ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 30 January 2019

Addressee: [redacted]

Decision number: TPE-D-2114455990-41-01/F
Substance name: Triethoxy(2,4,4-trimethylpentyl)silane
EC number: 252-558-1
CAS number: 35435-21-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/09/2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed tests for an Extended one-generation reproductive toxicity study in rats, (OECD TG 443) and Long-term toxicity testing on aquatic invertebrates (EU C.20./OECD TG 211) using the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2 are rejected, you are requested to perform:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

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

You are additionally requested to perform:

3. **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) using the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH

Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **8 February 2021**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for 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 Ofelia Bercaru, Head of Unit, Hazard Assessment, C4.

[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

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance Triethoxy(2,4,4-trimethylpentyl)silane (CAS No 35435-21-3, EC No 252-558-1, hereafter referred to as "target substance").

In relation to the testing proposals subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirements for an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) and a Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.). For both information requirements you propose to test the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2; hereafter referred to as "source substance") and to use the results to adapt the standard information requirements for your registered substance by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific validity of the proposed read-across and grouping approach (preliminary considerations; Section 0, below), before assessing the testing proposed (Section 1 and 2, below).

0. Grouping of substances and read-across approach

a. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis

The evaluation by ECHA of testing proposals submitted by registrants aims ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether programmes of testing proposed by you are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

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

The first Recital and the first Article of the REACH Regulation establish the *"promotion of alternative methods for assessment of hazards of substances"* as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to the present decision by using the results of the proposed tests is plausible based on the information currently available.

b. Description of the proposed grouping and read-across approach

You have provided the following hypothesis for the Extended one-generation reproductive toxicity study:

"The hypothesis is that the toxicology of the octyl alkoxysilanes is similar due to the structural similarity."

Additionally, you provided the following arguments to justify the read-across approach: *"There is currently insufficient information to judge whether any read-across within the group is appropriate. However, given the structural similarity, the trends in physicochemical*

properties and the consistency within most of the existing mammalian toxicology data, it is possible that read-across could be appropriate. Therefore, a stepwise testing plan is proposed (see test plan document "[redacted]").

Triethoxy(2,4,4-trimethylpentyl)silane (the target substance) is included in this group of trialkoxy(alkyl)silanes. According to the relevant REACH Annex requirements, this substance has a data gap for reproductive toxicity. The most appropriate source substance to fill each data gap will be selected once results of the first and second stage of testing are available.

90-Day repeated dose toxicity (OECD 408), reproductive toxicity (OECD 443) and developmental toxicity (OECD 414) tests are planned (awaiting an ECHA final decision TPE1_DEC_REG_01-2119972313-39-0000_TPE-D-2114331587-45-01) for triethoxy(octyl)silane (CAS 2943-75-1). In addition, initial OECD 422 screening tests are being commissioned for the structural analogues trimethoxy(octyl)silane (CAS 3069-40-7) and trimethoxy(2,4,4-trimethylpentyl)silane (CAS 34396-03-7).
The results of these tests will determine whether the read-across approach outlined in this report is appropriate.
Until the results of the above tests are available for the related substances, the data gap for reproductive toxicity is filled by read-across from a close structural analogue of triethoxy(2,4,4-trimethylpentyl)silane. As results of the planned tests become available the read-across approach and test plan will be revisited and adjusted as necessary. This might result in the need to test the registered substance. The current interim read-across approach is to read-across the planned Extended One Generation Reproductive Toxicity test from triethoxy(octyl)silane (CAS 2943-75-1)."

You have provided the following hypothesis for the Long-term toxicity testing on aquatic invertebrates:

"The registered substance and the substances used as surrogate for read-across are part of a class of low-functionality compounds acting via a non-polar narcosis mechanism of toxicity."

"Triethoxy(2,4,4-trimethylpentyl)silane and triethoxyoctylsilane are structural analogues; both are trialkoxysilanes with an octyl side chain, which is branched for the registration substance, linear for the read-across substance, and they have no other secondary feature."

"Both substances have very low water solubility (<0.1 mg/l and <0.13 - 0.79 mg/l at 20°C respectively), high log Kow (6.5 and 6.4 respectively), low vapour pressure (0.22 Pa and 0.11 Pa at 25°C respectively) and the same molecular weight ([redacted])."

"Their hydrolysis products, (2,4,4-trimethylpentyl)silanetriol and octylsilanetriol, are silanetriols with hydrocarbon side chains and have very similar physicochemical properties: high water solubility (24400 and 59000 mg/l, respectively, predicted), low log Kow (0.9 and 1.1, respectively), low vapour pressure (2.7E-05 Pa and 1.2E-04 Pa at 25°C, respectively) and the same molecular weight ([redacted])."

"Triethoxy(2,4,4-trimethylpentyl)silane (CAS 35435-21-3) and triethoxyoctylsilane (CAS 2943-75-1) both hydrolyse moderately rapidly in contact with water (43 h at pH 7, 20-25°C, and 30 h at pH 7, 20-25°C, respectively). The organosilicon hydrolysis products are (2,4,4-trimethylpentyl)silanetriol and octylsilanetriol respectively. "

"... the environmental hazard assessment is based on the properties of the parent substance, in accordance with REACH guidance."

"In addition, due to the moderate rate of hydrolysis, organisms in chronic studies are likely to be exposed to predominantly the hydrolysis products, and so this has been taken into account with the choice of read-across substance for the long-term test on invertebrates in order to take into account exposure to some of the parent."

c. Information submitted to support the grouping and read-across approach

In your registration dossier you have provided as separate attachments in IUCLID Section 13, relevant to the testing proposed:

[redacted]

The "[redacted]" outlines the stepwise testing plan proposed for alkyl alkoxysilanes.

The "[redacted] document is an overview of the grouping and read-across methods of Reconsile REACH submissions. The document describes the general principles applied but does not provide any substance-specific information. According to the report, substance specific information regarding which methods (i.e. category, analogue or QSAR) have been applied will be provided in the CSR and IUCLID.

Apart from the above general information you have provided the proposed substance and endpoint specific read-across hypothesis and justification in the attachment "[redacted]". This information includes the read-across hypothesis and justification, the identification of the source and target substances; discussion on the physico-chemical properties, the hydrolysis products, the repeated dose and developmental toxicity of the substances and a conclusion on your read-across approach.

The "[redacted]" document outlines the condensation of silanols to form oligomers and polymers, and how to interpret data from ecotoxicology studies with organosilanes that hydrolyse to silanols.

The "[redacted] document outlines approaches used in data gap filling for ecotoxicity for the members of the group with low functionality side chains. The document describes the general principles applied but does not provide any substance-specific information.

Apart from the above general information you have provided the substance specific read-across hypothesis and justification for the prediction of ecotoxicological effects, in the technical dossier, under the summary for Ecotoxicological information (Section 6) and in section 7 of the Chemical Safety Report (CSR).

In addition, you have provided in the technical dossier of the target substance the following toxicological studies relevant to the testing proposed.

For the target substance:

- an acute oral toxicity study (OECD TG 423, [redacted] 1998);

- an acute dermal toxicity study (OECD TG 402, [redacted], 2001a);
- a sub-chronic repeated dose (90-day) toxicity study, via oral route (OECD TG 408, [redacted], 2015, key study);
- a 28-day repeated dose toxicity study, via oral route (OECD TG 407, [redacted] 2001d);
- a 14-day repeated dose toxicity study, via oral route (similar to OECD TG 407, [redacted] 2001b);
- a 28-day repeated dose toxicity study, via oral route (OECD TG 407, [redacted], 2001)
- a pre-natal developmental toxicity study (OECD TG 414, [redacted], 2009a, key study);
- a dose range finding study ([redacted], 2009b).

For the source substance:
- results of a combined repeated dose toxicity with reproduction/developmental toxicity screening test via oral route (OECD TG 422, [redacted] 2010).

You provided the following ecotoxicological studies relevant to the testing proposed.

For the target substance:
- *Daphnia* acute immobilisation test (OECD TG 202, [redacted], 2001, Study no [redacted], key study)
- *Daphnia magna* Reproduction Test (OECD TG 211, [redacted] 2010, Study no [redacted], weight of evidence)
- Fish acute toxicity test (OECD TG 203, [redacted] 2001, study no 9543230, supporting study)
- Alga, Growth Inhibition Test (OECD TG 201, [redacted], 2010, study no [redacted], key study)

For the source substance:
- *Daphnia* acute immobilisation test (OECD TG 202, [redacted], 2008, Study no [redacted], supporting study)
- Fish acute toxicity test (OECD TG 203, [redacted], 2008, study no [redacted], supporting study)
- Alga, Growth Inhibition Test (OECD TG 201, [redacted], 2008, Study no [redacted], supporting study)

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

ECHA notes that the registrants of trialkoxy(alkyl)silanes including the octyl-alkoxysilanes have grouped the substances in 'Analogue group', including the substance subject to the current decision, but the category approach is not proposed. Based on the substance specific justification for read-across approach and supporting information provided by you, ECHA understands that no category hypothesis/justification has been included and the proposed prediction is based on the analogue approach using triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2) as a source substance.

According to ECHA's understanding in your read-across hypothesis you claim that based on their structural similarities target and source substances have similar toxicological and ecotoxicological properties.

You justify your claim by proposing that:
- target and source substances display similar physico-chemical properties;

- target and source substances would undergo similar hydrolysis process and as a result structurally similar silanol hydrolysis products are formed;
- the hydrolysis products have very similar physico-chemical properties;
- due to structural similarity and similarity in physico-chemical properties it is considered appropriate to read-across ecotoxicological properties (aquatic compartment) between the two substances;
- due to the similarity of the physico-chemical properties of the parent substances and their silanol hydrolysis product the substances would possess similar toxicokinetic profile in humans/rats; and
- irrespective of the differences in their physico-chemical, hydrolysis and toxicokinetic properties the toxicological properties of the substances are similar and predicting human health properties of the target substance from the data obtained with the source substance represents a worst case scenario.

In the following, ECHA examines whether the substances have indeed similar properties or that they would follow a regular pattern in their properties.

(i) Substance characterisation of source and target substances

The substance characterisation of the source substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 "How to report on Read-Across" it is recommended to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

ECHA notes that you have sufficiently characterised the target and source substances.

(ii) Structural (dis)similarities

Structural similarity is a prerequisite for applying the grouping and read-across approach, however ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You have described that both target and source substances are trialkoxysilanes with an octyl side chain. The octyl side chain is branched for the target substance, and linear for the source substance. The substances have no other differences in structure. ECHA notes that you have sufficiently described in your read-across justification document the structural (dis)similarities between the target and source substances. However ECHA notes that you have not fully justified how a structural difference, i.e. branching of the octyl side chain, between the target and source substances may impact the toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substance.

The provided explanation is therefore not sufficient to establish a scientifically credible link between the structural similarity and the prediction.

(iii) Similar toxicological properties or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that *"substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances"*. One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

Physico-chemical, hydrolysis and toxicokinetic properties

In your read-across justification you state that physico-chemical parameters of target and source substances are "*within a relatively small range*". You acknowledge the differences in the water solubility, partition coefficient (log Kow) and hydrolysis properties of the target and source substances. You explain that these differences are arising from the structural differences of the substances and have an impact on the concentration and distribution of the hydrolysis products. You add, *"This could mean that systemic availability of the different substances and products may be quantitatively different."* but you consider that these differences would not influence the possibility to read-across. However, as discussed further below, you have not provided any scientific evidence to substantiate your assumption.

Furthermore, you postulate that irrespective of the hydrolysis kinetics, the silanol monomers would be predominant in terms of bioavailability and hence would drive the toxicity of the substances. You also claim that potential formation of condensation products would not contribute to the toxicity of the substances as (*a*) the formed products would be large, insoluble molecules and hence uptake in the gastrointestinal tract would not occur (*b*) the condensation reactions are reversible at concentration(s) present in the gastrointestinal tract. Based on these assumptions you conclude that the condensation reaction and the formed products do not influence the possibility to read-across.

Firstly, ECHA observes that your dossier does not contain measured hydrolysis data for the target and source substances under conditions relevant for oral exposure. In your read-across justification document, in the data matrix comparing the physico-chemical properties of octyl-alkoxysilanes, you report very fast hydrolysis at pH 2 and 37°C for all substances. Therein you predict that the *"extrapolated hydrolysis half-life ($t_{1/2}$) at pH 2 and 37 °C"* is 11 seconds for the target substance and 9 seconds for the source substance, under the same conditions. ECHA considers that the hydrolysis half-life rate at pH 2 is based on assumptions, which are not substantiated by data. ECHA notes that you have postulated that the rate of the hydrolysis reaction is dependent on hydronium ion concentration and that there will be a 100-fold increase in hydrolysis rate on going from pH 4 to pH 2. ECHA accepts that the hydrolysis is catalysed by the hydronium ion, however there is no evidence provided to suggest such a dependence on the hydronium ion concentration and consequently ECHA considers the assumption of a 100 fold increase in hydrolysis rate on going from pH 4 to pH 2 as not supported by scientific evidence.

Secondly, you explain that in recent hydrolysis studies on a trialkoxy(alkyl)silane substance, methyltrimethoxysilane the half-life for disappearance of methyltrimethoxysilane applied in corn oil to gastric simulation buffer was 33 mins at pH 3 and 37°C. You mention that, *"Mammalian studies with alkoxysilanes typically use dried corn oil (or another vegetable-based oil) as vehicle. The source, target and supporting substances could thus potentially hydrolyse more slowly than their predicted half-lives at pH 2 and 37°C would suggest."* and

that *"high concentrations and dosing in a vehicle such as corn oil may slow down hydrolysis in the rat stomach during in vivo animal studies."*

Although you acknowledge the difference between the postulated hydrolysis half-life rates of the target and source substances and the hydrolysis data measured for methyltrimethoxysilane under condition simulating gastric environment, your current read-across justification does not address the impact of this difference on the possibility to read-across. ECHA points out that the difference in the hydrolysis kinetics could lead to qualitatively and quantitatively different systemic availability of the hydrolysis products and condensation products.

Moreover, ECHA observes that your dossier does not contain information, neither for the target nor for the source substance, about the conditions under which the condensation reaction occurs. In particular, substance specific concentration limit, specific pH, temperature and impact of the groups bound to the Si atom are not defined. Most importantly, the nature of the condensation products (e.g. size distribution) and their rate of formation under conditions relevant to the proposed test(s) are not clear.

In summary, from the presented information it is not clear whether the parent substances, the monomer form of the silanol hydrolysis products or the condensation products will be predominant in terms of bioavailability and hence would drive the toxicity of target and source substances. ECHA considers that your postulation that the toxicity of the substances would be independent from the hydrolysis/condensation kinetics is not substantiated by data and cannot be accepted.

In general, ECHA notes that you have currently not provided data to substantiate your read-across hypothesis. You acknowledge these deficiencies yourself and conclude that further data is needed. In particular, you refer to your plan to verify the rate of hydrolysis and to investigate the condensation reaction/products as well as conducting additional toxicological studies on the substances to confirm the assumption of consistent properties, to prove that the difference in the hydrolysis rates and physicochemical properties of the hydrolysis products and the formation of condensation products does not impact the read-across.

ECHA agrees that at this moment you have not provided the necessary evidence to support your hypothesis and additional studies may strengthen the overall read-across approach. However, ECHA notes that the results may or may not confirm your hypothesis.

Comparison of the toxicological profiles

You propose that irrespective of the differences in their physico-chemical, hydrolysis and toxicokinetic properties, target and source substances have similar toxicological profile. To support your claim you provide comparison of the available *in vivo* toxicological studies. You acknowledge the differences in the repeated dose toxicity profile of the substances, in particular with respect of neurotoxicity, observed only for the source substance.

You also propose that *"read-across an EOGRT test from triethoxy(octyl)silane to triethoxy(2,4,4-trimethylpentyl)silane is conservative and represents a worst case scenario."*

You base your worst case approach on observations in the available toxicological studies: the sub-chronic toxicity study with the target substance (OECD TG 408, [redacted], 2015, key study) did not show sign of toxicity and/or neurotoxicity; the available pre-natal developmental toxicity study with the target substance (OECD TG 414, [redacted] 2009a, key

study) did not display developmental and maternal toxicity effects; contrary, in the combined repeated dose toxicity with reproduction/developmental toxicity screening test via oral route (OECD TG 422, [redacted] 2010) with the source substance both developmental and neurotoxicity toxicity were observed.

You conclude: *"Overall, it is acknowledged that the repeated dose toxicity profile for this potential analogue group is not currently well developed and that there are differences in the profiles, particularly with respect to neurotoxicity. However, it is envisaged that the planned testing strategy will allow a more in depth investigation of the neurotoxic effects observed in the screening test on triethoxy(octyl)silane. Since, no neurotoxicity was observed in the 90-day oral toxicity test with the target substance, the current proposal to read-across an EOGRT test from triethoxy(octyl)silane to triethoxy(2,4,4-trimethylpentyl)silane is conservative and represents a worst case scenario."*

Firstly, ECHA observes that indeed no treatment related findings in any of the animals in the sub-chronic toxicity study with the target substance (OECD TG 408, [redacted], 2015, key study) were reported.

However, ECHA points out that the doses used in the above mentioned sub-chronic toxicity study with the target substance (15, 50 and 150 mg/kg bw/day) were not sufficiently high according to the test guideline EU B.26 / OECD TG 408 describing that *"Dose levels may be based on the results of repeated dose or range finding studies and should take into account any existing toxicological and toxicokinetic data available for the test compound or related materials. Unless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering."*

You state in your robust study summary of the OECD TG 408 study your dose selection reasoning, namely: *"The doses were selected in consultation with the sponsor"* and *"The highest dose level was chosen with the aim of inducing toxic effects, but no death or severe suffering."*

ECHA notes that results of GLP compliant short term repeated dose toxicity studies (OECD TG 407, [redacted], 2001d; OECD TG 407, [redacted], 2001b; OECD TG 407, [redacted], 2001) are available for the target substance applying doses up to 2000 mg/kg bw/day. These studies are relevant for selecting the appropriate dose level in the OECD TG 408. However, ECHA considers that no toxicity was observed in the 90-day study at the top dose level. Further, no toxicity was seen in the short term repeated dose toxicity studies at this dose level (i.e. at ~150 mg/kg/day) and so ECHA considers that you did not have the aim to induce toxicity in the 90-day study. Hence, for read-across purposes, the high dose selection in the sub-chronic toxicity study is not justified and cannot be considered as adequate. Therefore, the sub-chronic toxicity study with the target substance (OECD TG 408, [redacted], 2015, key study) cannot be considered as adequate to compare the repeated dose toxicity profile of the substances.

In relation to the repeated dose toxicity profile of the substances ECHA observes that in the short term repeated dose toxicity studies with the target substance (OECD TG 407, [redacted] 2001d; OECD TG 407, [redacted], 2001b; OECD TG 407, [redacted] 2001) the available histopathological investigations and clinical observations did not show sign of effects on the nervous system. Thus, ECHA agrees with your conclusion that the target and source substances display different repeated dose toxicity profile.

Secondly, ECHA observes that the developmental toxicity effects in the combined repeated dose toxicity with reproduction/developmental toxicity screening test (OECD TG 422, [redacted] 2010) with the source substance you refer to were post-partum effects *e.g.* effects on the viability of the delivered pups and the body weight gains of the pups on PND4 (post-natal day 4).

ECHA notes that contrary to the combined repeated dose toxicity with reproduction/developmental toxicity screening test (OECD TG 422) which investigates the foetuses post-partum, in a pre-natal developmental toxicity study according to OECD TG 414 the foetuses are investigated immediately after caesarean section for sex, body weight, skeletal and soft tissue alteration etc. Hence a pre-natal development toxicity study does not provide any information on the viability and/or the body weight gain of the delivered pups post-partum.

Consequently, the different study design of the above mentioned toxicological studies does not allow a comparison of the above listed effects. Thus, it cannot be concluded that based on the absence of such effects for the target substance in the pre-natal developmental toxicity study the target substance would not have effects on the offsprings. Therefore, in relation to reproductive/developmental toxicity your claim of consistency in the mammalian toxicity data, and that read-across from data obtained on triethoxy(octyl)silane would represent conservative and/or a worst case scenario cannot be confirmed.

In summary, ECHA considers that due to all above mentioned reasons your claim of consistency in the mammalian toxicity data and that "*to read-across an EOGRT test from triethoxy(octyl)silane to triethoxy(2,4,4-trimethylpentyl)silane is conservative and represents a worst case scenario* is not supported by data and hence cannot be confirmed.

Consequently, currently there is not an adequate basis for predicting the human health properties of the target substance from the data obtained with the source substance.

(iv) Similar ecotoxicological properties or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

Physico-chemical properties, hydrolysis and bioavailability

You propose that the target and source substances (parent substances) and their hydrolysis products are likely to have similar physico-chemical properties. You further state in your CSR that the environmental hazard assessment of the target substance is based on the properties of the parent substance due to hydrolysis half-life of 43 h at pH 7 for the target substance and 30 h at pH 7 for the source substance.

ECHA acknowledges the similarity in physico-chemical properties and the basis to focus the hazard assessment on the parent substance (target). ECHA therefore understands that the

read-across hypothesis is also based on parent substances despite the statements on hydrolysis and hydrolysis products.

While you acknowledge the difference in hydrolysis rates between the source and target substances, your current read-across justification does not address the impact of the above mentioned difference on the possibility to predict the ecotoxicological effects of the target substance. In particular, ECHA notes that you have not addressed the difference in hydrolysis rates in terms of parent substance stability in the test solution and its influence on the predicted property in your read-across justification.

ECHA points out that the difference in the hydrolysis kinetics could lead to quantitatively different bioavailability of the parent substance in the test system. If the target substance is likely to be hydrolysed at a lower rate than the source substance during the test, the test organisms would be exposed to higher concentrations of the target substance (if a test with the target would be performed). This in turn may cause higher toxicity of the target substance than will be observed with the source substance. Consequently, the prediction that you suggest to be made based on the source substance may cause underestimation of hazards of the target substance.

ECHA also notes that you have not considered or provided evidence if the source and target substances have differences in uptake potential which may lead to differences in toxic effects.

Comparison of the ecotoxicity profiles

You propose that source and target substances are part of a class of low-functionality compounds acting via a non-polar narcosis mechanism of toxicity. You further provided a data matrix which compares the available data from aquatic short-term toxicity studies and you also provide a long-term toxicity study on *Daphnia* for the target substance.

ECHA notes that toxicity profiles of the source and target substances cannot be compared with the data provided in the registration dossier for the target substance due to the following reasons:

Firstly, you have not submitted long-term studies on both the target and the source substances allowing to adequately compare their toxicities. ECHA considers that long-term studies would provide more information on toxicity of such poorly water soluble substances (logKow >6). Poorly soluble substances require longer time to be significantly taken up by the test organisms and consequently steady state conditions are likely not to be reached within the duration of a short-term toxicity test. The absence of toxicity observed in the short-term tests cannot, therefore, be used to compare the toxicity profiles between the source and target substances.

Secondly, with regards to short-term toxicity, ECHA notes that the *Daphnia* acute immobilisation test (OECD TG 202, [redacted] 2001, Study no [redacted], key study) and Fish acute toxicity test (OECD TG 203, [redacted] 2001, study no [redacted], key study) on the target substance do not provide reliable information on the toxicity of the parent substance. The preparation of a stock dispersion was several orders of magnitude above the water solubility of the target substance and undissolved material was observed in the test vessels. Due to the presence of the undissolved material the exposure concentrations were not monitored. It is therefore not possible to know the level of the parent substance the organisms were exposed to.

Thirdly, with regards to toxicity to aquatic algae you have reported a 72-h EC50 >1.2mg/L (measured initial, growth rate) for the target substance (OECD TG 201, [redacted] 2010, study no [redacted], key study) and 72-h EC50 >0.13mg/L (nominal, growth rate) for the source substance (OECD TG 201, [redacted], 2008, Study no [redacted], supporting study). While in the study with the target substance some effects were observed, in the study with the source substance no effects were observed. ECHA notes that in either of the studies the effects were not severe enough to allow you to derive EC50/EC10 values and thus you report the EC50 values only as higher than the maximum tested concentrations. In the absence of effects in these short-term studies ECHA notes that based on these tests the toxicity profiles cannot be compared between the target and source substances.

In summary, ECHA considers that due to above mentioned reasons, you have not provided clear arguments to justify why the properties of the target substance can be predicted with the studies on the source substance, nor supported the prediction by reliable data.

Consequently, currently there is not an adequate basis for predicting the toxicity of the target substance to aquatic invertebrates from the data obtained with the source substance.

e. Conclusion on the read-across approach

Based on the above considerations ECHA concludes that you have not provided adequate and reliable information to demonstrate that the proposed read-across approach is plausible for the endpoint(s) in consideration (Extended one-generation reproductive toxicity study, Long-term toxicity testing on aquatic invertebrates).

ECHA therefore concludes that the criteria of Annex XI, Section 1.5, are not met, and consequently the testing proposed on the read-across substance(s), is not appropriate to fulfil the information requirement(s) of the substance subject to the present decision.

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

Examination of the testing proposal

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral route to be performed with the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2) with the following specification of the study design:
Ten weeks premating exposure duration for the parental (P0) generation (or: Two weeks premating exposure duration for the parental (P0) generation if an extension of Cohort 1B to produce an F2 generation is requested);

- Dose level setting shall aim to induce systemic toxicity at the highest dose level or should be based on toxicokinetic considerations;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation
- Cohorts 2A and 2B (Developmental neurotoxicity).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance (CAS No 2943-75-1, EC no 220-941-2). As explained in the Section 0 *'Grouping of substances and read-across approach'* of this decision, your adaptation of the information requirement cannot be accepted. Hence there is a need to test the registered substance.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed to have a ten weeks premating exposure duration for the parental (P0) generation or two weeks premating exposure durations for the parental (0) generation if an extension of Cohort 1B to produce an F2 generation is requested.

ECHA agrees with a ten-week premating exposure duration because there is no substance specific information in the dossier supporting shorter premating exposure duration In this specific case ten weeks exposure duration is also supported by the lipophilicity of the substance (Log Kow> 6.5) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.
You proposed not to include an extension of Cohort 1B.

ECHA has evaluated whether the column 2 conditions of 8.7.3., Annex X for the registered substance are met, and Cohort 1B should be extended to produce the F2 generation by mating the Cohort 1B animals.

ECHA considers that the criteria to extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You propose to include Cohorts 2A and 2B. You base your reasoning on the effects seen with the structurally analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2).

ECHA agrees with you that these effects, as described below, are relevant for the testing needs of the registered substance i.e. triggering of Cohorts 2A and 2B.

Firstly, the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2) is a structural analogue to the registered substance, in the meaning of column 2 of Section 8.7.3., Annex X, existing information on effects caused by structurally analogous substances to the substance being studied).
Secondly, the existing information on triethoxy(octyl)silane derived from available *in vivo* studies show evidence of neurotoxicity. In particular the combined repeated dose toxicity with reproduction/developmental toxicity screening test (OECD TG 422, [redacted] (2010)) triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2) shows evidence of neurotoxicity such as:

- Adverse effects on the central nervous system: *"The main finding in the central nervous system was white matter degeneration of the brain and spinal cord in Group 4 toxicity group and reproductive group females, with an increased incidence in the reproductive group females compared to the toxicity group females";*
- Adverse effects on the peripheral nerves: *"In the peripheral nerves examined, the sciatic and tibial nerves, there was a statistically significant increase in the incidence of minimal to severe demyelination/degeneration in 8/10 (sciatic) ($p<0.01$) and 9/9 (tibial) ($p<0.01$) Group 4 reproductive group females and not in the controls";*
- Neurological clinical signs: *"statistically significant changes in the incidence of neurological clinical signs only in Group 4 reproductive group females compared to controls. Hind limb dragging (5/10) and incoordinated gait (5/10) ocurred in Group 4 reproductive group females";*
- Muscle atrophy: *"Animals affected with neurological findings also showed gross muscle atrophy, diffuse decreased muscle fibre size, fibre fragmentation, increased density of myofibre nuclei, and focal areas of inflammation around necrotic fibres".*

Therefore, ECHA considers that the criteria to include Cohorts 2A and 2B are met.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

You proposed not to include Cohort 3.

ECHA has evaluated whether the column 2 conditions of 8.7.3., Annex X for the registered substance are met, and Cohort 1B should be extended to produce the F2 generation by mating the Cohort 1B animals.

ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in 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.

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity);

while your originally proposed test for Extended one-generation reproductive toxicity study (test method OECD TG 443) with the analogue substance (triethoxy(octyl)silane (CAS No 2943-75-1, EC no 220-941-2) is rejected according to Article 40(3)(d) of the REACH Regulation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements.

In your dossier you have submitted a OECD Guideline 211 study (Daphnia magna Reproduction Test, [redacted] 2010, [redacted]) on the registered substance and a OECD Guideline 211 study (Daphnia magna Reproduction Test, [redacted] 2009, [redacted]) on an analogue substance trichloro(2,4,4-trimethylpentyl)silane (EC No 242-262-0, CAS No 18379-25-4). You consider neither of the studies adequate to be used in the CSA of the registered substance, as described below. Therefore, you also provided a testing proposal for this information requirement, on an analogue substance triethoxy(octyl)silane (CAS 2943-75-1; EC 220-941-2).

You consider that the existing study with registered substance is not suitable for the hazard assessment of the registered substance. You claim that the concentrations of the equally relevant hydrolysis products were not measured in the test solutions and are therefore not considered in the no effect concentration value. ECHA however notes that in the CSR section 7 you indicate that due to the hydrolysis half-life of 43 hours at pH 7, the environmental hazard assessment is based on the properties of the parent substance, in accordance with REACH guidance.

Firstly, ECHA considers that as you intend to use the parent substance as a basis for the hazard assessment, it is not essential to measure the concentration of the hydrolysis products during testing. As the concentrations of the parent substance were monitored, these concentrations may be used for the hazard assessment of the parent substance. However, ECHA acknowledges that the study design may not be optimal to measure the effects of the parent substance alone if the test solution likely contained additionally the hydrolysis products and if the test substance has not been properly dissolved and solid particles are observed in the test solution, as indicated by you in the endpoint study record. ECHA notes that indeed the test solution likely had contained also hydrolysis products as the test solution was prepared by using a loading rate of 100mg/L, which is orders of magnitude over the water solubility of the target (parent substance), with additional ultrasonic

treatment for 15 minutes and intense stirring by a magnetic stirrer over 96 hours. The concentration of the hydrolysis products were not measured and it cannot be verified if they were present in the solution, if and to what extend they may have caused the toxicity observed in the test. Therefore, ECHA agrees that the study on the registered substance, which did not follow an optimal study design for the registered substance, may not be accurate to describe the toxicity of the parent substance alone.

Secondly, with regards to use of parent substance for the hazard assessment ECHA acknowledges that due to hydrolysis half-life of 43 hours at pH 7 the parent substance may be more appropriate to be used in hazard assessment rather than hydrolysis products according to ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017) Chapter R.7b, Table R.7.8—2 Critical parameters for aquatic toxicity testing. Furthermore ECHA notes that in the document "[redacted] attached to the registration dossier, you state that solubility of a parent substance can limit the rate of silanol production even when the alkoxysilane hydrolysis rate is fast. ECHA notes that as the water solubility of the registered substance is low (<0.1 mg/l at 20°C) the production of hydrolysis products may be limited, which further supports the use of the parent substance for the hazard assessment.

You also provided a long-term study with *Daphnia magna* on the analogues substance trichloro(2,4,4-trimethylpentyl)silane (CAS 18379-25-4) which is currently used to derive the hazard assessment, as "*its silanol hydrolysis product is the same as that of the registration substance*". You reported a NOEC of 32 mg/l.

With regards to read-across justification regarding the use of trichloro(2,4,4-trimethylpentyl)silane, you provide (under the endpoint summary in section 6 of IUCLID technical dossier and section 7 of the CSR) general arguments on fast hydrolysis of the analogue substance (<1 min at pH 7) and some considerations on the non-silanol hydrolysis products. You state that "*As the hydrolysis rate for trichloro(2,4,4-trimethylpentyl)silane is so rapid, and test organisms will be exposed to its hydrolysis products, it is therefore considered appropriate to read-across between the two substances.*"

You further state in the endpoint summary for Long-term toxicity to aquatic invertebrates that "*While the data [*for trichloro(2,4,4-trimethylpentyl)silane*] are considered to be sufficient to derive a reliable hazard assessment for the silanol hydrolysis product of the registered substance, a long-term toxicity test with Daphnia magna has been proposed with the analogous substance triethoxyoctylsilane (CAS 2943-75-1). The study proposal is being read-across to the registered substance to determine effects of the parent substance.*"

In the study record for trichloro(2,4,4-trimethylpentyl)silane you have indicated that the preparation of the test solution was done by a dispersion of the test item to water with the loading rate of 100 mg/L under intense stirring. Furthermore, the dispersion was stirred on a magnetic stirrer at room temperature over 24 hours in the dark. ECHA thus acknowledges that such a preparation of the test solution for trichloro(2,4,4-trimethylpentyl)silane likely produces a test solution which mainly contains hydrolysis products.

As explained above, you intend to use the parent substance as a basis of the hazard assessment. Therefore ECHA considers that this study with trichloro(2,4,4-trimethylpentyl)silane, or mainly of its hydrolysis products, is not appropriate to provide information on the hazards of the registered substance.

In conclusion the existing studies on the registered substance and trichloro(2,4,4-trimethylpentyl)silane do not provide reliable information on the hazards of the registered substance (parent). Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You have proposed an OECD Guideline 211, *Daphnia magna* Reproduction Test with an analogue substance triethoxy(octyl)silane (CAS 2943-75-1; EC 220-941-2). ECHA has evaluated your proposal to perform the test with the analogue substance. As explained above in section 0 of this decision, the proposed read-across cannot be accepted. Hence there is a need to test the registered substance.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially less sensitive than aquatic invertebrates. In the acute toxicity study for fish you did not observe effects in the loading rate of 100mg/L. ECHA however notes that the short-term aquatic studies you have provided for the registered substance are not reliable as described in Section 0 to this decision. Furthermore, as stated in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017) Chapter R7b, page 32, with short-term toxicity tests it is not possible to fully evaluate the toxicity potential of a low water solubility substance, such as the registered substance with reported water solubility of <0.1 mg/l at 20°C. ECHA hence considers that a need for long-term studies are indicated for the registered substance and such test(s) are needed to derive reliable PNECaquatic values as indicated by you in your testing proposal justification.

In conclusion there is a data gap for both long-term daphnia and long-term fish toxicity.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following test using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (test method: *Daphnia magna* reproduction test, EU C.20/OECD TG 211), while your originally proposed test for Long-term toxicity testing on aquatic invertebrates (test method: *Daphnia magna* reproduction test, EU C.20/OECD TG 211) using the analogue substance triethoxy(octyl)silane (CAS 2943-75-1; EC 220-941-2) is rejected according to Article 40(3)(d) of the REACH Regulation.

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

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

Regarding the standard information requirement for Annex IX, Sections 9.1.6. of the REACH Regulation, you have provided the following justification: "*Testing for long-term toxicity to fish is not considered necessary because: In accordance with Column 2 of REACH Annex IX,*

there is no need to further investigate the effects of this substance in a long-term aquatic toxicity to fish study because, as indicated in guidance R.7.8.4.3 (ECHA 2016), the quantitative chemical safety assessment (conducted according to Annex I of REACH) indicates that the Risk Characterisation Ratio is well below 1, and therefore the risk is already adequately controlled and further testing is not justifiable. Long-term invertebrate toxicity data are available with the registered substance and have been read across from the structural analoguetrichloro(2,4,4-trimethylpentyl)silane (CAS 18379-25-4). The results from the test with trichloro(2,4,4-trimethylpentyl)silanehave been used to derive PNECs for the hydrolysis product. Due to uncertainties with the test with the registered substance, a long-term toxicity to invertebrate test proposal has been read-across from the structural analoguetriethoxyoctylsilane (CAS 2943-75-1). Results from this test will be used to derive reliable aquatic PNECs for the registered parent substance because there is no indication that fish would be significantly more sensitive than invertebrates, as indicated by the short-term data. A PNEC has been derived for the purpose of chemical safety assessment. An assessment factor of 50 was applied to derive the freshwater PNEC, based on long-term invertebrate data. For a narcotic chemical without a specific mode of toxic action, it is unlikely that the aquatic PNEC would be significantly over-estimated using this method. Overall it is concluded that the risk characterisation conclusion is sufficiently conservative in respect of any uncertainties and therefore further in vivo testing is not considered necessary or justified on ethical grounds. Details on how the PNEC and the risk characterisation ratio have been derived can be found in IUCLID Section 6.0 and Chapters 9 and 10 of the Chemical Safety Report, respectively."

ECHA considers that your justification is not conclusive to indicate that there are no risks to the aquatic compartment, as explained below. In consequence, there is a need to provide information on Long-term toxicity to fish.

Firstly, you state that the current PNEC derivation is based on the results from the test with trichloro(2,4,4-trimethylpentyl)silane, where the test solution you assumed to contain primarily the hydrolysis product of the substance due to its fast hydrolysis. However, in your CSR section 7 you indicate to use the parent substance as a basis of the hazard assessment. For this reason, ECHA considers that the study with trichloro(2,4,4-trimethylpentyl)silane, or mainly of its hydrolysis products, is not appropriate to provide information on the hazards of the registered substance as described in request 2.

Secondly, you argue that the OECD 211 Daphnia long-term study to be conducted will provide further evidence on chronic toxicity and the results from this test will be used to derive reliable aquatic PNECs for the registered parent substance because there is no indication that fish would be significantly more sensitive than invertebrates, as indicated by the short-term data. ECHA understands that by this you consider possibility to adapt the long-term testing on fish based on results from invertebrates, and hence to apply the aquatic Integrated Testing Strategy (ITS) given in ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017, Section R.7.8.5.3.). ECHA however notes that in order to apply the ITS you would need to predict relative differences (or lack of) in species sensitivity in order to provide evidence that the risks for fish are not underestimated by the data on aquatic invertebrates. However, as you have not provided sufficient data to compare the relative species sensitivity for the registered substance, as described further below, the aquatic ITS (ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), Section R.7.8.5.3.) is not applicable and it is necessary to provide long-term data on both aquatic invertebrates and on fish.

Specifically, for the derivation of the PNECaquatic, data on three trophic levels (aquatic invertebrates, fish and aquatic plants) is required (ECHA Guidance on information requirements and chemical safety assessment, version 4.0, June 2017, Chapter R7b, Section R.7.8.5.3). ECHA notes that Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble (e.g. water solubility below 1 mg/L or below the detection limit of the analytical method of the test substance based on ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), Section R.7.8.5.). This is indeed applicable to the registered substance, due to its low water solubility and due to absence of reliable short-term data that may reveal any indication of differences in sensitivity. Therefore, in this case long-term data for the three trophic levels are required to accurately assess the effects of the registered, substance on aquatic organisms.

Thirdly, you argue that no risks are indicated in the chemical safety assessment as all the RCR's are below 1. However, according to the ECHA Guidance on information requirements and chemical safety assessment (Version 4., June 2017), Chapter R7b, page 32, the need to conduct long-term aquatic toxicity testing may be triggered e.g. when due to low water solubility of a substance, short term toxicity tests do not reveal any toxicity. Poorly soluble substances require longer time to be significantly taken up by the test organisms and consequently steady state conditions are likely not to be reached within the duration of a short-term toxicity test. The absence of toxicity observed in the short-term tests with the registered substance having a low water solubility cannot, therefore, be used as an argument for adaptation of long-term tests. The available aquatic short-term data and the risk characterisation based on short-term data alone does hence not allow to conclude on aquatic toxicity.

Therefore, there is a data gap and you are requested to perform a long-term toxicity test on fish, with the registered substance.

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

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b, Section R.7.8.4.1.

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

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following test using the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: Fish, early-life stage toxicity test, OECD TG 210).

Notes for your consideration for requests 2. and 3.

ECHA notes that as the registered substance may be difficult to test, 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, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test. As you have indicated to use the parent substance in your hazard assessment, ECHA points out that a preliminary stability study as per ENV/JM/MONO (2000)6 should be performed and documented. Based on the results of the preliminary test, test conditions which result in highest stability of the hydrolytically unstable and poorly soluble test item should be used for ecotoxicity testing. The test conditions may cover daily water renewal and using solvents rather than direct addition with long stirring times, if those methods ensure the parent substance stability. ECHA agrees that analytical verification of the test item in the solution is essential to verify the reliability of the test results for such a difficult subtance to test. It is your responsibility to design the test in such a way that the effects on aquatic organisms are adequately assessed.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 30 September 2015.

ECHA held a third party consultation for the testing proposals from 28 February 2018 until 16 April 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **25 July 2018**, 30 calendar days after the end of the commenting period.

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 did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and did not modify 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 during its MSC-62 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.