ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 9 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114375740-47-01/F
Substance name: PROPANE-1,2,3-TRIYL 2-ETHYLHEXANOATE
EC number: 230-896-0
CAS number: 7360-38-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 14/12/2016
Registered tonnage band: 10-100

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. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance;**

2. **Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.; test method: EU B.7./OECD 407) in rats, oral route with the registered substance;**

3. **Pre-natal developmental toxicity study (Annex VIII, Section 8.7.1., column 2; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

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

5. **Long-term toxicity testing on fish (Annex VIII, section 9.1.3., column 2; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.**

You have to submit the requested information in an updated registration dossier by **16 May 2019**. You also have to 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 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 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.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

ECOTOXICOLOGICAL AND TOXICOLOGICAL INFORMATION

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

Your registration dossier contains for the endpoints *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), Sub-acute toxicity study (28-day) (Annex VIII, Section 8.6.1.) and Growth inhibition study aquatic plants (algae preferred) (Annex VII, Section 9.1.2.) adaptation arguments in form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1, 2 and 4).

Grouping of substances and read-across approach

You have sought to adapt the information requirements for an *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), a Sub-acute toxicity study (28-day) (Annex VIII, Section 8.6.1.) and a Growth inhibition study aquatic plants (algae preferred) (Annex VII, Section 9.1.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be 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 shall establish why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and target substances[2]. This hypothesis must explain why the differences in the chemical structures are considered not to influence the toxicological and ecotoxicological properties or do so in a regular pattern. The read-across approach must be justified scientifically and documented accordingly. There may be several lines of supporting evidence used to justify the read-across hypothesis thereby 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 prediction 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 lead to products with altered properties, such as fate, bioavailability hazard, bioaccumulation and persistency. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments.

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

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[3]:

(1) (Bio)transformation to common compound(s) where 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) where the read-across hypothesis is that the organism is not exposed to common compounds but rather, as a result of structural similarity, that different compounds have similar (eco)toxicological and fate properties.

Finally, Annex XI, Section 1.5. lists requirements concerning the quality of the studies on the source substances, which are the basis for the read-across prediction. The key requirements are in short "adequacy for classification and risk assessment", "coverage of the key parameters", "equal or longer exposure duration" and "adequate documentation".

You consider to achieve compliance with the REACH information requirements for the registered substance propane-1,2,3-triyl 2-ethylhexanoate using data of the following structurally similar substances (hereafter the 'source substances'):

1. Octanoic acid, monoester with glycerol (EC No. 247-668-1)
2. Propane-1,2,3-triyl trisheptanoate (EC No. 210-647-2)
3. Glycerides, mixed decanoyl and octanoyl (EC No. 277-452-2)
4. Glycerol trioctanoate (Tricaprylin) (EC No. 208-686-5)
5. Short- and long-chain fatty acid triacylglycerols (Salatrim, 23CA)* (no CAS or EC No. available)

You have provided a read-across documentation as a separate attachment in section 13 of IUCLID.

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

"*Structural similarity*

(1) common functional groups/backbone: Both the target substance and the read-across substances are structurally similar. They are all glycerides with medium chain carboxylic acids. The triglycerides have a similar molecular weight range. The alcohol moiety glycerol is common to all analogue substances. The fatty acid moiety comprises carbon chain lengths from C7-C10 and includes saturated, methyl-branched and linear chains bound to the alcohol resulting in mono- and tri-esters, with the exception of Short- and long-chain fatty acid triacylglycerols, which includes fatty acids with chain lengths of C2/C18 and a small amount of unsaturated fatty acids.

[3] Please see 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).

(2) common precursors and the likelihood of common breakdown products via biological processes, which result in structurally similar chemicals: The target substance and its analogues result from esterification of the alcohol with the respective carboxylic acids. [...] Thus, the alcohol and carboxylic acid moieties are simultaneously precursors and breakdown products of these substances. Following hydrolysis, carboxylic acids are enzymatically degraded primarily via β-oxidation (medium chain length). Alternative oxidation pathways (alpha- and omega-oxidation) are available and are relevant for degradation of branched carboxylic acids. Long chain carboxylic acids/fatty acids may also be again incorporated into triglycerides. Glycerol is fully metabolized and incorporated in the standard metabolic pathways to form glucose and glycogen.

Similar physico-chemical properties

Propane-1,2,3-triyl 2-ethylhexanoate (CAS 7360-38-5) and the source substances used for assessment are liquid and non-volatile (vapour pressure: < 0.001 Pa at 20 °C) with a molecular weight range from 218 for monoester to 555 g/mol for triester of Glycerides, mixed decanoyl and octanoyl. The calculated with KOWWIN v1.68 octanol/water partition coefficient (log Kow > 7) and the water solubility (< 1 mg/L at 20 °C) are comparable within all analogue substances.

Similar environmental fate pathway and ecotoxicological profile

The available ecotoxicological information on the target substance and the source substances show that no systemic effects up to the limit of water solubility occurred in either acute or chronic studies to aquatic organisms representing the target substance. Moreover, the target substance and the source substances are readily biodegradable and show a similar pattern in environmental distribution and behaviour characterised by low water solubility and high log Kow.

Similar toxicological profile

No human health hazard was identified with the target and the source substances. None of the substances has acute toxic properties, neither through the oral, dermal, nor the inhalation route. They are not irritating to skin or eyes, and possess no sensitising potential. No data for long term toxicity is available for the target substance.

For Glycerides, mixed decanoyl and octanoyl, Glycerol trioctanoate and Salatrim no adverse effects were observed regarding repeated dose toxicity. No effect on fertility and developmental toxicity was observed with Salatrim."

As an integral part of this prediction, you propose that the source and registered substance(s) have "*similar properties*" for 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, ecotoxicological and toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. ECHA notes that structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and some of the physico-chemical, ecotoxicological or toxicological properties does not necessarily provide evidence for predictability of other properties.

More specifically, considering the structual differences of the target substance and the source substances (*"mono- and tri- esters of glycerol and heptanoic-, octanoic- and decanoic fatty acids"*), significant differences in the toxicity of the substances and their metabolites may be anticipated. More specifically, for 2-ethylhexanoic acid, a metabolite of the registered substance, there is existing evidence concerning "developmental toxicity" and hence the metabolite is suspected of damaging the unborn child and has consequently a harmonised classification for reproductive toxicity Category 2 (H361d), whereas all the source substances are metabolised to different metabolites which do not have such properties. Hence, the systemic toxicity profiles of the target and source substances do not seem to be similar and the properties of the registered substance may not be predicted from the data of the proposed source substances. ECHA also considers that your read-across approach underestimates the risk to the unborn child and the condition of Annex XI, Section 1.5. "adequacy for classification and risk assessment" is not met.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that you will consider further testing, exposure scenario and risk assessment refinement and end use registration in light of the results from *in vitro* dermal absorption and metabolism studies. You lay out that you seek to investigate further metabolite kinetics and state that *"the metabolite which has caused ECHA concern, 2-ethylhexanoic acid, is formed in the analogue substance following biological hydrolysis within the mammalian metabolic cascade."*

However, as explained above, your read-across documentation does not suggest that 2-ethylhexanoic acid would be formed as result of mammalian metabolic cascade from any of the above source substances. More specifically, none of the source substance structures contain ethyl hexanoate moiety raising concern on the target substance hazard properties. In addition, intact parent compound structures are different and prediction of the target toxic properties therefore not justified by the read-across supporting documentation.

You seek to investigate further the dermal absorption of the registered substance in an *in vitro* study or studies because of the end uses in skin care products. ECHA notes that dermal route is not the preferred route of administration for toxicological investigations, because dermal absorption is low, based on the physico-chemical properties of the target substance. ECHA also notes that with the context of the existing exposure scenarios in the dossier, exposure via skin and inhalation has to be taken account.

Therefore, ECHA considers that your grouping and read-across approach does not provide a reliable basis whereby the human health effects and environmental effects / environmental fate 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 the adaptation following read-across is specific for the individual endpoints. Therefore, the conclusions are set out below also specifically under the endpoint concerned.

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier contains studies showing negative results for both of the latter information requirements. Therefore, adequate information *on in vitro* gene mutation in mammalian cells 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 for an *In vitro* mammalian cell gene mutation test (OECD TG 476) with the analogue substance "Short- and long-chain fatty acid triacylglycerols (Salatrim, 23CA) (no EC No. available)". You state that "*Data on bacterial mutagenicity and mammalian cytogenicity are available for Propane-1,2,3-triyl 2-ethylhexanoate. For the assessment of mammalian mutagenicity data from the analogous substance SALATRIM (short- and long-chain acyl triglyceride molecules; no CAS available) were used.*"

However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected in general. In addition and specifically, ECHA considers that you have not explained how and why the outcome of the *in vitro* mammalian cell gene mutation test with the analogue substance can be used to predict the outcome of the same test for the registered substance. ECHA concludes that the presented evidence on *in vitro* gene mutation in mammalian cells is not sufficient to support a similar or regular pattern of toxicity as a result of structural similarity or metabolic behaviour of the target and source substances. Therefore, it cannot be verified that the proposed analogue substance can be used to predict properties of the registered substance.

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.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you propose to undertake study OECD TG 490.

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490).

ECHA
EUROPEAN CHEMICALS AGENCY

2. Short-term repeated dose toxicity (28 day), one species (Annex VIII, Section 8.6.1.)

A "short-term repeated dose toxicity study (28 days)" is a standard information requirement as laid down in Annex VIII, Section 8.6.1. 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 not provided any study record of a short-term repeated dose toxicity study (28 days) in the dossier that would meet the information requirement of Annex VIII, Section 8.6.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing non-guideline studies for two oral chronic studies and an oral sub-acute toxicity study with 104 weeks, 26 weeks and 31 day treatment duration, respectively, with the analogue substance tricaprylin (EC No. 208-686-5). You state that *"based on their structural similarity, their supposed similar toxicokinetic behavior and metabolic fate, and the absence of toxicity a read-across for repeated dose toxicity is supposed to be appropriate within Propane-1,2,3-triyl 2-ethylhexanoate and Glycerol trioctanoate, indicating that no toxicity after repeated exposure is assumed for Propane-1,2,3-triyl 2-ethylhexanoate."*

You provided comments on the draft decision according to Article 50(1) of the REACH Regulation, which have been discussed under Appendix 1, section 'Grouping of substances and read-across approach'.

As explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your read-across adaptation of the information requirement is rejected because due to the different toxicity prolifes of the metabolites, the properties of the registered substance may not be predicted from the data of the proposed source substances.

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.

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.7.5.4.3.2 - is the most appropriate route of administration. Even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the substance has very low vapour pressure (<0.0001 Pa) and the exposure concentrations reported in the chemical safety report for the inhalation route are relatively low (maximum 2.0 mg/m^3) considering the (currently assumed) toxicity and classification of the substance (not classified). Hence, the test shall be performed by the oral route.

According to the test method OECD TG 407 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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 28-day oral toxicity study (test method: OECD TG 407) in rats.

3. Pre-natal developmental toxicity study (Annex VIII, Section 8.7.1., column 2) in a first species

"Screening for reproductive/developmental toxicity" is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation "*if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant.*"

In the case of your substance, ECHA considers that such evidence of potential developmental toxicity is present in the dossier: You indicate that the registered substance is metabolised to 2-ethylhexanoic acid, which was demonstrated to have teratogenic potential (Ritter et al. 1987; Teratology 35: 41-46). Additionally, there is further information that is inconsistent with respect to the magnitude and type of the leading effect. In one experiment, teratogenicity was observed at maternal non-toxic doses of 100 mg/kg bw/d and above (Pennanen et al. 1992; Fundam Appl Toxicol 19: 505-511), whereas in another experiment, 2-ethylhexanoic acid was shown to lead to embryotoxicity and growth retardation but not to malformations only at already maternal toxic doses of 500 mg/kg bw/d and above (Hendrickx et al, 1993; Fundam Appl Toxicol 20:199-209). Consequently, 2-ethylhexanoic acid is "*suspected of damaging the unborn child*" and therefore classified (*Reproductive toxicity Class 2 (H261d)*).

Since the registered substance is metabolised to 2-ethylhexanoic acid, which is showing developmental toxicity, there is a serious concern about the potential for similar adverse effects of the parent substance subject to this decision. In such case, a pre-natal developmental toxicity study (Annex XI, Section 8.7.2) "*may be proposed by the registrant instead of the screening study*" as laid down in Annex VIII, Section 8.7.1., column 2, last indent. However, you did not submit a testing proposal for a pre-natal developmental toxicity study with the registered substance.

You have instead sought to adapt the information requirement for a pre-natal developmental toxicity study according to Annex XI, Section 3.2. governing 'no exposure/no significant exposure'. You provided the following justification for the adaptation:

"*As required under Regulation (EC) 1907/2006, Annex XI, Section 3.2 (a)(i), the exposure assessment, covering all relevant exposure throughout the life cycle of the substance, demonstrated the absence of or no significant exposure in all the manufacturing scenarios and identified uses as defined in Annex VI section 3.5 of Regulation (EC) 1907/2006.*

There are no repeated dose toxicity studies available for Propane-1,2,3-triyl 2-ethylhexanoate. However, the substance is anticipated to undergo enzymatic hydrolysis in the gastrointestinal tract and/or the liver resulting in the formation of glycerol and 2-ethylhexanoic acid (see Section Toxicokinetics, metabolism and distribution). A reproductive toxicity study is available, in which effects on the male reproductive system were observed in rats orally exposed to 2-ethylhexanoic acid, with the lowest LOEL for reproductive toxicity at 100 mg/kg bw/d (supporting study, 1993).
As required under Regulation (EC) 1907/2006, Annex XI, 3.2 (a)(ii) and in a worst-case assumption, DNELs were derived using this study, and applied to derive Risk Characterisation Ratios (RCRs).

As required under Regulation (EC) 1907/2006, Annex XI, 3.2 (a)(iii), the RCRs were < 1, showing that exposures are always well below the derived DNEL. The developed exposure scenarios demonstrating and documenting the fulfilment of the conditions mentioned above are provided in the Chemical Safety Report."

Your proposed adaptation relates to 86 exposure scenarios covering industrial, professional and consumer uses, which you have presented in your chemical safety report. Many of these exposure scenarios also contain contributing scenarios indicating a significant potential for exposure of humans to the substance.

You have used tier 1 exposure modelling tool, EasyTRA, to estimate exposures. ECHA notes that for a number of exposure scenarios the calculated RCRs are close to 1. More specifically and for example, exposure scenario 31, professional use in open system, application of lubricant, dipping, brushing or spraying, contributing scenario 8, you have estimated a long term inhalation exposure of [redacted] mg/m^3. When comparing this to the respective DNEL of [redacted] mg/m^3, this yields an RCR of [redacted]. Another example is that in exposure scenario 83 (PROC 9), industrial formulation of lubricant additives, lubricants and greases, you have estimated a combined RCR for both dermal and inhalation exposure of [redacted]. Especially when taking into account the uncertainties of exposure modelling, this level of exposure and RCR cannot be considered as insignificant.
In order to demonstrate that the requirement of "*absence or no significant exposure*" is fulfilled, evidence demonstrating the absence or no significant exposure is required in the dossier for each of the exposure scenarios. You are expected to provide measured data and/or use higher tier exposure modelling tools to strengthen your basis to demonstrate that exposures are absent, or insignificant when compared with the respective DNEL.

ECHA concludes that your adaptation does not meet the conditions for substance-tailored exposure-driven testing set by Annex XI, Section 3.2.(a)(i) and (ii). This is the case because:

(a) You did not specifically justify that "*the results of the exposure assessment covering all relevant exposures throughout the life-cycle of the substance demonstrate absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI, Section 3.5*"; and
(b) The derived DNEL is not based on the property "pre-natal developmental toxicity" and thus not relevant for the endpoint in question.

Thus it cannot be assumed that exposure is always well below a no-effect level for developmental toxicity and "*absence of or no significant exposure*" with respect to developmental toxicity cannot be confirmed therefore.

You provided comments on the draft decision according to Article 50(1) of the REACH Regulation which have been discussed under Appendix 1, section 'Grouping of substances and read-across approach'.

ECHA notes further that you provided a one-generation reproductive toxicity study performed with the metabolite 2-ethylhexanoic acid. This could be interpreted as an adaptation following the weight-of-evidence approach. However, this study does not cover the key parameters of a pre-natal developmental toxicity study according to OECD TG 414. More specifically, the provided study does not give information on skeletal and visceral anomalies of the developing fetuses. Therefore information of the study cannot be used for addressing this endpoint.

Because of the deficiencies highlighted above, ECHA considers that the adaptation of the information requirement you have provided does not meet the conditions set in Annex XI, Section 3.2.(a)(i) and (ii).

Therefore, ECHA concludes that your adaptation of the information requirement pursuant to Annex XI, Section 3.2 (a) is rejected.

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 rat or rabbit 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) 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit 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.

4. 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 for an algal inhibition test according to test guideline 88/302/EWG (similar to OECD test guideline 201) with the read-across substance propane-1,2,3-triyl trisheptanoate (EC No. 210-647-2). However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected and therefore does not meet the information requirement for growth inhibition study aquatic plants (Annex VII, Section 9.1.2.).

In the document attached to the dossier ("[redacted]"), you are mentioning several studies performed with the read-across substance propane-1,2,3-triyl trisheptanoate (EC No. 210-647-2). Some of those studies are reported in the IUCLID dossier, either as key studies (e.g. for the growth inhibition study in algae and the short-term toxicity study on *Daphnia*) or as supporting studies (e.g. for the short-term toxicity testing on fish).

Based on the information presented elsewhere in the dossier (*e.g.* on toxicokinetics or on bioaccumulation), the primary metabolites for the registered substance are expected to be 2-ethylhexanoic acid and glycerol. ECHA notes that 2-ethylhexanoic acid is not expected to be a metabolite for the source substances; those are metabolised to heptanoic-, octanoic or decanoic fatty acids. Therefore, ECHA disagrees with your claim that differences in branching between the registered substance and the read-across substance are not relevant since those differences imply that different metabolites are formed. There is no indication that the toxicity of the metabolites for the registered substance and of those for the read-across substance is equivalent. On this basis, ECHA considers that the proposed read-across cannot be used to predict the aquatic toxicity of the registered substance.

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) an algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you indicated your agreement to perform an aquatic plant toxicity study but that you were considering performing a *Lemna* growth inhibition test (OECD 221) instead of the requested alga growth inhibition test (OECD 201). You explained that the registered substance being poorly water-soluble, you deemed the *Lemna* test to be more appropriate to maintain a quantifiable exposure concentration over the study period.

ECHA notes that Annex VII Section 9.1. of the REACH Regulation specifies that a study with algae should be preferred but does not preclude the use of other aquatic plant species. ECHA still considers that a growth inhibition study on algae (OECD 201) should be preferred since you can find guidance on how to test poorly soluble substances in the OECD "*Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures*, ENV/JM/MONO (2000)6" and in ECHA "*Guidance on information requirements and chemical safety assessment*", Chapter R7b, Table R.7.8-3. However, ECHA agrees that a valid *Lemna* growth inhibition test (OECD 221) could also fulfil the information requirement of Annex VII Section 9.1. of the REACH Regulation.

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: growth inhibition study aquatic plants, with the test method being preferably an algae growth inhibition test (EU C.3./OECD TG 201).

Notes for your consideration

Due to the low solubility of the substance in water 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 tests and for calculation and expression of the result of the tests.

5. Long-term toxicity testing on fish (Annex VIII, Section 9.1.3., Column 2)

The "*guidance note on fulfilling the requirement of Annexes VI to XI*" laid down in Annex VI to the REACH Regulation, explicitly indicates that "*in some cases, the rules set out in Annexes VII to XI may require certain tests to be undertaken earlier than or in addition to the standard requirements*". More specifically, column 2 entries in Annexes VII-X of the REACH Regulation provide that the standard information required in Column 1 of those Annexes may in some cases be adapted, *i.e.* waived or augmented, when appropriately justified. In particular, Column 2 of Annex VIII, Section 9.1.3. of the REACH Regulation ('Short-term toxicity testing on fish') indicates that:

"*Long-term aquatic toxicity testing as described in Annex IX* [of the REACH Regulation] *shall be considered if the chemical safety assessment according to Annex I* [of the REACH Regulation] *indicates the need to investigate further effects on aquatic organisms. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.*

The long-term aquatic toxicity study on fish (Annex IX, Section 9.1.6) shall be considered if the substance is poorly water soluble".

ECHA notes that the registered substance is poorly water soluble as a water solubility of less than 0.05 mg/L at 20°C and pH 6.1-6.4 is reported in your registration dossier. Poorly soluble substances require longer time to be 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.

ECHA notes that the only available result for fish and for the registered substance is from a short-term study ([redacted], 1998)[4]. In this study, a limit test was performed with a 100 mg/L test solution prepared by directly weighing the test substance into the test vessels. No mortality was observed in the treatment and the control throughout the test period of 96 h. However ECHA considers that this result does not rule out potential long-term effects to fish.

Information on long-term toxicity testing on fish shall be considered for the risk assessment and for the classification and labelling of the substance. ECHA notes that no PNEC can currently be derived for the registered substance. Information on algae (see section 3 of the present decision) and on long-term toxicity to fish need to be generated in order to definitively conclude whether the PNECs can be derived or not. Furthermore, if long-term toxicity to fish is to be observed below the water solubility limit of the substance, the substance will have to be classified. Therefore, as the hazard and risk assessments provided in your dossier are not conclusive, ECHA considers that the available information in your chemical safety assessment does not rule out the need to investigate further long-term effects to fish.

Therefore, pursuant to Column 2 of Annex VIII, Section 9.1.3. of the REACH Regulation, it is considered that a long-term aquatic toxicity study on fish (Annex IX, Section 9.1.6) is warranted.

"You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation:

"*In accordance with Regulation (EC) No. 1907/2006, Annex IX, Column 2, 9.1 a study on the long-term toxicity to fish does not have to be conducted since the chemical safety assessment indicates no need to investigate further the effects of the substance and/or relevant degradation products on fish. All short-term studies studies, available for the substance or for a well-founded read-across substance, indicate no effects up to the limit of water solubility (WS < 0.05 mg/L measured in aqua dest). Also NOEC/EC10 obtained from algal growth studies are clearly above the water solubility for this substance. Additionally, the substance is poorly soluble and readily biodegradable, which will result in low test substance concentrations within the aquatic compartment.*

[4] [redacted]

Hence due to animal welfare reasons and to avoid unnecessary vertebrate tests, no further long-term test with fish is required".

You claim that "*the chemical safety assessment indicated no need to investigate further the effects of the substance and/or relevant degradation products on fish*". However, as explained above, ECHA notes that the only available result for fish and for the registered substance is from a short-term study whereas the registered substance is poorly soluble. Long-term toxicity cannot be excluded and shall be investigated. Annex VIII 9.1.3. of the REACH Regulation explicitly requires to consider long-term toxicity test on fish if the substance is poorly water soluble. As explained above, ECHA considers that the available information in your chemical safety assessment does not rule out the need to investigate further long-term effects to fish. Therefore your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 and cannot be accepted. 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 accepted 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), and 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. Therefore, the FELS toxicity test is the preferred guideline study to be used (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 under a longer-term exposure, or which require a longer period of time to reach steady state (for example for those substance with a high log Kow) (ECHA Guidance Chapter R7b, version 4.0, June 2017).

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you acknowledged that Annex VIII Section 9.1.3. of the REACH Regulation requires long-term aquatic toxicity testing to be considered if the chemical safety assessment (CSA) indicates the need to. However, you disagreed that the poor water solubility of the registered substance was enough to trigger that need. You further claimed that poor water solubility could be in itself a reason to waive the endpoint. You proposed to review the exposure scenarios and to wait for the results of the requested test on aquatic plants (see section 4 of the present decision) before deciding whether the chemical safety assessment indicates the need for long-term aquatic testing.

ECHA notes that contrary to your claim, poor-water solubility is not a valid reason to waive long-term aquatic toxicity testing. Annex VIII Section 9.1.3. of the REACH Regulation actually indicates that *short-term* aquatic toxicity testing does not need to be conducted if the substance is *highly* insoluble in water. If the substance is *poorly* soluble, Annex VIII Section 9.1.3. of the REACH Regulation explicitly requires long-term testing to be considered.

In your comments, you have assumed that chronic exposure of the environment is limited because the substance is readily biodegradable. However, ECHA notes that even if the registered substance is biodegradable, its concentration might still be locally significant if there are continuous releases into the environment.

Since the registration dossier does not contain a quantitative environmental exposure assessment, it is not possible to assess how significant the environmental concentrations of the registered substance are.

With regard to the hazard assessment, you explained in your comments that it could be refined based on the results of the requested study on aquatic plants, and, if necessary, of a fish embryo toxicity (FET) test (OECD 236) or of a long-term study on a non-vertebrate species. ECHA notes that for the hazard assessment and in particular, for the derivation of the PNECs, valid information is needed on three trophic levels. Long-term data on a non-vertebrate species is already available for *Daphnia* and you have agreed to perform a study on aquatic plants (see issue 4 of the present decision). For fish, ECHA notes that the only available result is from a short-term study. As explained above, the substance is poorly soluble in water and short-term tests may not give a true measure of toxicity for poorly water-soluble substances since steady state conditions are likely not to be reached within the duration of a short-term test. Therefore, ECHA considers that no valid information on the toxicity of the substance to fish is available and that additional acute toxicity tests would not be useful for assessing the hazard of the registered substance. In particular, the FET test you have proposed is an acute test which besides would not necessarily take properly into account the metabolism of the substance. As indicated in the OECD test guideline for the FET test (OECD 236), the metabolic capacity of embryonic fish is not normally similar to that of juvenile or adult fish.

Furthermore, the dossier indicates that the registered substance will likely be metabolised to 2-ethylhexanoic acid and glycerol. For 1 mole of the registered substance (molecular weight of 470.68 g/mol) absorbed, up to 3 moles of 2-ethylhexanoic acid (molecular weight of 144.22 g/mol) can theoretically be formed in the organism. According to the registration dossier, the water solubility of the registered substance is <0.05 mg/L. Therefore, up to 0.05 mg/L (i.e. 1.06E-7 mol/L) of the registered substance could be bioavailable from water (for this calculation oral intake is not taken into account). Assuming a bioaccumulation factor of 360 (as reported in the registration dossier), up to 3.82E-5 mol/kg of the registered substance could accumulate internally in aquatic organisms from exposure to contaminated water. Assuming that this entire amount is metabolised, up to 1.15E-4 mol/kg of metabolite 2-ethylhexanoic acid can then be formed inside the organisms (i.e. 3 times more than the parent substance).

Information on metabolite 2-ethylhexanoic acid can be found in the literature and on the ECHA dissemination website where in particular a PNEC of 0.36 mg/L (i.e. 2.50E-6 mol/L) in water is reported. Assuming a BCF of 3 for 2-ethylhexanoic acid (estimated from QSAR EPISUITE), the corresponding concentration inside the organism would be 7.49E-6 mol/kg, which could be interpreted as the predicted no effect concentration inside an organism for 2-ethylhexanoic acid.

The predicted internal concentration of 1.15E-4 mol/kg of 2-ethylhexanoic acid that could be formed from the metabolism of the registered substance clearly exceeds this predicted no effect concentration in the organism of 7.49E-6 mol/kg. This suggests that effects to aquatic organisms can be expected from the internal concentration of metabolite 2-ethylhexanoic acid formed after long-term aqueous exposure at the water solubility limit to the registered substance.

A long-term study on *Daphnia* is available for the registered substance. It shows that no-long term effects are expected for *Daphnia* up to the water solubility of the substance. For metabolite 2-ethylhexanoic acid, a 21d-NOEC of 25 mg/L is reported for *Daphnia* on the ECHA dissemination website.

The corresponding calculated NOEC inside *Daphnia* would then be 5.20E-4 mol/kg. This concentration is above the concentration of 1.15E-4 mol/kg of 2-ethylhexanoic acid that could be formed from the metabolism of the registered substance, which corroborates that the registered substance is not expected to cause long-term toxicity to *Daphnia*.

However, both concentrations are of the same order of magnitude. A long-term NOEC on fish is not reported for 2-ethylhexanoic acid and it is thus not possible to establish whether fish is less or more sensitive to this metabolite than *Daphnia*. Even if fish is just slightly more sensitive than *Daphnia*, effect to fish cannot be ruled out because the predicted concentration of 2-ethylhexanoic acid as metabolite of the registered substance is close to the internal NOEC for *Daphnia* in the organism. Besides, as indicated in your dossier, exposure of fish to the substance is likely to be higher via the oral route than via water, which implies that the internal concentrations of the registered substance and of its metabolites could be much higher than those estimated above.

ECHA concludes that the information currently available indicates clearly that the registered substance could induce long-term effects to fish and considers that the request for a long-term toxicity test on fish is justified.

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

Due to the low solubility of the substance in water 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).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time line indicated to provide the requested information was 18 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline "*to allow time for the SIEF to receive quotes, decide upon a laboratory, contract the study, undertake the study, evaluate and summarise the study, review all exposure scenarios and the CSA / CSR, to submit an updated dossier and to consider any further requirements / studies.*" You also note that "*due to the May 2018 REACh deadline and the numbers of studies being placed currently, the lead-in time for many study types is longer than is usually experienced by the registrant*" and that the required study time for the intended metabolite kinetics investigations will be "*dependent on number of studies and pharmacokinetic behaviour of the metabolite.*"

ECHA notes that you do not specify how many months more would be sufficient. According the timelines you have provided in your comments, the current timeline, 18 months, which has been set to allow for sequential testing, is considered sufficient to carry out the requested tests. Therefore, ECHA has not modified the deadline of the decision.

Cosmetic uses of the substance subject to testing

In your comments on the draft decision, you note "*the end use of the substance is predominantly a dermal application cosmetic ingredient (>90%)*" and that it is "*highly unlikely that a substance with over 90% cosmetic end use would be accepted by the laboratories the registrant would feel comfortable using (from a variety of European districts).*" Furthermore, you state that you "*will propose alternatives to vertebrate testing pending the decision of the ombudsman on the legality of testing cosmetic ingredients on vertebrates to comply with REACH regulations*" and that you are "*in discussion with the co-registrants as to whether non-cosmetic end uses may be removed from the registration.*"

ECHA notes that the current registration and the reported uses indicate non-cosmetic uses of the registered substance (e.g. industrial, professional and consumer uses in lubricants and greases). ECHA also notes that the current registration does not indicate any amount of the registered substance for different uses. Therefore, in the current circumstances you are permitted to perform animal testing, as a last resort, for human health endpoints and for environmental endpoints. Further information can be found from the ECHA webpage Clarity on interface between REACH and the Cosmetics Regulation[5].

ECHA further refers to the decision of 21 July 2017 of the European Ombudsman in case 1130/2016/JAS concerning the joint statement made by the European Commission and the ECHA on the conduct of animal tests for substances used in cosmetics. The statement is available at the ECHA website, as indicated in the paragraph above. In her decision the European Ombudsman concluded that there was no maladministration by the European Commission and ECHA[6].

The Ombudsman, *inter alia*, considered that: ''*the joint statement is concerned only with how the REACH Regulation is interpreted and applied in the light of the Cosmetics Regulation. The joint statement does not purport to deal with the interpretation and application of the Cosmetics Regulation in the light of the REACH Regulation. The Ombudsman concludes, therefore, that the joint statement is not contrary to the Cosmetics Regulation or to EU law more generally. ---*

Regarding the right of the Commission and ECHA to issue the joint statement, since they both have responsibility under the REACH Regulation, the Ombudsman finds that both the Commission and ECHA do have such a right. Finally, no clarifications of the joint statement are needed concerning the labelling of cosmetics as that issue falls under the Cosmetics Regulation, and not under the REACH Regulation''.'[7]

"*The Ombudsman agrees with the Commission and ECHA that the Cosmetics Regulation does not cover questions of safety related to the production of a cosmetic product. The potential risks from chemical ingredients during the production process are thus to be assessed within the context of the REACH Regulation, and any animal tests carried out in that context are subject to the REACH Regulation's rules and limitations* (...) *the joint statement makes no reference to the issue of labelling and makes no reference to the use of testing carried out under the REACH Regulation being submitted as part of a cosmetics safety assessment submitted to a Member State authority under the Cosmetics Regulation*"

[5] ECHA webpage Clarity on interface between REACH and the Cosmetics Regulation: https://echa.europa.eu/-/clarity-on-interface-between-reach-and-the-cosmetics-regulation
[6] https://www.ombudsman.europa.eu/cases/decision.faces/en/81713/html.bookmark
[7] https://www.ombudsman.europa.eu/cases/decision.faces/en/81713/html.bookmark

The Ombudsman makes similar considerations with respect to testing of substances under REACH which have both cosmetic and non-cosmetic uses and testing of a substance for the purposes assessing environmental risks (the "*Cosmetics Regulation deals with risks to human health only and does not cover environmental risks*").

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 14 December 2016.

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) or the deadline.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

ECHA
EUROPEAN CHEMICALS AGENCY

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.