EUROPEAN CHEMICALS AGENCY

Helsinki, 23 April 2018

Addressee: [redacted]

Decision number: CCH-D-2114401221-74-01/F
Substance name: CASTOR OIL, SULFATED, SODIUM SALT
EC number: 269-123-7
CAS number: 68187-76-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 07.09.2017
Registered tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

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

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

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

You are required to submit the requested information in an updated registration dossier by **30 April 2020**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard Head of Unit, Evaluation E1

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

Appendix 1: Reasons

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have sought to adapt standard information requirements, for:

- Sub-chronic toxicity study (Annex IX, Section 8.6.2.) and

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

0.1 Description of the grouping and read-across approach proposed by the Registrant

In your read-across justification report you refer to the class of "Fat Liquors and Lubricants" which are prepared by sulfonation of fatty acids or oils. You identified two sub-categories, namely "Sulfated Fat Liquors" to which the registered substance belongs and "Sulfited Fat Liquors".

For the sub-category of "Sulfated Fat Liquors" you indicate the following:

> *"Sulfated fat liquors are a group of closely related substances with the primary difference being the origin of the raw materials ([redacted]). The sulfated oil derivatives in this category have the same chemical structure of fatty acids or glycerine triesters with sulfated groups on previous double bonds. Sulfonation of triglycerides is generally a complete reaction and residual double bonds are not expected within the sulfated fat liquors. Sulfated substances have a carbon – oxygen – sulfer bond (C-O-S). Depending upon the sulfonation chemistry process the sulfated fat liquors have either a sodium (Na+) or ammonium (NH4+) counterion. The salts are expected to dissociate completely in water.*

Although the counter ion can play a role in the physical and chemical behaviour of the compounds, the chemical reactivity and classification for this purpose is not expected to be affected by the difference in counter ion (i.e., Na+, NH4+). Solubility testing for both sodium and ammonium salts of sulfated fat liquors show similarly low water solubility for substances in this group."

For the sub-category "Sulfited Fat Liquors" you indicate the following:

"The group of Sulfited Fat Liquors Substances consists of [redacted]. Note that the terms [redacted] are deemed to refer to the same process whereby the natural oil is reacted to add a sulfonate group [redacted] to the molecular structure, directly on the hydrocarbon chain of the fatty acid portion, and in particular at the unsaturated carbon-carbon bonds. Although the origin of the oils may vary, the manufacturing process is similar and each FLL Substance can be described as consisting of an [redacted]. At the end of the sulfonation reaction the [redacted] content falls within the range of [redacted]; and the [redacted] falls within the range of [redacted]. […] Given the structural similarities of all of the Sulfited FLL Substances (i.e., they are all triglyceride molecules that have been subjected to a sulfonation process), it is expected that substances manufactured from the same type of source oil will have similar physicochemical and toxicological properties, and that these properties are also likely to be similar even among different source oils."

You consider "Fat Liquors and Lubricants" as a class of substances, which share analogous ecotoxicological and toxicological characteristics and which are characterized by a comparable behaviour. More specifically, you have indicated that:

"Given that both the Sulfated Fat Liquors and the Sulfited Fat Liquors are triglyceride molecules from the same source oils that have been subjected to a sulfonation process, it is expected that substances manufactured from the same type of source oil will have similar physicochemical and toxicological properties, and that these properties are also likely to be similar even among different source oils. Testing has been conducted on subsets of both of the substances.

In general, there was good agreement in endpoint results among each of the substances tested, and between the Sulfated Fat Liquors and Sulfited Fat Liquors providing support for the read-across approach that is being applied for assessment of the Sulfated Fat Liquors group. Given the small percentage of the sulfated/sulfited moiety within the molecules in both groups, the soluble/salted oil is expected to exercise the main influence on the toxicological and ecotoxicological behaviour of these substances, as well as the degradation and environmental fate of these substances."

To support your read-across from sulfited to sulfated derivatives on the same back-bone, you have referred to information from the [redacted]

You have concluded your read-across justification by claiming that:

> *"For the three toxicological areas has been demonstrated that the existing data on sulfited derivatives are a conservative surrogate for the sulfated derivatives, therefore Read Across is justified.*
> *The substance don't present toxicological alerts and the existing tests show no effect at the highest tested dose, therefore no further testing is proposed for the substance."*

ECHA considers this as forming the hypothesis under which you make predictions for the properties listed above.

The studies made with the source substances of the read-across are specified in chapters below per each information requirement and endpoint.

0.2 Support of the grouping and read-across approach

You have provided a read-across justification as a separate attachment in your updated registration dossier. In summary you provide the following arguments to support the read-across approach:

Support for the grouping:

Concerning the structural comparison, you have claimed that both the Sulfated Fat Liquors and the Sulfited Fat Liquors are triglyceride molecules from the same source oils that have been subjected to a sulfonation process. While you provided information in your comments demonstrating the similarities between source and target substances, it remains still to be demonstrated, why the structural difference, *i.e.* the oxidation state of sulphur, does not have a significant impact on the prediction for the toxicological properties in question.

You have provided the following information on the toxicokinetics on certain moieties of the target and source substances of the read-across:

"It can be expected that the absorption of sulfated fat liquor will be very high, due to their low solubility, high log Kow, and due to their similarity with the fatty oil derivatives, which are basic components of human nutrition system.

Commonly used as preservatives, sulfites are continuously formed in the body during the metabolism of sulfur-containing amino acids. Sulfite moiety is rapidly oxidized to sulfate ion by sulfite oxidase in the liver. Four rats, which received oral doses of sodium metabisulfate as a 0.2% solution eliminated 55% of the sulfur as sulfate in the urine within the first four hours (Bhagat, 1960). A rapid and quantified elimination of sulfites as sulfate was also observed in man and dog (Rost, 1933).
As a consequence the systemic toxicity of sulphated can be extrapolated from sulfited analogous.
For linear alkyl sulfates, which contain 6 or more carbons the process starts with enzymatic hydrolysis of the ester bond, producing the corresponding alcohol and inorganic sulfate salt. The alcohol is enzymatically oxidised to aldehyde and carboxylic acid, which is further metabolized by beta-oxidation (Gilbert, 1984) As a consequence the toxicological profile of sulfated castor oil can be also described with the profile of the corresponding castor oil."

However, no evidence has been provided to demonstrate the similarity of the metabolism of source and target substance, i.e. to demonstrate that the sulphur containing group in the sulphited analogue is hydrolysed alike the sulphate ester of the target.

Specific elements concerning Human health

You have provided a data matrix, which addresses the following human health endpoints: skin and eye irritation/corrosion, skin sensitisation, acute toxicity, genotoxicity, sub-acute toxicity, and the reproductive toxicity screening studies (OECD 422). Concerning the sub-acute toxicity and the reproductive toxicity screening studies, information is provided for the source substances of the read-across, i.e. sulfited rape oil and sulfited fish oil, but no data is provided for the registered substance or for sulfited castor oil.

You have further provided the following study summaries, all performed with analogue substances belonging to the sub-category of "Sulfited Fat Liquors":

- Repeated dose toxicity, oral
  - Two Combined repeat dose toxicity study with reproduction/developmental toxicity screening test in the rat (OECD TG 422), GLP, [redacted] 2010 (study report), performed with Rape oil, bisulfited, sodium salt, CAS No 84082-27-9; Oils, fish, oxidized, bisulfited, sodium salts, CAS No 97488-98-7; NOAELs 1000 mg/kg bw/d

0.3 ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

ECHA understands that the read-across approach for repeated dose toxicity and reproductive toxicity is based on structural similarity, on similar physico-chemical properties and on similarities in acute toxicity, in skin and eye irritaion/corrosion and in genotoxicity for which information on source and target substances have been compared in the read-across justification document. Furthermore, you have provided limited information on the toxicokinetics; more notably that the sulfited moieties in general will produce sulfate moieties.

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

(i) Substance characterisation of source and target substances

ECHA notes that the target substance is a UVCB substance consisting of [redacted]. The ranges of these constituents are relatively narrow. In your dossier update recorded on 7 September 2017, you have provided information on the starting materials and on the composition of the registered substances and of the sources substances of the read-across.

In your comments and in your dossier update, you submitted substantial new information regarding the composition of the source substances. ECHA notes that this information is relevant to address the notion of structural similarity. The remaining issue of the structural similarity concerns potentially different toxicokinetics and toxicity that sulfated versus sulfited glycerides may show; this part of the read-across assessment is addressed below in more detail.

(ii) Structural similarity and dissimilarity

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You refer to the class of "Fat Liquors and Lubricants" with two sub-categories, namely "Sulfated Fat Liquors" to which the registered substance belongs and "Sulfited Fat Liquors". ECHA acknowledges that the substances within each sub-category seem to be closely related.

More specifically, for human health endpoints addressed in this decision, you provided study summaries for tests performed with Rape oil, bisulfited, sodium salt (CAS No 84082-27-9); Oils, fish, oxidized, bisulfited, sodium salts (CAS No 97488-98-7) and Rape oil, sulphonated, sodium salt (CAS No 93348-42-6).

ECHA acknowledges the possibility that the differences of type of fatty acids used in the manufacturing process might not lead to relevant toxicological differences between the registered substance (castor oil) and the source substances (rape oil and fish oil).

However, concerning the sulfate group in the registered substance and the sulfite groups in the analogue substance, there are structural differences that could potentially lead to differences in toxicokinetics and toxicity. As you indicated in you justification document, metabolism of alkyl sulfates and alkane sulfonates share some similarities, but also are partly different. Hence, differences in metabolism can also be expected for fatty acids sulfated and sulfited. Furthermore, the type of linkage to the fatty acid chain might impact the stability of the substance e.g. in gastrointestinal fluids.

These differences may lead to different dissociation pattern, to different absorption and metabolism, and/or to differences in toxicodynamics. These dissimilarities have not been addressed in your read-across justification.

Furthermore, a comparison which would cover the other constituents of the target and sources substances has not been provided. As an example, the fatty acid concentrations vary between the target and the sources substances of the read-across. Castor oil, which is the raw material of the registered substance, contains [redacted], and the fish oil contains only about [redacted]; the rest of fish oil consists of [redacted]. You have not explained how the constituents "other than triglyceride" and the differences in their composition could affect the outcomes in terms of predicting toxicological properties for the source substance in comparison to the target substance.

Therefore, ECHA concludes that you have not sufficiently addressed the structural and chemical differences between the source and target substances and did not explain, why those differences would not lead to differences in the toxicity profile of target and source substances and thus affect the possibility to predict the properties of the target substance from the data of the source substance.

(iii) Support of a similar or regular pattern as a result of structural similarity

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

Concerning repeated dose toxicity you provided study summaries for two combined repeated dose toxicity study with reproduction/developmental toxicity screening test (OECD TG 422) performed with two substances from the sub-category "Sulfited Fat Liquors" (i.e. Rape oil, bisulfited, sodium salts (CAS no 84082-27-9) and Oils, fish, oxidized, bisulfited, sodium salts (CAS no 97488-98-7) resulting in NOAELs of 1000 mg/kg bw/d. However, ECHA notes that you did not provide information that would be compliant with the endpoint sub-chronic toxicity (90-days; REACH Annex IX, Section 8.6.2.). Furthermore, ECHA notes that in your data matrix you refer to information on "sulphated alkyl chain" (EC 273-258-7) with a NOAEL of 430 mg/kg bw/d in a sub-chronic toxicity study (90-days) and with a NOAEL of 250 mg/kg bw/d in a developmental toxicity study with rats. Therefore, ECHA considers that there is obviously a concern for effects due to the *sulfatation* and read-across from substances of the sub-category "Sulfited Fat Liquors" to substances of the sub-category "Sulfated Fat Liquors" does not seem to be a "worst case approach" and cannot be used to predict the property of the registered substance.

Furthermore, you have provided no mechanistic explanation in order to link structure of these substances to prediction of the relevant toxic properties.

ECHA concludes that while similarity is observed on relevant physico chemical data, acute toxicity, skin and eye irritation/corrosion, the presented evidence of toxicological information on repeated dose toxicity is insufficient and does not allow an assessment of whether these toxic properties of the target substance can be predicted from the source substance. Furthermore, there are indications that the sulfated substances may lead to higher toxicity than the sulfited substances. Therefore, the information from the proposed analogue substances cannot be used to predict properties of the registered substance.

(iv)Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

ECHA notes the following observations:

While the general information provided by you is considered relevant, ECHA notes that it does not sufficiently cover the relevant aspects of toxicokinetics, since you have not provided toxicokinetic information, which is specific to the target substance and sources substances of the read-across.

More specifically, you have explained that "*Sulfite moiety is rapidly oxidized to sulfate ion by sulfite oxidase in the liver. Four rats, which received oral doses of sodium metabisulfate as a 0.2% solution eliminated 55% of the sulfur as sulfate in the urine within the first four hours (Bhagat, 1960). A rapid and quantified elimination of sulfites as sulfate was also observed in man and dog (Rost, 1933). As a consequence the systemic toxicity of sulphated can be extrapolated from sulfited analogous.*" While ECHA considered this information indicative of potential toxicological similarity, you have not proved by experimental data that the sulfite and sulfate moieties **of the source and target substances** follow the same toxicokinetic path as suggested above. Furthermore it is ECHAs view this argumentation would only support the read-across if the metabolism is rapid and complete. ECHA also notes that the toxicokinetic properties of the other constituents have not been addressed.

In conclusion, ECHA observes that in the technical dossier you have provided only a general toxicokinetic assessment of the registered substance. However, you have not provided experimental data or information which is specific to the target substance and source substances of the read-across. Consequently, it is not possible to conclude whether there are differences in the toxicokinetic behaviour, in particular in metabolic fate and (bio)transformation of the substances and how these differences may influence the toxicity profile of the target and source substances. ECHA considers that based on the lack of comprehensive toxicokinetic data, there is not an adequate basis for predicting the toxic properties specified above from the data of the source substances.

0.4 Conclusion on the read-across approach

ECHA considers that structural similarity alone is not sufficient for predicting toxicological properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. ECHA notes that in view of the issues listed above it has not been demonstrated that the source and read-across substances have the same properties or follow a similar pattern with regard to studies on sub-chronic repeated dose toxicity and reproductive toxicity. ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints Sub-chronic toxicity study (Annex IX, Section 8.6.2.) in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects those adaptations in the technical dossier that are based on Annex XI, 1.5.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100-1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). The study was performed in 2010, was indicated by you as reliability 1, and was made with a read-across substance rape oil sulfited. The NOAEL observed in that study was 1000 mg/kg bw/d, and no effect were reported at that level. You also provided a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with another read-across substances fish oil sulfited. The study was performed in 2010, and was indicated by you as reliability 1. The NOAEL observed in that study was also 1000 mg/kg bw/d, and no effect seen at that level. However, none of these studies does provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records specified above with the analogue substances Rape oil, bisulfited, sodium salts (CAS no 84082-27-9) and Oils, fish, oxidized, bisulfited, sodium salts (CAS no 97488-98-7) . However, as explained above in the preceding paragraph and in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the available information does not indicate a specific concern for local effects in the respiratory tract that would require information derived by the inhalation route. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat. ECHA Secretariat acknowledges your comments submitted during the 30-day lead registrant's commenting period on the draft decision. In your comment, you agreed to perform the study that was required in the draft decision. ECHA Secretariat has not amended the draft decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

Note for your consideration

ECHA notes that a revised version of OECD TG 408 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.
Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm)

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100-1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In your comments to the draft decision, you have claimed that "the test may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report." However, in order to adapt an information requirement in accordance with Annex XI, section 3.1., also the conditions set out in in Annex XI, section 3.2 should be met, i.e., adequate justification and documentation shall be provided and the justification meets one of the criteria set out in sections 3.2 (a) to 3.2 (c) of Annex XI.

ECHA considers that no adequate justification has been provided to show that any one of these criteria has been met.

First, your adaptation does not satisfy the conditions for meeting the criterion set out in Annex XI, Section 3.2 (a). Indeed, you have not provided a DNEL that is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes (condition (ii) of section 3.2 (a)). A DNEL derived from a sub-chronic oral study with analogous substances does not provide information, which is "relevant and appropriate" with regard to the parameters and observations, which are included in a prenatal developmental toxicity study. More notably, a sub-chronic study does not allow identification of effects on foetuses and their development, since there is no reproductive cycle included in a sub-chronic study.

Second, your adaptation does not satisfy the conditions for meeting the criterion set out in Annex XI, Section 3.2 (b), as you have not demonstrated and documented that throughout the life cycle of the substance strictly controlled conditions apply.

Third, you have not documented that the conditions for meeting the criterion of Annex XI, Section 3.2 (c) have been met.

Finally, you have reported risk characterisation ratios up to [redacted], and therefore it cannot be considered that the exposure to the substances is "not significant" or "negligible".

Therefore, your adaptation of the information requirement is rejected.

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

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

ECHA Secretariat acknowledges your comments submitted during the 30-day lead registrant's commenting period on the draft decision.

In your comments you claimed that "the test may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report." The legal interpretation of ECHA is, however, that point Annex XI, 3.1. is not an independent adaptation possibility, but a prerequisite of the use of the adaptation possibility specified in Annex XI, 3.2.

Also you recalculated the DNEL and provided exposure information in order to show that exposures "are always well below the derived DNEL", which refers to point Annex XI, 3.2.(iii). However, that addresses only one of three criteria that need to be met under the adaptation of Annex XI, 3.2.

The second criterion requires that the DNEL, which is used, shall be "relevant and appropriate both for the information requirement to be omitted and for risk assessment purposes". When comparing the information available with the information required, ECHA Secretariat finds that the sub-chronic oral study with analogous substances does not provide information, which is relevant and appropriate in regard of the parameters and observations, which are included in a prenatal developmental toxicity study. Therefore, the criterion set out in Annex XI, 3.2. (ii) is not met and the adaptation possibility of Annex XI, 3.2 cannot be applied to this case.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Note for your consideration

ECHA notes that a revised version of OECD TG 414 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.
Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement. You provided the following justification for the adaptation: "*Because of the extremely low water solubility of the substances, conventional acute testing was not possible. A WAF approach was taken and no effects were observed at the highest loading (100 mg/L) tested, m ost likely because very little of the substance dissolved in the water. Long-term testing is not expected to be feasible and, overall, aquatic toxicity is expected to be low.*"

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 2.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 2. The OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3, provide advice on the best approach for performing aquatic toxicity testing of difficult substances to test, such as the registered substance.

Furthermore, ECHA notes that the ECHA Guidance on information requirements and chemical safety assessment (Version 4, June 2017), Chapter R7b,indicates that the need to conduct further testing according to column 2 of Annex IX, section 9.1., may be triggered e.g. when due to low water solubility of a substance, short term toxicity tests do not reveal any toxicity.

Therefore, your adaptation of the information requirement cannot be accepted.

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

In your comments to the draft decision, you have stated that "the test may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report." The legal interpretation of ECHA is, however, that Annex XI, 3.1. is not an independent adaptation

possibility, but a prerequisite of the use of the adaptation possibility specified in Annex XI, 3.2.

Also, you have recalculated the PNEC aquatic and provided updated exposure information in order to demonstrate that Annex XI, 3.2.(a) (i, ii and iii) is fulfilled.

However, the second criterium, Annex XI, 3.2.(a)(ii), requires that the PNEC shall be "relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes". Due to the physicochemical properties of the registered substance (low water solubility), in order to have a relevant and appropriate PNEC aquatic, information derived from long term tests on three trophic levels is required.

Therefore, the criterium set out in Annex XI, 3.2. (ii) is not met and the adaptation possibility of Annex XI, 3.2 cannot be applied to this case.

As explained below, the absence of toxicity observed in the short-term tests with the registered substance having a low water solubility can, therefore, not be used as an argument for adaptation of long-term tests.

Based on the information provided in your dossier, ECHA considers that the registeresd substance is poorly soluble (water solubility [redacted]). Poorly soluble substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for poorly soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short.

Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

ECHA considers that the available information in your chemical safety assessment does not rule out long-term effects to aquatic organisms and that further long-term effects on aquatic organisms need to be investigated. Consequently ECHA concludes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 and cannot be accepted.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement. You provided the following justification for the adaptation : "*Because of the extremely low water solubility of the substances, conventional acute testing was not possible. A WAF approach was taken and no effects were observed at the highest loading (100 mg/L) tested, most likely because very little of the substance dissolved in the water. Long-term testing is not expected to be feasible and, overall, aquatic toxicity is expected to be low.* "

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 2.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 2. The OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3, provide advice on the best approach for performing aquatic toxicity testing of difficult substances to test, such as the registered substance.

Furthermore, ECHA notes that the ECHA Guidance on information requirements and chemical safety assessment (Version 4, June 2017), Chapter R7b, indicates that the need to conduct further testing according to column 2 of Annex IX, section 9.1., may be triggered e.g. when due to low water solubility of a substance, short term toxicity tests do not reveal any toxicity.

Therefore, your adaptation of the information requirement cannot be accepted.

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

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth (see ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b, Figure R.7.8-4).

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA Guidance Chapter R7b, version 4.0, June 2017).

In your comments to the draft decision, you have stated that "the test may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report." The legal interpretation of ECHA is, however, that Annex XI, 3.1. is not an independent adaptation possibility, but a prerequisite of the use of the adaptation possibility specified in Annex XI, 3.2.

Also, you have recalculated the PNEC aquatic and provided updated exposure information in order to demonstrate that Annex XI, 3.2.(a) (i, ii and iii) is fulfilled.

The second criterium, Annex XI, 3.2.(a)(ii), requires that the PNEC shall be "relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes". Due to the physicochemical properties of the registered substance (low water solubility), in order to have a relevant and appropriate PNEC aquatic, information derived from long term tests on three trophic levels is required.

Therefore, the criterium set out in Annex XI, 3.2. (ii) is not met and the adaptation possibility of Annex XI, 3.2 cannot be applied to this case.
As explained below, the absence of toxicity observed in the short-term tests with the registered substance having a low water solubility can, therefore, not be used as an argument for adaptation of long-term tests.

Based on the information provided in your dossier, ECHA considers that the registered substance is poorly soluble (reported water solubility <0.6 mg/L)). Poorly soluble substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test.

For this reason, short-term tests may not give a true measure of toxicity for poorly soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

ECHA notes that for the derivation of the $PNEC_{aquatic}$ data on three trophic levels, on aquatic invertebrates, fish and aquatic plants, is required (ECHA Guidance on information requirements and chemical safety assessment, v.4.0, June 2017, Chapter R7b, Section R.7.8.5.3). As discussed below, the short-term data is not applicable in this case, long-term data on all three trophic levels is needed for the derivation of $PNEC_{aquatic}$ and to perform the chemical safety assessment.

Furthermore, ECHA notes that due to the low water solubility the short-term data cannot serve as a compelling evidence to predict relative differences (or lack of) in species sensitivity required to apply the aquatic ITS (*ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 3.0, February 2016), Section R.7.8.5.3.).

ECHA notes further that REACH requires the registrant to consider a long-term study when the substance is poorly water soluble (e.g. water solubility below 1 mg/L or below the detection limit of the analytical method of the test substance based on *ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 3.0, February 2016), Section R.7.8.5.). Therefore, in this case long-term data is required to accurately assess the effects of the low water solubility substance on aquatic organisms.

For the reasons stated above, the aquatic ITS (*ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 3.0, February 2016), Section R.7.8.5.3.) is not applicable and it is necessary to provide long-term data on both aquatic invertebrates and on fish.

ECHA considers that the available information in your chemical safety assessment does not rule out long-term effects to aquatic organisms and that further long-term effects on aquatic organisms need to be investigated. Consequently ECHA concludes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 and cannot be accepted.

A Member State Competent Authority (MSCA) submitted a Proposal for Amendment (PfA) for this endpoint. In the MSCA's PfA, it was pointed out that the substance could be highly insoluble in water and therefore, conducting additional long-term tests on a substance with extremely low water solubility is unlikely to add to the knowledge of the substance's aquatic hazards and risks. It was also noted that some parts of the Integrated testing strategy (ITS) could still apply for this kind of substance. Also, the MSCA's PfA considers that the registrant may have alternatives for conducting potentially unnecessary animal test.

The Registrant in their comments on the MSCA's PfA, expressed their support and agreement to the MSCA's PfA.

ECHA agrees that the substance could be highly insoluble in water, however, there is no underlying evidence in the current technical dossier what would indicate the actual water solubility value/range of the substance. Hence, based on the available data, it is currently assumed that the substance is poorly water soluble.

ECHA disagrees with the MSCA's PfA aspect on the applicability of the ITS for this kind of substance. However, to further clarify this aspect, ECHA has included a paragraph to the draft decision (See in the 'Notes for your consideration for request 3 and 4' below) on Guidance on ITS/ weight of evidence. Regarding alternatives to testing, ECHA highlights that acute studies do 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 as outlined in Step 6 of the Weight of evidence approach (Section R.7.8.5 of ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017 – Figure R7.8-2.). ECHA notes, it is the responsibility of the registrant to develop any adaptation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration for request 3 and 4

Before conducting the above test under request 4 you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapters R.4 (v.1.1, December 2011), R.5 (v.2.1, December 2011), R.6 (May 2008), R.7b (v 4.0, June 2017) and R.7c (v 3.0, June 2017). If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, you are referred to the advice provided in practical guides on "How to use alternatives to animal testing to fulfil your information requirements for REACH registration".

In particular, before conducting the above test you are adviced to consult Section R.7.8.5 of ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017) which outlines the Integrated testing strategy / Weight of evidence considerations which may be used to conclude aquatic pelagic toxicity.

Due to the physicochemical properties of the registered substance, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Once results of the long-term toxicity to fish test are available, you shall revise the chemical safety assessment and update the dossier as necessary according to Annex I of the REACH Regulation, *i.e.* addressing the repercussions for secondary poisoning and re-considering the need for bioaccummulation testing.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested an in vitro gene mutation in bacteria (Annex VII, Section 8.4.1.), In vitro cytogenicity study in mammalian cells (Annex VIII Section 8.4.2.), In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), Screening study for reproductive/developmental study (Annex VIII, Section 8.7.1.), Ready biodegradability (Annex VII, Section 9.2.1.1.), Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.), Growth inhibition test (Annex VII, Section 9.1.2.) and Activated sludge respiration inhibition test (Annex, VIII, Section 9.1.4). As these studies are not addressed in the present decision as consequence of information provided in your comments anymore, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

Appendix 2: Procedural history

ECHA notes that the tonnage band for one member of the joint submission is 100 to 1000 tonnes per year.

You were notified that the draft decision does not take into account any updates after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. However, following your comments on the draft decision and the related information provided in the updated dossier received on 7 September 2017, ECHA has taken into account all the updated information relevant to the draft decision reflecting the information provided in your comments to the initial draft decision.

The compliance check was initiated on 9 September 2016.

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

You updated your registration on 7 September 2017 (submission number UT403571-16). ECHA took the information in the updated registration into account. As a result, the following requests in the draft decision were removed: in vitro gene mutation study in bacteria, in vitro cytogenicity study in mammalian cells or in vitro micronucleus study, in vitro gene mutation study in mammalian cells, screening for reproductive/developmental toxicity, ready biodegradability, bioaccumulation in aquatic species, growth inhibition study aquatic plants, and activated sludge respiration inhibition testing.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.
ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-58 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.