ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 April 2019

Addressee: [redacted]

Decision number: CCH-D-2114460730-54-01/F
Substance name: Propane-1,2,3-triyl 3,5,5-trimethylhexanoate
EC number: 260-257-1
CAS number: 56554-53-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/03/2017
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. **Composition of the registered substance (Annex VI, Section 2.3.);**
   - **Nature of impurities, including isomers and by-products**
2. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD [421/422]) in rats, oral route with the registered substance;**
3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**
4. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**
5. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Algae growth inhibition test, EU C.3./OECD TG 201) 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 have to submit the requested information in an updated registration dossier by **2 November 2021**. 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 **Wim De Coen**, Head of Unit, Hazard Assessment, NC2

[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

IDENTIFICATION OF THE SUBSTANCE

1. Composition of the substance (Annex VI, Section 2.3.)

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations.

More specifically you identified the registered substance as a well defined mono-constituent substance. In line with paragraph 4.3 of the Guidance for identification and naming of substances under REACH, the following applies to all mono-constituent substances, including the registered substance:

- All the impurities present at ≥ 1 % shall be identified and reported individually; and
- All the impurities relevant for the classification and/or PBT assessment shall be identified and reported individually.

For each constituent, including the main constituent and any impurity, the typical, minimum and maximum concentration level shall be specified.

In the legal entity composition, in IUCLID section 1.2, you reported only one constituent with a concentration range between [redacted] and no other constituents or impurities are reported.

ECHA notes that up to [redacted] of the composition has therefore not been accounted for and therefore it is missing to be reported potential impurities of the substance.

ECHA therefore concludes that the compositional information has not been provided to the required level of detail, and the registration does not contain sufficient information for establishing the composition of the registered substance and therefore its identity.

In your comments to the draft decision you indicate your agreement to "*update the dossier composition of the registered substance to have a composition range more fully in line with the characterisation data that shows the substance to be* [redacted] *pure*" and fulfil this request.

You are accordingly requested to revise the information on the composition of the registered substance in order to establish a precise chemical representation of what the substance consists of.

More specifically, you are requested to report the potential impurities and to provide for each impurity, the typical, minimum and maximum concentration levels.

Further technical details on how to report the composition of substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" (version: 4.0, May 2017) on the ECHA website

TOXICOLOGICAL INFORMATION

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.

Your registration dossier contains for multiple endpoints adaptation arguments in the 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 2, 3, 4).

Grouping of substances and read-across approach

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

- Acute toxicity by the oral route (Annex VII, Section 8.5.1)
- Screening for toxicity to reproduction (Annex VIII, Section 8.7.1)
- Sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

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, 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 establishes 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 registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ 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

[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.

toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and 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[3]- (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 propane-1,2,3-triyl 3,5,5-trimethylhexanoate using data of structurally similar substances, hereafter the 'source substances':

1. Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates (EC 293-170-2)
2. Propane-1,2,3-triyl tri-heptanoate (EC 210-647-2)
3. Propane-1,2,3-triyl tri-octanoate (EC 208-686-5)
4. Glycerol (EC 200-289-5)
5. 3,5,5-tri-methylhexanoic acid (EC 221-975-0)

You have provided a read-across documentation as a separate attachment. Furthermore you have provided a literature survey and reference list.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: *"For the purpose of the analogue approach, enzymatic hydrolysis in the gastrointestinal tract and/or liver is identified as the biological process, by which the breakdown of Propane-1,2,3-triyl 3,5,5-trimethylhexanoate results in the generation of free Glycerol and free 3,5,5-trimethylhexanoic acid."*

As a basis for your read-across justification you have submitted information on the alleged two main metabolites of the target substance (glycerol and 3,5,5-trimethylhexanoic acid), and on substances with similar structures as the target substance (mono-, di- and triglycerides with linear fatty acids).

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

[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).

Your proposed adaptation argument is that the similarity in chemical structure between the source and registered substances, and its likely metabolism, 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 the likelihood of a proposed metabolic conversion does not necessarily lead to predictable or similar human health properties in other endpoints.

Metabolism of the target substance
Your justification is based on structural similarity and a likely metabolic conversion. However, it does not include adequate experimental evidence concerning the enzymatic hydrolysis of the registered substance to glycerol and 3,5,5-trimethylhexanoic acid. More specifically, the provided data does not demonstrate rapid hydrolysis. More specifically, there is no evidence on the speed of enzymatic conversion. Furthermore, there is no information available whether (rapid) hydrolysis precedes absorption into the systemic circulation. The available information does not exclude that the organism may be exposed to the parent compound through systemic circulation. The resulting concern regarding adverse effects by the parent compound, and the mono- or diglycerides of the parent substance, has not been addressed by the justification, and by the provided experimental data. Therefore, your justification has not established why the prediction is reliable for the human health end-points for which the read across is claimed, based on "bio-transformation to common compounds" (ECHA 2017[3]).

Comparison of hazard profiles
You provide toxicological data which allows the comparison of some toxicological properties between the source substances, but not with the target substance. Furthermore, the available data demonstrate that the postulated metabolite 3,5,5-trimethylhexanoic acid (EC 221-975-0) seems considerably more toxic compared to the other source substances. ECHA therefore concludes that the source studies with mono-, di- and triglycerides with linear fatty acids are inadequate to predict properties of the registered substance. Also, a concern for hazardous effects by partial metabolites of the target substance, such as mono- and di-glycerides, remains.

Furthermore, you explain why certain substances were chosen and included in the read-across approach as source substances, and that you intend to predict properties of the target substance by following a worst-case approach. However, you have not predicted from the postulated metabolite 3,5,5-trimethylhexanoic acid (EC 221-975-0) to the target substance. There are no relevant toxicological information on the target substance provided that would allow such comparison.

Lastly, you note that there are newly available studies (and some are also in the process of being generated) on the postulated metabolite 3,5,5-trimethylhexanoic acid (EC 221-975-0) and you state your intention to update the dossier with the respective studies to strengthen your read-across. However, ECHA notes that any studies on the source substance, by itself, will only provide information about the relevant property of the source substance, but not about the target substance. In the absence of relevant toxicological studies with the target substance ((e.g. Combined repeated dose toxicity study with the reproductive/developmental screening test (OECD TG 422)) it is impossible to compare the toxicological profile between the target and the source. In absence of such comparison that would confirm your hypothesis (that the source substance is indeed similar or worst-case to the target substance), the source data cannot be used to predict the properties of the target substance.

Conclusion

ECHA considers that your grouping and read-across approach does not provide a reliable basis whereby the human health 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 further notes that there are 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.

Further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. As described above, 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 human health properties. However, as addressed above, currently you have not provided such evidence.

Consideration on uses of the substance in relation to the tests requested in the decision

In your comments on the draft decision you indicated that the substance has only cosmetic uses. However, ECHA notes that stages of manufacturing of chemical and formulation of cosmetic products are taking place in the EEA and there is no indication that they are carried out under strictly controlled conditions. You have reported the following PROCs: 5, 8a, 8b, 9 and 14, which point out the potential/existence of worker exposure.

As you have not excluded worker exposure by handling the substance only under strictly controlled conditions, testing for human health endpoints is necessary to assess the risks from exposure to workers and therefore in order to fulfil the relevant REACH requirements. This is in accordance with ECHA's factsheet[4] on the interface between REACH and Cosmetics Regulations, which was developed jointly with the European Commission. It provides that registrants of substances that are exclusively used in cosmetics may not perform animal testing to meet the information requirements of the REACH human health endpoints unless such tests are needed to assess the risks from exposure to workers. In addition, animal testing for all environmental endpoints is permitted.

As is apparent from the Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135)) such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation[5].

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH

[4] https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf
[5] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013DC0135&from=EN

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. No such evidence is presented in the dossier. Therefore, 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 screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for analogue substances:

1. Screening for reproductive toxicity study (OECD TG 421, [redacted] 1998) with 3,5,5-trimethylhexanoic acid (EC 221-975-0),
2. Two-generation reproductive study (no TG, Wegener 1953) with Glycerol (EC 200-289-5),
3. Combined repeated dose and reproductive toxicity screening study (OECD TG 422, [redacted] 2010) with Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates (EC 293-170-2).

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. ECHA further notes that you have assigned a Klimisch reliability score of 4 to study 1 ([redacted] 1998), based on the limited reporting in the form of an abstract from a secondary literature source. Therefore, the reporting of the provided study does not fulfil the information requirement, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision, you state that "*ECHA ignores column 2 in [...] Annex [VIII, Section 8.7.1, Column 2]*", which regards adaptation possibilities for this endpoint based on an existing pre-natal developmental toxicity study.

ECHA considers the technical dossier of the registered substance incompliant in its current form, as it does not contain neither the screening for reproductive toxicity study, nor a pre-natal developmental toxicity study (adaptation according to A.VIII, 8.7.1, column 2) conducted with the registered substance. Therefore, requests for information as set out in this decision are justified. At the same time ECHA informed you in the "Notes for your consideration", below, to consider the order of testing to ensure that unnecessary animal testing is avoided.

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

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

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 the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your consideration

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

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

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for analogue substances:

1. Repeated dose toxicity studies (31 days, no TG, [redacted] 1970; 2yr, no TG, [redacted] 1994) with propane-1,2,3-triyl trioctanoate (EC 208-686-5).
2. Sub-acute repeated dose toxicity study (OECD TG 407, [redacted] 2002) with 3,5,5-trimethylhexanoic acid (EC 221-975-0),
3. Chronic repeated dose toxicity study (no TG, Hine 1953) with Glycerol (EC 200-289-5),
4. Combined repeated dose and reproductive toxicity screening study (OECD TG 422, [redacted] 2010) with Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates (EC 293-170-2).

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. More specifically, the studies under 1. and 4. concern source substances whose lower toxicity renders them insufficient to predict properties of the registered substance. For the analogous substance 3,5,5-trimethylhexanoic acid (EC 221-975-0) ECHA observes that you have provided a study record for a "repeated dose 28-day oral toxicity study" (test method: OECD TG 407) in the technical dossier. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408) . Therefore, the sensitivity of a 28-day study is

much lower than that of a 90-day study and thus it cannot be used to address the information requirement.

Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision, you state that "*Based on the now available 90 day toxicity study for EC 221-975-0, the request of this study is no longer justified.*"

ECHA notes that your read-across adaptation is rejected in its current form, for the reasons explained in section "grouping and read-across approach." Therefore, studies with the source substance 3,5,5-tri-methylhexanoic acid (EC 221-975-0) can currently not be used to predict properties of the registered substance for this endpoint.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

According to the test method OECD TG 408 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 90-day oral toxicity study (test method: OECD TG 408) in rats.

4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first 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. 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 study records for analogue substances:

1. Developmental toxicity studies (8 rabbits, no TG, [redacted] 1970) with propane-1,2,3-triyl trioctanoate (EC 208-686-5);
2. Developmental toxicity studies (20 mice, no TG, [redacted] 1970) with propane-1,2,3-triyl trioctanoate (EC 208-686-5);
3. Two-generation reproductive study (no TG, Wegener 1953) with Glycerol (EC 200-289-5).

However, as explained above in Appendix 1, *Grouping of substances and read-across approach* of this decision, your adaptation of the information requirement is rejected. More specifically, the studies under 1. to 3. concern source substances whose lower toxicity renders them insufficient to predict properties of the registered substance.

ECHA further notes that these source studies exhibit deviations from the test guidelines and the following additional shortcomings:

Ad 1) non-test guideline study, one dose, method of delivery not reported, no visceral examinations;
Ad 2) non-test guideline study, two doses, method of delivery not reported, no visceral examinations;
Ad 3) non-test guideline study, 10 females, one dose only, no caesarean section, no skeletal and visceral examinations.

According to the provisions of Annex IX, Section 8.7.2., information on pre-natal developmental toxicity as specified in the OECD TG 414 shall be provided. ECHA considers that the provided source studies do not fulfil the requirement of Annex XI, Section 1.5. of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

Therefore, your adaptation of the information requirement is rejected.

In the technical dossier you have provided a study record for a "reproduction/ developmental toxicity screening test" (test method: OECD TG 421). However, this study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision, you state that "*Based on the now available OECD 414 study in rats [...] for EC 221-975-0, the request of this study is no longer justified.*"

ECHA notes that your read-across adaptation is rejected in its current form, for the reasons explained in section "grouping and read-across approach." Therefore, studies with the source substance 3,5,5-tri-methylhexanoic acid (EC 221-975-0) can currently not be used to predict properties of the registered substance for this endpoint.

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

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) 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 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 first species (rat or rabbit) by the oral route.

ECOTOXICOLOGICAL INFORMATION

5. 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 VII, Section 9.1.1., column 2. You provided the following justification for the adaptation: "*Experimental data on the toxicity of Propane-1,2,3 triyl 3,5,5-trimethylhexanoate (CAS No. 56554-53-1) to aquatic algae is not available. According to Regulation (EC) No 1907/2006, column 2, 9.1.2., short-term toxicity testing with aquatic algae does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water (WS < 0.05 mg/L). Significant concentrations in the water phase are thus not expected to be reached, and the substance is not expected to be bioavailable for algae. Additionally, since the algal test (OECD 201) is a static test, the low water solubility and high adsorption potential (log Kow > 10) may critically hinder the technical feasibility of the study. Highly hydrophobic and adsorptive substances tend to adsorb to the walls of the test vessels and to the surface of algae cells, often causing effects on biomass and growth by direct physical interaction with the algae (e.g. hindering the access to light and nutrients, whereas dissolved concentrations in the test medium are actually close to zero (OECD Guidance document No. 23, OECD, 2000)). Based on the available studies on aquatic toxicity of the substance to fish and Daphnia, effects to algae are not expected up to the limit of water solubility. Short-term toxicity testing with fish (Danio rerio) determined no acute toxicity of the substance up to the limit of water solubility (LC50 (96 h) > 100% v/v (nominal)). The lack of aquatic toxicity was confirmed by a long-term toxicity study on survival and reproduction of Daphnia magna. Mortality or a significant effect on the number of produced offspring was not observed (NOEC (21 d): 100% v/v). Thus toxic effects of the substance to aquatic algae are not expected within the range of water solubility and therefore toxicity testing on aquatic algae is not proposed.*"

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex VII, Section 9.1.2., column 2. However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VII, Section 9.1.2., column 2 due to the following.

You claim that due to its low water solubility and high adsorption potential it will be technically difficult to conduct the study and that due to its properties the substance will not be bioavailable to algae. While ECHA agrees that the substance may be difficult to test, ECHA notes that there is no scientific basis to define a cut off limit value for solubility below which no toxicity could occur (ECHA *Guidance on information requirements and chemical safety assessment,* version 4.0, June 2017, Chapter R7b). Furthermore, ECHA notes that in

the long-term toxicity study on aquatic invertebrates there were some effects, although not statistically significant, both on parental survival and number of live young per female which were reduced in the single concentration tested. As the registered substance is poorly water soluble, absence of adverse effects in acute tests cannot be used to adapt chronic tests, since poorly soluble substances require longer time to be taken up by test organisms and consequently steady state conditions are likely not reached within the duration of short-term toxicity tests. For this reason, short-term tests may not give a true measure of toxicity for this type of substances and long-term effects to aquatic organisms cannot be excluded. Therefore, information on long-term aquatic toxicity is needed for risk assessment and for the classification and labelling. It is also necessary to derive data on three trophic levels ie on aquatic plants and invertebrates and fish. While the algal test (OECD TG 201) is a short-term test it provides both acute and chronic endpoints and can hence be considered to provide also information on long-term aquatic toxicity to aquatic plants.

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

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

As your substance may be difficult to test in aquatic media, ECHA refers you to the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6/REV1 (6 July 2018) 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 advice on the design of the study requested here and for calculation and expression of its results.
According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) 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.

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).

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 sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: *"According to Regulation (EC) No. 1907/2006, Annex IX, Column 2, 9.1.6, 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 aquatic organisms. Propane-1,2,3 triyl 3,5,5-trimethylhexanoate (CAS No. 56554-53-1) is a biodegradable (60% biodegradation after 28 days) and poorly soluble substance (water solubility < 0.05 mg/L).*

Due to these characteristics, extensive biodegradation and adsorption to activated sludge within conventional STPs can be expected and therefore, only low concentrations, if any, are likely to be released into the water phase. Fish exposure to this substance is thus expected to be low. The available acute fish test showed no adverse effects of the substance up to the highest attainable concentration in test medium (LC50 (96 h) > 100% v/v (nominal)).

Based on the short term value, fish cannot be identified as the most sensitive organism for this substance. According to the Guidance on information requirements and chemical safety assessment, Chapter R7.b (ECHA, 2012), long-term toxicity testing on fish should only be conducted if it represents the most sensitive taxonomic group. The Guidance states that if invertebrates are likely to be more sensitive than fish and algae or the relative sensitivity of invertebrates cannot be predicted, long-term testing on Daphnia sp. should be preferred instead of fish. The chronic study conducted on aquatic invertebrates showed no toxicity up to the limit of the water solubility of the substance. Thus, based on the results of the long-term toxicity study on aquatic invertebrates a long-term toxicity test with fish was not conducted."

ECHA also considers that you have provided information that could be interpreted as an attempt to adapt the information requirement according Annex XI, Section 3: "*Propane-1,2,3 triyl 3,5,5-trimethylhexanoate (CAS No. 56554-53-1) is a biodegradable (60% biodegradation after 28 days) and poorly soluble substance (water solubility < 0.05 mg/L). Due to these characteristics, extensive biodegradation and adsorption to activated sludge within conventional STPs can be expected and therefore, only low concentrations, if any, are likely to be released into the water phase. Fish exposure to this substance is thus expected to be low.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 or the general rules for adaptation of Annex XI, Section 3.

The registered substance is poorly water soluble (WS < 0.05 mg/L) and hence long-term testing is justified. ECHA *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b, Section R.7.8.5.3.*, states that, for substances with logKow>3, such as here, chemical safety assessment indicates no risk for aquatic life if PEC (Predicted Environmental Concentration) is lower than WS/100. However, you did not calculate PECs and did not do this comparison, hence a risk for aquatic life cannot be excluded.

Furthermore, ECHA notes that in the long-term toxicity study on aquatic invertebrates there were some effects, although not statistically significant, both on parental survival and number of live young per female which were reduced in the single concentration tested.

Regarding potential fish exposure, ECHA observes that according Annex XI, Section 3.1. of REACH, exposure assessment for all registered exposure scenarios and relevant PNECs need to be evaluated in order to adapt information requirement. ECHA indicates that you have not provided environmental exposure assessment for the registered substance and PNEC based on WS/100. Further, you have not demonstrated that the other conditions of that section are met.

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

In your comments to the draft decision you indicate your disagreement with the

interpretation of ECHA regarding Annex VIII Section 9.1.3. of the REACH Regulation. According to this annex, long-term aquatic toxicity testing has to be considered if the chemical safety assessment (CSA) indicates the need to. You disagree that the poor water solubility of the substance is enough to trigger that need. You further state that the poor water solubility could be in itself a reason to waive the requested long-term toxicity test on fish. However, 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*, then column 2 of Annex VIII Section 9.1.3. of the REACH Regulation explicitly requires long-term testing to be considered instead of short term testing (already at the tonnage level of 10-100 tonnes per annum).

You also claim that the bioavailability of the substance is limited because of its very high log Kow value and low water solubility. However, as already explained above, ECHA notes that some effects (although not statistically significant) were observed in the long-term toxicity study on *Daphnia*. This suggests that the substance could still be bioavailable and cause long-term effects to fish.

You have proposed to review the exposure scenarios for the substance and to conduct an algae study before deciding whether the CSA indicates the need for a long-term toxicity test on fish.

However, ECHA notes that the current dataset is insufficient to conclude on the absence of risk for the substance: data are missing to derive PNECs and no quantitative environmental exposure assessment is provided. As already mentioned above, in the absence of PNEC for poorly water soluble substances, PEC could be compared to 1/100th of the water solubility. If PEC do not exceed 1/100th of the water solubility for any of the exposure scenarios, then no further testing for aquatic toxicity will be needed. However, it is currently not possible to apply this approach, as the registration dossier does not contain a quantitative environmental exposure assessment. Therefore, ECHA considers that the safe use of the registered substance has not been demonstrated and based on available information on the substance properties and effects seen, there is a need to investigate further effects on aquatic organisms.

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

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

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly 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, Figure R.7.8-4).*

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

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

Notes for your consideration for sections 5 and 6

ECHA notes that due to lack of effects in short-term studies it is not possible to determine the sensitivity of species. Therefore, the Integrated testing strategy (ITS) outlined in 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), is not applicable in this case and long-term studies on three trophic levels, i.e. invertebrates, fish and algae, are required.

Due to the low solubility and high adsorption potential 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/REV1 (6 July 2018) 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).

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 28 September 2017.

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.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-63 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the 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.