauryl thiodipropionate (EC No. 204-614-1) presents a much higher predicted dermal permeability coefficient than the constituents of the target substance, thereby indicating that the branching might be a barrier to the absorption of the molecule through the skin. In addition, you state that the skin metabolism predictions you provided in your comments do not allow to conclude whether the difference in the structure and the properties of the metabolites of the source and target substance could have an impact on the skin sensitisation potential of the substances.

This also puts into question the validity of your read-across hypothesis, which assumes that the source and target substances present a biological equivalence because of the structural similarity and comparable physicochemical properties.

Therefore, your hypothesis that the absorption, metabolism and toxicity profiles of the source and target substances are similar cannot be demonstrated by the information provided. Furthermore, your assumption that a potential similarity of these properties would imply a similarity of the toxicological properties with respect to sensitisation and mutagenicity is not supported either.

B. Predictions for ecotoxicological properties

You have provided the following reasoning for the prediction of ecotoxicological properties: *"The Read-across (RA) approach* [...] *is based on the structural similarity and the comparable physicochemical properties between the analogue substances and the target substance. It is expected that the Target substance will have a similar (eco)toxicological profile and environmental fate to the Source Substances".*

You read-across between:

- dilauryl thiodipropionate, EC No. 204-614-1 (CAS No. 123-28-4),
- distearyl thiodipropionate, EC No. 211-750-5 (CAS No. 693-36-7), and
- ditridecyl 3,3'-thiodipropanoate, EC: 234-206-9 (CAS No. 10595-72-9) (for some physicochemical properties)

as source substances and the Substance as target substance.

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 quantitatively equal to those of the source substances.

ECHA notes the following shortcomings with regards to predictions of aquatic toxicity.

[7] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

Read-across hypothesis

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

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological, ecotoxicological or environmental fate property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[8]. It should explain why the differences in the chemical structures should not influence the toxicological, ecotoxicological or environmental fate properties or should do so in a regular pattern.

Your read-across hypothesis assumes that the sources and target substances have similar structures and similar physicochemical properties and that this could support the assumption that the sources and target substances have similar ecotoxicological properties and environmental fate.

i. Structural similarity

The Substance is produced from the esterification of the 3,3'-thiodipropionic acid with the (UVCB) fatty alcohols, C11-C14-iso, C13-rich. It is composed of a mixture of dialkylthioesters ([redacted] of the substance composition) which are characterised by two branched alkyl chain consisting from 11 to 14 carbon atoms and [redacted] of unreacted alcohols, C11-C14-iso, C13-rich. More detailed information on the exact composition of the target Substance is not available. In particular, there is no information on the degree and positions of branching.

As for the source substances:

- dilauryl thiodipropionate (EC: 204-614-1) contains two linear C12 alkyl chains
- distearyl thiodipropionate (EC: 211-750-5) contains two linear C18 alkyl chains
- ditridecyl 3,3'-thiodipropanoate (EC: 234-206-9) contains two linear C13 alkyl chains

The source substances do not contain branched chains whereas the target Substance does. The presence of branching on the alkyl chains may prevent the biodegradation of the target Substance and increase its ecotoxicity.

This is acknowledged in your dossier, but you claim that the degradation may be initiated by the hydrolysis of the esters groups. You further claim that chain branching would not influence significantly the biodegradation of the Substance because "*the UVCB alcohols that make the [redacted] of the substance are considered as readily biodegradable*".

However, no experimental data on hydrolysis of the Substance is provided to support the hypothesis of fast hydrolysis. Even if biotic or abiotic hydrolysis of the esters groups were demonstrated, this would only result in the partial degradation of the Substance. Branching on the alkyl chains would possibly still represent a possible obstacle to further biodegradation of the putative hydrolysis products. In particular, you have not provided any data or evidence to support your claim that the fatty alcohols would be readily biodegradable. Besides, no

[8] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.

information on the exact identity of these fatty alcohols is provided, in particular the degree and positions of branching.

Therefore, the presence of branching in the target substance is a structural difference that may be significant for the assessment of its ecotoxicological or environmental fate properties. Therefore, your hypothesis of structural similarity is not supported by the information provided.

ii. Similarity of physico-chemical properties

For vapour pressure, water solubility and log Kow, no experimental data are available for the Substance but QSAR predictions for source substance ditridecyl 3,3'-thiodipropanoate (EC: 234-206-9) are present.

For the other two source substances, experimental data are missing for most physicochemical endpoints. Unbounded values of water solubility, extremely high values of log Kow and extremely low values for vapour pressure are reported for these two source substances.

As such, those results do not allow to conclude whether the physico-chemical properties of the substances are similar or if on the contrary they follow a trend.

As explained above, these three source substances do not cover all the constituents present in the target substance. In particular, they do not contain branched alkyl chains. Branching may actually not have an important impact on physico-chemical properties such as water solubility or log Kow. On the contrary, as explained above, branching can be expected to affect the ecotoxicological and environmental fate properties. This implies that similarities for physico-chemical properties such as water solubility or log Kow would not necessarily translate into similarities for ecotoxicological or environmental fate properties. Therefore, a potential similarity of physico-chemical properties between the source and the target substance would anyway not be sufficient to support a read-across approach for ecotoxicological or environmental fate properties.

Therefore, your hypothesis that the physico-chemical properties of the source substances and the target substance are similar cannot be demonstrated by the information provided. Furthermore, your assumption that a potential similarity of the physico-chemical properties would imply a similarity of the ecotoxicological and environmental fate properties is not supported either.

C. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

Additional issues related to read-across approach are addressed under the corresponding endpoints.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Skin sensitisation

Skin sensitisation is a standard information requirement in Annex VII to REACH (Section 8.3.). Column 1 of Section 8.3. requires the registrants to submit information allowing a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and risk assessment, where required.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.5 (grouping of substances and read-across) of REACH.

In support of your adaptation, you have provided the following source of information:

i. *in vivo* Guinea Pig Maurer optimisation test (according to the US FDA guideline for the "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (1959)) with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1976)

In your comments to the draft decision you also provide the following sources of information:

ii. sensitisation predictions from the QSAR Toolbox and VEGA models for the Substance constituents and for the analogue substance dilauryl thiodipropionate (EC No. 204-614-1), and sensitisation predictions from the Derek Nexus model for a representative constituent of the Substance.

In addition, although you do not explicitly claim this adaptation, ECHA understands that you rely on Annex VII, section 8.3.2, column 2, third paragraph, regarding the use of *in vivo* skin sensitisation studies that were carried out or initiated before 10 May 2017.

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

Read-across

As explained in the Appendix on Reasons common to several requests, section 1. (Assessment of your read-across approach under Annex XI, Section 1.5.), your adaptation under Annex XI, Section 1.5 is rejected.

Inadequate study

According to Annex VII, section 8.3.2, column 2, third paragraph, *in vivo* skin sensitisation studies that were carried out or initiated before 10 May 2017 must be considered appropriate to address this standard information requirement provided that they were carried out according to GLP and the test methods referred to in Article 13(3), in this case OECD TG 406 study.

The conditions of OECD TG 406 include:

- Dose level selection rationale
- The induction concentration should be the highest causing mild-to moderate irritation to the skin and the challenge dose should be the highest non-irritation concentration.

You have provided an *in vivo* Guinea Pig Maurer optimisation study (i) according to the US FDA guideline for the "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics"

(1959), non-GLP with an analogue substance (1976), similar to the OECD TG 406 (Guinea Pig Maximization test).

In the provided study (i):

- No dose level selection rationale was provided ("*no pilot-/range-finding study was conducted to find appropriate test concentrations*").
- No information was provided whether the concentration used for induction caused mild-to-moderate irritation and whether the challenge concentration was the highest non-irritating concentration.

Therefore the study does not fulfil the conditions set in the OECD TG 406.

In your comments to the draft decision, you agree that this study report does not fulfil current guideline requirements.

Assessment of your (Q)SAR predictions provided in your comments

Annex XI, Section 1.3. specifies that the following conditions must be fulfilled whenever a (Q)SAR approach is used:

1. the prediction needs to be derived from a scientifically valid model,
2. the substance must fall within the applicability domain of the model,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

With regard to these conditions, we have identified the following issue(s):

Inappropriate measures of robustness of the model

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness using the learning data set) and predictivity (using a test data set) of the model are available.

In your comments to the draft decision, you use a Toolbox profiler to make a prediction for the endpoint without measures of internal performance and predictivity of the profiler for the prediction of this endpoint.

ECHA notes that Toolbox profilers are models developed for the purpose of identifying analogues and not to make predictions (as indicated on the official QSAR Toolbox website https://qsartoolbox.org/features/profiling/). In absence of measures of internal performance and predictivity, a profiler is not considered a scientifically valid approach to meet this information requirement.

The prediction is not adequate due to low reliability

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

In your comments to the draft decision, you provide the following information:

- Predictions of sensitisation from Derek Nexus model

You have not demonstrated that the input is reliable because no similar substances were used in the training set of the model. This indicates that the Substance may be outside the applicability domain of the model and that substances that are similar to the Substance may not be well predicted by the model.

Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

The substance is outside the applicability domain of the model.

Under ECHA Guidance R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

In your comments to the draft decision, you indicate that the VEGA model (v.1.1.4) was used for all the isoalkyl esters composing the Substance.

All isoalkyl esters were predicted as "Sensitisers".

However, you claim that these results may be not reliable, as the predicted substances are outside the Applicability Domain of the model. To support your claim, you identified the following issues:

- only moderately similar compounds with known experimental value in the training set have been found
- 1 descriptor(s) for this compound have values outside the descriptor range of the compounds of the training set.
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (2 infrequent fragments found).

ECHA agrees that there are general issues with reliability and applicability domain of this model.

Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model.

Lack or inadequate documentation of the model (QMRF)

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

In your comments to the draft decision, you have not provided sufficient information about the Derek Nexus model.

The QMRF for this model is missing and ECHA notes the following issues:

- Missing information on the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model
- Missing definition of the algorithm and of its applicability domain
- Missing information on the estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics

In particular, the lack of quantitative measures on the estimate of the goodness-of-fit and of the predictivity of the model is of particular concern for negative results from alert/based systems Like Derek Nexus because negative results might result from lack of alerts but also lack of knowledge.

In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

Lack of or inadequate documentation of the prediction (QPRF)

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

In your comments to the draft decision, you have not provided information about the prediction for the Derek Nexus and QSAR Toolbox models.

The QPRF is missing and ECHA notes the following issues:

- Missing documentation of the Derek Nexus model prediction, including the endpoint
- Missing documentation of the relationship between the modelled substance and the defined applicability domain for the Derek Nexus and QSAR Toolbox models
- Missing documentation of close analogues, including considerations on how predicted and experimental data for analogues support the prediction for the Derek Nexus and QSAR Toolbox models.

In particular, you state in your comments on the Derek Nexus results that the structure "*is predicted as NON SKIN SENSITISER with high reliability, since the target molecule does not contain any unclassified or misclassified features.*"

However, for inactive substances, there is only a statement and no further information in the Derek Nexus results. The lack of misclassified or unclassified features is supposed to provide support to the "Non-sensitiser" prediction but it is not sufficient. For instance, results from close analogues are neither included nor discussed.

In absence of such information, ECHA cannot establish that the predictions can be used to meet this information requirement.

Based on the above, your adaptation is rejected and the information you provided does not fulfil the information requirement.

In your comments to the draft decision, you also provide your considerations regarding the limited applicability of the available *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) to the Substance and the potential need to test the Substance *in vivo*. You mention

animal welfare as an additional justification for not performing the requested studies.

However, you have not provided any legal basis for your claimed adaptation based on limited applicability and animal welfare does not constitute as such a valid justification for omitting the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

Based on the above, your adaptation is rejected and the information you provided does not fulfil the information requirement.

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (OEDC TG 429) is considered as the appropriate study.

2. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH (Section 8.4.1.).

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. In support of your adaptation, you have provided the following sources of information:

i. *in vitro* gene mutation study in bacteria (OECD TG 471) with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1992)
ii. non-guideline, non GLP, host-mediated assay with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1973)
iii. *in vitro* gene mutation study in mammalian cells (OECD TG 476) with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1993)
iv. *in vitro* chromosome aberration study in mammalian cells (OECD TG 473) with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1992)
v. *in vivo* chromosome aberration study in bone marrow (OECD TG 475) after repeated administration with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1973)
vi. *in vivo* chromosome aberration study in bone marrow (OECD TG 475) after single administration with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1973)
vii. *in vivo* rodent dominant lethal test (OECD TG 478) with the analogue substance dilauryl thiodipropionate (EC No. 204-614-1) (1973)

In your comments to the draft decision, you further provide the following sources of information:
viii. mutagenicity predictions from the QSAR Toolbox and VEGA models for the Substance constituents and for the analogue substance dilauryl thiodipropionate (EC No. 204-614-1), and mutagenicity predictions from the Derek Nexus model for a representative constituent of the Substance.

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

Annex XI, Section 1.2 states that there may be sufficient weight of evidence weight of evidence from several independent sources of information leading to assumption/conclusion

that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, Section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

To fulfil the information requirement, normally a study according to OECD TG 471 must be provided. OECD TG 471 requires the study to investigate gene mutations in bacteria using 5 different bacterial strains.

The source of information iii. investigates gene mutation in mammalian cells and not in bacteria. Therefore, it does not provide relevant information on *in vitro* gene mutations in bacteria.

The sources iv. to vii do not investigate gene mutation. Therefore, they do not provide relevant information on *in vitro* gene mutations in bacteria.

The sources of information i., ii. and viii. may provide relevant information on *in vitro* gene mutations in bacteria. However, the reliability of these sources of information is significantly affected by the following deficiencies:

Read-across

Information from source substance(s) can contribute to weight of evidence adaptation only if the read-across is acceptable.

Studies i. and ii. are performed with an analogue substance.

However, for the reasons explained under Section 1 of the Appendix on Reasons common to several requests, there are deficiencies identified with the read-across adaptation. These deficiencies affect significantly the reliability of the sources of information relating to analogue substances and relied upon in your weight of evidence adaptation. Therefore, the sources of information i. and ii. cannot contribute to the weight of evidence adaptation.

Inadequate source studies

In addition the reliability of the source of information ii. is also affected by the following issue:

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 471. One of the specifications of OECD TG 471 includes that the test must be performed with 5 strains, four strains of *S. typhimurium* (TA98/TA100/TA1535/TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

However, the source of information ii. reports *in vitro* data on two strains of bacteria (*S. typhimurium* TA1530 and G46) and one strain of yeast (*Saccharomyces cerevisiae* D3), but not on the required strains.

Therefore, the provided study cannot be considered as a reliable source of information that could contribute to the conclusion on this information investigated by the required study.

Assessment of your (Q)SAR predictions

Annex XI, Section 1.3. specifies that the following conditions must be fulfilled whenever a (Q)SAR approach is used:

5. the prediction needs to be derived from a scientifically valid model,
6. the substance must fall within the applicability domain of the model,
7. results need to be adequate for the purpose of risk assessment or classification and labelling, and
8. adequate and reliable documentation of the method must be provided.

With regard to these conditions, we have identified the following issue(s) with the source of information viii. provided in your comments to the draft decision:

Modelled endpoint not well defined

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:

- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in this case includes effects in the 5 strains of bacteria required (OECD TG 471).

You specify that the effect that is modelled is Mutagenicity *in vitro* (Ames test).

You have provided a (Q)SAR model Derek Nexus which is based on data generated using the following methodologies: among others, *"Primary data used for alert development include Ames test data in both Salmonella typhimurium and Escherichia coli. Supporting data include: a) in vivo rodent transgenic mutagenicity assays; b) in vitro L5178Y TK+/- assay; c) in vitro HGPRT gene mutation assay; d) in vitro Na+/K+ ATPase gene mutation assay."*.

You also indicate that you used different VEGA (v.1.1.4) models for mutagenicity to provide predictions for all the substances composing the Substance, but did not include details on the models (QMRFs) and the predictions (QPRFs).

However, ECHA notes that, based on the above and lacking information on the potential close analogues and their experimental data, you have not demonstrated that the endpoint predicted by the (Q)SAR is the same as the endpoint measured by the relevant test protocol

since the predictions from the Derek Nexus and VEGA models may not account for all the 5 strains of bacteria required.

Therefore, the endpoint of the model is not well defined and you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

Inappropriate measures of robustness of the model

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness using the learning data set) and predictivity (using a test data set) of the model are available.

In your comments to the draft decision, you use a Toolbox profiler to make a prediction for the endpoint without measures of internal performance and predictivity of the profiler for the prediction of this endpoint.

ECHA notes that Toolbox profilers are models developed for the purpose of identifying analogues and not to make predictions (as indicated on the official QSAR Toolbox website https://qsartoolbox.org/features/profiling/). In absence of measures of internal performance and predictivity, a profiler is not considered a scientifically valid approach to meet this information requirement.

The prediction is not adequate due to low reliability

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

In your comments to the draft decision, you provide the following information:

- Predictions of mutagenicity *in vitro* (Ames test) from Derek Nexus model

You have not demonstrated that the input is reliable because no similar substances were used in the training set of the model. This indicates that the Substance may be outside the applicability domain of the model and that substances that are similar to the Substance may not be well predicted by the model.

Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

Inadequate documentation of the model (QMRF)

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its

applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

In your comments to the draft decision, you have not provided sufficient information about the Derek Nexus and VEGA models.

The QMRFs for these models are missing and ECHA notes the following issues:
- Missing information on the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model
- Missing definition of the algorithm and of its applicability domain
- Missing information on the estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics

In particular, the lack of quantitative measures on the estimate of the goodness-of-fit and of the predictivity of the model is of particular concern for negative results from alert-based systems like Derek Nexus because negative results might result from lack of alerts but also lack of knowledge. The lack of misclassified or unclassified features is supposed to provide support to the "inactive" prediction but it is not sufficient.

In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

Lack of or inadequate documentation of the prediction (QPRF)

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:
- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

In your comments to the draft decision, you have not provided information about the prediction for the Derek Nexus, VEGA and QSAR Toolbox models.

The QPRF is missing and ECHA notes the following issues:
- Missing documentation of the model prediction for the Derek Nexus and VEGA models, including the endpoint
- Missing documentation of the relationship between the modelled substance and the defined applicability domain for the Derek Nexus, VEGA and QSAR Toolbox models
- Missing documentation of close analogues, including considerations on how predicted and experimental data for analogues support the prediction for the Derek Nexus, VEGA and QSAR Toolbox models.

In particular, you state in your comments on the Derek Nexus results that "for non-alerting compounds the possible outcomes are the following: "Inactive" prediction (all features in the molecule are found in accurately classified compounds from the reference set); "Inactive with Misclassified features" (features in the molecule are found in non-alerting mutagens in the Lhasa reference set), "Inactive with Unclassified features" (features in the molecule are not found in the Lhasa reference set. For alerting compounds, the matched alerts are provided with an image of the alert, description, comments, validation comments, references and examples of matching toxic structures."

However, for inactive substances, there is only a statement and no further information in the Derek Nexus results. For instance, results from close analogues are neither included nor discussed.

In absence of such information, ECHA cannot establish that the predictions can be used to meet this information requirement.

Conclusion on your weight of evidence

As a conclusion, sources of information as indicated above, provide information on *in vitro* gene mutations in bacteria but their reliability is affected so significantly, due to the deficiencies explained above, that they cannot be taken into consideration in a weight of evidence approach.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 471 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

3. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2).

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.5 (grouping of substances and read-across) of REACH.

In support of your adaptation, you have provided a non GLP study ([redacted] 1992) performed with analogue substance didodecyl 3,3'-thiodipropionate (EC: 204-614-1) and according to the test guideline listed in Annex V to Directive 67/548/EEC (as amended by Directive 87/302/EEC).

As explained in the Appendix on Reasons common to several requests, section 1. ('*Assessment of your read-across approach under Annex XI, Section 1.5.*'), your adaptation under Annex XI, Section 1.5 is rejected. In addition, the following additional deficiency was found:

i. Invalid study

Annex XI, Section 1.5 requires that whenever read-across is used, the results should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

OECD TG 201 is the preferred test method to fulfil the information requirement of Section 9.1.2 of Annex VII to REACH. The study must also comply with the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test. In particular, the following requirements must be met:

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range must be available.

Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;

- the test media prepared specifically for analysis of exposure concentrations during the test is treated identically to those used for testing (*i.e.* inoculated with algae and incubated under identical conditions);
- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.

  For volatile, unstable or strongly adsorbing test substances, additional samplings for analysis at 24 hour intervals is required.
- the results can be based on nominal or measured initial concentrations only if the concentrations of the test material has been maintained within 20 % of the nominal or measured initial concentrations throughout the test.

However, no analytical monitoring of exposure concentrations was conducted for the study provided in your dossier.

ii. Conclusion

Therefore, the requirements of OECD TG 201 are not met.

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

In your comments to the draft decision you agree to perform the study with the Substance, according to the OECD TG 201 and to the recommendations of OECD GD 23.

Study design

The Substance is difficult to test due to the low water solubility (<< 1 mg/L) and potential adsorptive properties (log Kow predicted to be >12). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

4. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2)

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided an OECD TG 202 study with analogue substance didodecyl 3,3'-thiodipropionate (EC: 204-614-1) but no information on long-term toxicity on aquatic invertebrates for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

You have provided information which indicate that the Substance is poorly water soluble (water solubility < 1 mg/L at 20°C).

Therefore, information on long-term toxicity on aquatic invertebrates must be provided.

In your comments to the draft decision you agree to perform the study with the Substance, according to the OECD TG 211 and to the recommendations of OECD GD 23.

Study design

The Substance is difficult to test due to the low water solubility (<< 1 mg/L) and potential adsorptive properties (log Kow predicted to be >12). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solutions.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. 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 on How to report robust study summaries[9].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. *Selection of the Test material(s)*

   The Test Material used to generate the new data must be selected taking into account the following:
   a) the variation in compositions reported by all members of the joint submission,
   b) the boundary composition(s) of the Substance,
   c) the impact of each constituent/ impurity 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.

2. *Information on the Test Material needed in the updated dossier*

   a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

The reported composition must also include other parameters relevant for the property to be tested. Considering the specific characteristics of the registered substance, in identifying each constituent (or group of constituents), the following characteristics must be reported:

- The distribution of carbon chain lengths in the alkyl substituent
- Any information known on the specific degree and type of branching
- If the substance contains also linear alkyl moieties, the ratio between the linear and branched alkyl moiety for each carbon chain length should be specified.

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

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[10].

[10] https://echa.europa.eu/manuals

Appendix C: General recommendations when conducting and reporting new tests for REACH purposes

A. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in ECHA Guidance R.11 (Section R.11.4.2.2), you are advised to consider the following approaches for persistence, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesise its relevant constituents and/or fractions.

Appendix D: Procedure

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 11 December 2019.

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

ECHA took into account your comments and did not amend the requests and the deadline.

> In your comments on the draft decision, you requested an extension of the deadline to provide information from 12 to 18 months for requests A.1., A2., and from 27 to 33 months for all other requests from the date of adoption of the decision.
>
> In your comments to the draft decision, you state the following: *"The substance is extremely difficult to test in aquatic test systems. It is poorly soluble, adsorptive, and readily biodegradable. The development of an appropriate analytical method and thorough pre-tests on e.g. test solution preparation and adsorption behaviour are needed. Therefore, the proposed date (27 months from the date of the decision) is allowed for the individual aquatic toxicity studies if they were run in parallel. For a tiered approach, as recommended above, an additional 6 months are needed."*.
>
> However, you did not provide supporting documentation to demonstrate based on laboratory capacity why an additional 6 months are necessary. ECHA considers that a tiered approach for the aquatic toxicity studies is not needed and does not require extra time.
>
> On this basis, ECHA has not modified the deadline to provide the information.

Due to cease of manufacture, the following requests have been removed from this draft decision: In vitro cytogenicity study in mammalian cells or In vitro micronucleus study; In vitro gene mutation study in mammalian cells; Short-term repeated dose toxicity to be combined with the Screening for reproductive/developmental toxicity; Long-term toxicity testing on fish; Soil simulation testing; Sediment simulation testing; and Identification of degradation products.

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.

Appendix E: List of references - ECHA Guidance[11] and other supporting documents

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 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[12]

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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[13]

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

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

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

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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.