ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114449846-34-01/F
Substance name: 2-ethylhexanoic acid, monoester with propane-1,2-diol
EC number: 285-503-5
CAS number: 85114-00-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/10/2017
Registered tonnage band: 100-1000

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. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: OECD TG 414) in a second species (mice), oral route with the registered substance;**

2. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: Daphnia sp. Acute immobilisation test, EU C.2./OECD TG 202) with the registered substance;**

3. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

4. **Robust study summary (RSS) for "[redacted]", Short-term toxicity testing on fish (Annex VIII, Section 9.1.3. in conjunction with Annex I, Section 3.1.5) OR Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203);**

5. **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;**

6. **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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***2 June 2020***. You also have to update the chemical safety report, where relevant.

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

Appeal

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

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[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

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

TOXICOLOGICAL INFORMATION

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

A "pre-natal developmental toxicity study" (test method 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. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a pre-natal developmental toxicity study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the first test and all other relevant and available data. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet these information requirements.

The technical dossier contains a pre-natal developmental toxicity study ([redacted] 2015) with rats by the oral route (according to OECD 414; GLP study; reliability score of 1). This study fulfils the standard information requirement for a pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.). Based on the results of this study, ECHA considers that the findings indicate a concern for developmental toxicity.

The study in a first species was conducted according to OECD TG 414 (GLP) with the registered substance, at doses of 0, 100, 300 and 1000 mg/kg bw/day (in corn oil). No mortality or remarkable clinical signs were observed in dams up to the highest dose tested. No effects were observed on the number of resorptions (either early, late or total), pre- and post-implantation loss. No dead foetuses were noted on termination at day 20 of gestation in either the control group or any of the treatment groups. No effect on pregnancy duration was noted and no early deliveries or still births were observed.

However ECHA noted that:

(i) Male, female and overall foetal weights were significantly lower for females dosed at 1000 mg/kg bw/day, when compared with controls (about 10% lower). This difference was considered to reflect an effect of treatment on foetal growth and not to be due to the slightly higher mean litter size in the 1000 mg/kg bw/day group.

(ii) Foetal developmental effects were observed at 1000 mg/kg bw/day and characterized by an increased incidence of various malformations (including *"large nasofrontal suture* [(107 foetuses in 20 litters)]*; thoracic vertebral abnormality; short supernumerary cervical rib and 14th rib; delayed/incomplete ossification/unossified cranial centres, cervical, thoracic and sacral caudal vertebrae, sternebrae, pelvic bones, metacarpals/metatarsals and a decrease in ossified cervical vertebral centra; variation in lens shape; small/absent lobe of thyroid; partially undescended lobe of thymus; small/absent renal papilla and dilated ureter"*). In addition, as mentioned in your technical dossier, the incidence of these malformations *"were outside of the Historical Control Data (HCD) with the exception of delayed and/or incomplete ossification and/or*

unossified cervical vertebrae".

Based on the substance evaluation report of 2-ethylhexanoic acid (EC number 205-743-6, 2017, submitting MSCA: Spain)[2], ECHA also notes that "*effects upon development observed in rats are the basis for the current classification of this substance as toxic for reproduction, category 2 for development (H361d: suspected of damaging the unborn child)*". ECHA points out that 2-ethylhexanoic acid is found in the registered substance as a minor constituent (0-3%) and that it shares structural similarity with the main constituents of the registered substance (2-hydroxypropyl 2-ethylhexanoate and 1-hydroxypropan-2-yl 2-ethylhexanoate).

The aforementioned substance evaluation reports states that "*in two oral prenatal developmental toxicity studies in Fischer 344 rats and New Zealand white rabbits, conducted in accordance with GLP and EPA Guidelines, the developmental toxicity of 2-EHA was evaluated*". In rats, "*there was a growth retardation related to a reduction in ossification of the axial and appendicular skeletons at 500 mg/kg bw/d. An increase in the number of foetuses with unossified anterior arch of the atlas and proximal phalanges of the forelimb and hindlimb was also observed at 250 mg/kg bw/d. [...] only the variation concerning extra 14th thoracic centrum and arches at the high dose was statistically significant.* On the contrary, in rabbit no findings related to embryotoxic, foetotoxic or teratogenic effects were observed up to the highest dose tested (250 mg/kg bw/day). In another non-GLP study, equivalent or similar to OECD 414, on Wistar rats "*results showed that 2-EHA affected normal development of foetuses at all dose levels. Dose-dependent increases in the number of foetuses with skeletal or visceral anomalies were observed at all dose levels, compared to controls*". The reports also specifies that in a recent EOGRTS (2016) "*performed in Wistar rats dosed at* [up to] *800 mg/kg bw/d, 2-EHA did not show any treatment-related effects regarding developmental effects or developmental neurotoxicity and immunotoxicity in the corresponding cohorts*". The aforementioned data from reproductive and developmental studies were considered as sufficent to indicate that 2-ethylhexanoic acid is harmful to the embryos and/or foetuses at dose levels that do not trigger maternal toxicity.

ECHA also note that 2-ethylhexyl 2-ethylhexanoate (EC number 231-057-1), a substance structurally similar to the registered substance, is also subject to harmonised classification[3] as toxic for reproduction, category 2 (H361d: suspected of damaging the unborn child).

ECHA considers that the combined evidence from (i) the results of the prenatal developmental toxicity study conducted on the registered substance and (ii) the data available on the structurally similar substances 2-ethylhexanoic acid and 2-ethylhexyl 2-ethylhexanoate, raises sufficient concern to trigger a prenatal developmental toxicity study in a second species.

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.

The test in the first species was carried out with rats. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit is the preferred non-rodent species. Based on the assumption that, due to structural similarity between the registered

[2] https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e3672
[3] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/4461

substance and 2-ethylhexanoic acid (EC number 205-743-6), these substances may share a similar mode of action and that no effect were seen in the pre-natal developmental toxicity study in rabbit, ECHA considers that the test should be performed with mice as a second 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) Chapter R.7a, Section 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.

In your comments on the draft decision you agreed to perform the requested study.

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: OECD TG 414) in a second species (mice) by the oral route.

ECOTOXICOLOGICAL INFORMATION

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- Short-term toxicity testing on invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

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 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for an ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[4]. This hypothesis explains why the differences in the chemical structures should not influence the ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability

[4] ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[5]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance 2-ethylhexanoic acid, monoester with propane-1,2-diol (EC number 285-503-5) (hereafter the 'target substance' or the 'registered substance') using data of structurally similar substance 2-hydroxypropyl 7,7-dimethyloctanoate (EC number 276-138-2) (hereafter the 'source substance').

You have provided a read-across documentation as a separate attachment in section 13.2 of the IUCLID dossier and as an attached justification under the endpoints covered by the read-across hypothesis.

You use the following arguments to support the prediction of properties of the registered substance from data for the selected source substance:

- You based your justification of the validity of the read-across hypothesis on the structural similarities and structural differences between the source and target substance. In your justification document, you state that both substances are "*fatty acid esters of propan-1,2-diol which determines similar properties with regard to toxicity endpoints*". You specified that in the case of the target substance, the fatty acid carbon chain is 2-ethylhexyl (branched C8), while for the source substance it is 7,7-dimethyloctyl (branched C10). You further note that the target substance is a multi-constituent substance consisting predominantly of two ester isomers and that, as the source substance is produced through a similar manufacturing process (i.e. [redacted]), you hypothesised that it may also contains a mixture of two isomers.
- You compared the water solubility (WS) of the source substance (WS = 33 mg/L) and the target substance (WS = 1790 mg/L). Based on QSAR predictions, you suggested that the observed difference may not be entirely explained by the structural differences in the fatty acid chain. You further hypothesised that the source substance may include a higher relative amount of a di-ester impurity and that overall the log Kow of the source substance could be higher than that of the target substance. You concluded that these properties will lead to a greater toxicity of the source substance compared to that of the target substance.

[5] ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

- You summarised available data on the toxicity of the source and target substances towards aquatic organisms in a data matrix. While you note that no reliable bridging study is available, you consider that the studies included in your registration dossier are generally supportive of the fact that both substances have similar ecotoxicological properties.

As an integral part of this prediction, you propose that the source should have similar or greater toxicity compared to the registered substance and that it may be considered as a worst-case to predict the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and ecotoxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical and ecotoxicological does not necessarily lead to predictable or similar environmental properties in other endpoints. Your justification based on structural similarity, similar physico-chemical and ecotoxicological properties has not established why the prediction is reliable for the environmental end-points for which the read across is proposed.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

More specifically, ECHA notes the following:

- Your read-across justification is based on the structural similarity of the main constituents of the source and target substances. However, toxicity may actually be determined by an impurity. Although a read-across hypothesis may seem convincing, it is necessary to provide adequate data to justify that the impurity profiles of the source and target substance allow the claimed predictions. ECHA notes that you did not provide an adequate description of the composition of the source substance and that no information were provided on its impurity profile. You stated that "*although impurities were also not reported for these ecotoxicity studies, impurities probably have a negligible or no impact on the ecotoxicity of the test substances*". ECHA does not consider this statement as an adequate justification that differences in the impurity profiles of the source and target substances do not impact the prediction of the selected environmental properties.
- You consider that the lower solubility of the source substance is likely associated to a greater log Kow and to a greater toxicity towards aquatic organisms. However, you did not provide any evidence to support that the source substance has a greater log Kow nor that it is sufficient to predict greater toxicity.
- You acknowledged that the source and target substance displays structural differences regarding the fatty acid carbon chain. Furthermore, you specified that the two main constituents of the target substance are structural isomers and hypothesised that, as it

is produced through a similar manufacturing process, the source substance should be similar in that regard. However, you did not justify to what extent structural variations among isomers, and more generally among the source and target substance, may impact the prediction.

- You did not provide any bridging study to support that the magnitude of the effect induced by the source and target substances on aquatic organisms is similar or that the source substance may be reliably considered as a worst-case. You consider that the effect value obtained in an acute fish toxicity test with the target substance is similar to the effect values obtained with the source substances when tested on aquatic invertebrates and algae. However, ECHA does not consider this observation as a reliable indication that the ecotoxicological properties of the selected substances are similar. In addition, as specified below in sections 2-4, ECHA has noted a number of shortcomings with the selected studies.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the environmental effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are also specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5., and these are set out under the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for an ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of environmental properties.

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

"Short-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record ([redacted] 2004) entitled [redacted] (according to ESA SOP 101; not GLP; reliability score of 2) with the analogue substance 2-hydroxypropyl 7,7-dimethyloctanoate (EC number 276-138-2).

However, as explained above in Appendix 1, section 'Ecotoxicological information' of this decision, your adaptation of the information requirement cannot be accepted. In addition to the lack of appropriate justification on why the ecotoxicological properties of the target substance may be predicted by the properties of the source substance, ECHA notes that there are significant deficiencies with the selected read-across study.

ECHA notes that no analytical monitoring was included in the study and accordingly the exposure levels are uncertain. In addition, pursuant to Article 10(a)(vii) of the REACH

Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. ECHA notes that, contrary to Article 3(28) of the REACH Regulation, the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the following elements are missing: the chemical identification of the test substance (including purity) and a detailed description of the test conditions (including for example the number of daphnids per test vessel and the number of replicates). Guidance on the preparation of the robust study summaries is provided in the Practical Guide on "How to report robust study summaries".

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* sp. acute immobilisation test (test method EU C.2. / OECD TG 202) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.1.

In your comments on the draft decision you agreed to perform the requested study.

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* sp. Acute immobilisation test, EU C.2./OECD TG 202).

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

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record ([redacted] 2004) entitled "[redacted]" (claimed similar to OECD 201; GLP status not specified; reliability score of 2) with the analogue substance 2-hydroxypropyl 7,7-dimethyloctanoate (EC number 276-138-2).

However, as explained above in Appendix 1, section 'Ecotoxicological information' of this decision, your adaptation of the information requirement cannot be accepted. In addition to the lack of appropriate justification on why the ecotoxicological properties of the target substance may be predicted by the properties of the source substances, ECHA notes that there are significant deficiencies with the selected read-across study.

ECHA notes that no analytical monitoring was included in the study and accordingly the exposure levels are uncertain. In addition, pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. ECHA notes that, contrary to Article 3(28) of the REACH Regulation,

as described in section 2 above, the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the following elements are missing: the chemical identification of the test substance (including purity) and a detailed description of the test conditions (including for example the test temperature, water quality parameters etc.). Guidance on the preparation of the robust study summaries is provided in the Practical Guide on "How to report robust study summaries".

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.

In your comments on the draft decision you agreed to perform the requested study.

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: Algae growth inhibition test, EU C.3./OECD TG 201).

4. Robust study summary (RSS) for "[redacted]", Short-term toxicity testing on fish (Annex VIII, Section 9.1.3. in conjunction with Annex I, Section 3.1.5) OR Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Pursuant to Articles 10(a)(vii) of the REACH Regulation, the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I. Article 3(28) of the REACH Regulation defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the ECHA Practical Guide 3: 'How to report robust study summaries'.

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. 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. Furthermore, pursuant to Article 10(a)(vii) and Annex I, Section 3.1.5. where there is more than one study addressing the same effect, then the study or studies giving rise to the highest concern shall be used to draw a conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust study summaries will be required of all key data used in the hazard assessment.

In the technical dossier you have provided the following study record to fulfil the standard information requirement of Annex VIII, Section 9.1.3.: Key study, reliability 2, "[redacted]", GLP compliance: no, test method: according to OECD Guideline 203 (Fish, Acute Toxicity Test) with the registered substance.

ECHA notes that you have not provided sufficient information in the technical dossier to allow assessing the reliability of the study. In particular you did not specify if an analytical monitoring of exposure concentrations was conducted and you did not report any analytical monitoring data. Therefore, it is not possible to verify if the validity criteria (*i.e.*, the

concentration of the substance being tested has been satisfactorily maintained throughout the test) described in OECD TG 203 have been fulfilled.

In your comments on the draft decision you sought to address the concern raised by ECHA on the lack of analytical data reported in the above mentioned study. You referred to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) which specifies that studies lacking measured test substance concentrations data may still be acceptable if the physical-chemical properties suggest a low potential for biodegradation, volatilisation and sorption. To support your hypothesis that the test concentrations were adequate, you provided the following arguments:

1. The test substance is soluble in water (1.79 g/l at 20°C);
2. The test substance has low log Kow (2.98) and losses due to adsorption are expected to be low;
3. The vapour pressure of the registered substance is 1.2 Pa at 25°C and losses due to volatilization are expected to be low;
4. Based on data from other experiments, the substance is expected to be stable under the test conditions (i.e. the 24-hour period between media renewal): (i) the registered substance was found to be stable up to one day at 10 and 200 g/L in corn oil in a study conducted according to OECD TG 422 ([redacted] 2015), (ii) a single sharp peak was observed in the HPLC analysis performed in the reported partition coefficient study ([redacted] 2012), (iii) you state that a similar substance (2-hydroxypropyl neodecanoate, EC number 276-138-2) was found to be hydrolytically stable (Half-life > 1 year) in a study conducted according to OECD 111, (iv) the test substance is considered to be stable at room temperature and (v) the test was conducted under a semi-static regime and the daily renewal of the test solution is expected to mitigate losses due to biodegradation.

Based on the above, you conclude that the substance was stable under the experimental conditions of the acute fish toxicity test. Finally, you state that the reported 96h-LC50 (*i.e.* > 10 mg/L) is similar to the predicted values generated using the US EPA ECOSAR software (v 1.1.) using the SMILES formula of the registered substance. You also consider that the results of the analytical monitoring that will be conducted in the requested short-term toxicity testing on invertebrates and growth inhibition study on aquatic plants should further support the reliability of the acute fish study.

Based on your comments on the draft decision, ECHA understands that the above mentioned study did not include a measurement of test concentrations.
Furthermore, ECHA disagrees that the reported arguments are sufficiently convincing to demonstrate that exposure concentrations were adequately maintained in the acute toxicity study on fish. For instance, on the impact of sorption of the registered substance ECHA notes that the reported log Kow value (i.e. 2.98) is close to the cutoff value of log Kow = 3 for adsorption potential as specified in ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), section R.7.1.15.4. In addition, it is specified that "*caution should be exercised in using this criterion, as substances that are water soluble and have a low octanol-water partition coefficient do not necessarily always have a low adsorption potential*" and that "*measured values will normally be needed for surface active substances (e.g. surfactants), because Kow values (predicted or measured) are likely to be poor predictors of adsorption for these types of substance*".
ECHA notes that in your technical dossier you report that the surface tension of a solution of the registered at 1 g/L is 41.5 mN/m (GLP compliant study according to OECD TG 105).

Accordingly, the registered substance should be considered as surface active and ECHA concludes that you did not convincingly demonstrate that the registered substance has low adsorption potential. The fact that the registered substance was stable in the test sample used in the OECD TG 422 study (i.e. at 10 and 200 g/L in corn oil) or in the OECD TG 117 study (i.e. at 1.19 g/L in methanol) does not demonstrate that the registered substance is stable at lower concentrations in the test water. Similarly, the fact that the registered substance, as a pure liquid, is stable at room temperature does not provide significant additional support. You also claim that a similar substance (2-hydroxypropyl neodecanoate, EC number 276-138-2) is hydrolytically stable. However, you did not demonstrate that differences in the chemical structure of the target and source substances would have no impact on the prediction and you did not provide a robust study summary of the cited study. Finally, while you claim that the reported effect value is similar to 96h-LC50 values predicted by ECOSAR, you did not provide any documentation to allow ECHA to evaluate the reliability of the prediction.

ECHA concludes that based on available information there is still a concern that nominal exposure levels did not appropriately reflect real exposure of test animals in the acute toxicity study on fish. However, ECHA agrees that the results of the experimental monitoring that will be conducted in the short-term toxicity testing on invertebrates and growth inhibition study on aquatic plants may provide valuable information to evaluate the stability of the registered substance in aqueous media.

Hence, 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.

In order to allow an independent assessment of the study submitted, pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to provide a complete robust study summary with a valid argumentation that, despite the lack of analytical monitoring, nominal exposure concentrations may be considered as adequate to characterize true exposure of test animals in this semi-static study.

Alternatively, if you cannot appropriately demonstrate the reliability of this study as per the criteria indicated above and/or not adequate to fulfil the information requirement, 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, acute toxicity test (test method: EU C.1./OECD TG 203).

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

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement 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 not provided any study record of a long-term toxicity on aquatic invertebrates in the dossier that would meet the information requirement of Annex IX, Section 9.1.5.

Instead, you have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2.

The justification of the adaptation given by you is: "*Under Column 2 of the Annex IX of Regulation (EC) No 1907/2006 the specific rules for adaptation from Column 1 are that the long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on invertebrates. It is proposed that testing is waived based on unlikely exposure potential and low toxicity of test substance. Testing is waived as potential for exposure is low as the substance is readily biodegradable. In the environment, ready biodegradability means it can be assumed that FX511 will be biodegraded within the STP process and as a consequence a transfer to the aquatic compartment via STP effluent is not expected. Furthermore, for substances not passing the STP-process but being readily biodegradable, it can be assumed that they will be also biologically degraded in the surface water within a short time. Additionally, the partition coefficient of FX511 was determined in a reliable study (Walker 2012) where the measured log Kow is 2.98. Therefore, FX511 is considered to have low potential for bioaccumulation. The key short-term fish study by Krassoi (2004) reported in this assessment provides evidence of the low toxicity to invertebrates of the analogue, FX510, with a 48 hr EC50 13.1 mg/L. Therefore, unlikely long-term exposure to aquatic organisms and no adverse long-term effects to invertebrates are expected. Therefore, no further testing is needed.*"

ECHA understands that you consider that long-term toxicity testing towards aquatic invertebrates is not required as the substance is readily biodegradable, it does not fulfil the bioaccumulation criteria and the data on the acute toxicity to invertebrates of the analogue substance 2-hydroxypropyl 7,7-dimethyloctanoate (EC number 276-138-2) suggest that the registered substance has low toxicity towards aquatic invertebrates.

As explained in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R.7b, Section R.7.8.5.3, in order to adapt the information requirement according to Annex IX, Section 9.1.5., column 2, the chemical safety assessment should demonstrate that the risks posed by the registered substance to the environment are adequately controlled. As described above, ECHA notes that your technical dossier does not contain any reliable data allowing to characterize the acute toxicity of the registered substance towards aquatic organisms. Accordingly no valid PNECs can be derived. In addition, in order to be considered as a valid adaptation, the chemical assessment should demonstrate that the exposure of the environment does not lead to unacceptable risks. In this context, an exposure assessment and risk characterisation, as described in Annex I, section 5-6 of the REACH Regulation, may be conducted to support this claim.

You may consider re-evaluating the adequacy of such adaptation once valid short-term toxicity data are included in your registration dossier. However, considering information gaps in your registration dossier, the proposed adaptation according to Annex IX, Section 9.1.5., column 2 does not currently meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Therefore, as explained above, the proposed adaptation according to Annex IX, Section 9.1.5., column 2 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 on the draft decision, you specify that you will re-evaluate the need to conduct a long-term toxicity study on aquatic invertebrates once reliable information on the short-term toxicity of the registered substance to aquatic organisms will be available. You propose to assess the possibility to waive the information requirement for this endpoint according to Annex IX, Section 9.1.5, column 2 by re-evaluating the "*environmental risk assessment*". You state that "*this will include information on the potential exposure for aquatic organisms, such as ready biodegradability and a low potential for bioaccumulation*".

ECHA points out that ready biodegradability and bioaccumulation data are not sufficient arguments to demonstrate low exposure of aquatic organisms. Such an adaptation should be based on a robust exposure assessment. You are advised to refer to Annex I, section 5 of the REACH Regulation and to the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016) for further details on how to conduct and report a reliable environmental exposure assessment.

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).

Notes for your consideration

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4) if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

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

"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 not provided any study record of a long-term toxicity on fish in the dossier that would meet the information requirement of Annex IX, Section 9.1.6.1.

Instead, you have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2.

The justification of the adaptation given by you is: "*Under Column 2 of the Annex IX of Regulation (EC) No 1907/2006 the specific rules for adaptation from Column 1 are that the long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on fish. It is proposed that testing is waived based on unlikely exposure potential and low toxicity of test substance. Testing is waived as potential for exposure is low as the substance is readily biodegradable. In the environment, ready biodegradability means it can be assumed that FX511 will be biodegraded within the STP process and as a consequence a transfer to the aquatic compartment via STP effluent is not expected. Furthermore, for substances not passing the STP-process but being readily biodegradable, it can be assumed that they will be also biologically degraded in the surface water within a short time. Additionally, the partition coefficient of FX511 was determined in a reliable study (Walker 2012) where the measured log Kow is 2.98. Therefore, FX511 is considered to have low potential for bioaccumulation. The key short-term fish study by Fougler et al (1995) reported in this assessment provides evidence of the low toxicity to fish with a 96 hr LC50 >10 mg/L. Therefore, unlikely long-term exposure to aquatic organisms and no adverse long-term effects to fish are expected. Therefore, no further testing is needed.*"

ECHA understands that you consider that long-term toxicity towards fish is not required as the substance is readily biodegradable, it does not fulfil the bioaccumulation criteria and the data acute toxicity to fish of the registered substance suggest that it has low toxicity to fish.

As explained in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R.7b, Section R.7.8.5.3, in order to adapt the information requirement according to Annex IX, Section 9.1.6., column 2, the chemical safety assessment should demonstrate that the risks posed by the registered substance to the environment are adequately controlled. As described above, ECHA notes that your technical dossier does not contain any reliable data allowing to characterize the acute toxicity of the registered substance towards aquatic organisms. Accordingly no valid PNECs can be derived. In addition, in order to be considered as a valid adaptation, the chemical assessment should demonstrate that the exposure of the environment does not lead to unacceptable risks. In this context, an exposure assessment and risk characterisation, as described in Annex I, section 5-6 of the REACH Regulation, may be conducted to support this claim.
You may consider re-evaluating the adequacy of such adaptation once valid short-term toxicity data are included in your registration dossier. However, considering information gaps in your registration dossier, the proposed adaptation according to Annex IX, Section 9.1.5., column 2 does not currently 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) can be performed 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 fertilized 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, Section R.7.8.4.1.*

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 on the draft decision, you specify that you will re-evaluate the need to conduct a long-term toxicity study on fish once reliable information on the short-term toxicity of the registered substance to aquatic organisms will be available. You propose to assess the possibility to waive the information requirement for this endpoint according to Annex IX, Section 9.1.6.1., column 2 by re-evaluating the "*environmental risk assessment*". You state that "*this will include information on the potential exposure for aquatic organisms, such as ready biodegradability and a low potential for bioaccumulation*".

ECHA points out that ready biodegradability and bioaccumulation data are not sufficient arguments to demonstrate low exposure of aquatic organisms. Such adaptation should be based on a robust exposure assessment. You should refer to Annex I, section 5 of the REACH Regulation and to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016) for further details on how to conduct and report a reliable environmental exposure assessment.

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

Before conducting any of the tests mentioned in sections 5-6 you shall consult the ECHA *Guidance on information requirements and chemical safety assessment (version 2.0, November 2014)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 17 January 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.