EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114428342-57-01/F
Substance name: triethoxyoctylsilane
EC number: 220-941-2
CAS number: 2943-75-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26.06.2017
Registered tonnage band: 1000+T

DECISION ON YOUR TESTING PROPOSAL

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

Your testing proposal is accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance;**
2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./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 some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**
3. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) using the registered substance.**

You are additionally requested to perform:

4. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) 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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***26 July 2021***, except for the information requested under point 1 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **26 July 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 2 after **28 October 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

In relation to the testing proposal subject to the present decision, ECHA notes the followings.

In the preceding dossier with the submission number [redacted] you proposed a testing strategy intending to fulfil the standard information requirement for

- a Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) and
- an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443).

In your testing strategy you proposed to test the analogue substance triethoxy(2,4,4-trimethylpentyl)silane (CAS No 35435-21-3, EC No No 252-558-1). The results from the structural analogue(s) will then be used to adapt the standard information requirements by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation.

ECHA has considered the scientific validity of the proposed read-across and grouping approach and assessed the testing proposed.

ECHA concluded that you did not provide adequate and reliable information to demonstrate that the proposed read-across approach is plausible for the endpoint in consideration. Consequently the testing proposed on the read-across substance(s) was not considered to be appropriate to fulfil the information requirement(s). ECHA requested you to perform

- a Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rat, using the registered substance and
- an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route, using the registered substance, specified as follows:
  - Ten weeks premating exposure duration for the parental (P0) generation;
  - Dose level setting shall aim to induce some toxicity at the highest dose level;
  - Cohort 1A (Reproductive toxicity);
  - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;
  - Cohorts 2A and 2B (Developmental neurotoxicity).

The major reasons for rejecting your read-across approach as proposed in the dossier with the submission number [redacted] are briefly summarised below. Based on the provided data, the read-across hypothesis and justification ECHA concluded that you did not sufficiently demonstrated,

- that structural similarity as well as physico-chemical and basic toxicological parameters are in the same range;
- that the hydrolysis of the target and source substances is both rapid and complete, leading to the formation of similar silanol hydrolysis products (i.e. octylsilanetriol and 2,4,4-trimethylpentyl silanetriol) which differ in the structure of the octyl group attached to the Si atom;
- and that the formed silanol substances were exclusively relevant in terms of bioavailability, hence would drive the systemic toxicity and possessing similar toxicological profile.

After receiving the draft decision you updated your registration. The current decision of ECHA is based on the examination of the testing proposal submitted by you in the updated dossier with the submission number [redacted] for the registered substance triethoxyoctylsilane (EC No 220-941-2; CAS No 2943-75-1).

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

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.

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. 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 a sub-chronic toxicity study (90 day) in rats, by the oral route according to EU B.26./OECD TG 408 with the registered substancetriethoxyoctylsilane (EC No 220-941-2; CAS No 2943-75-1). 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 proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route is low (maximum [redacted] mg/m^3). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

You proposed testing in rats. According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408).

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

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* R.7a, chapter R.7.6 (version 6, 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 EU B.56./OECD TG 443 by the oral route in rats, to be performed with the registered substance.

ECHA notes that in the updated dossier you provided your considerations for alternative methods to fulfil the information requirement for an extended one-generation reproductive toxicity study according to EU B.56./OECD TG 443, by the oral route in rats. You concluded that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA notes that you have not provided any justification and specification of the cohorts. ECHA therefore concludes that you have submitted a testing proposal for the basic study design according to column 1 of Section 8.7.3., Annex X. ECHA considers that based on the currently available information this basic study design requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. 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.

In your comments to the draft decision you submitted your consideration on the study design of the requested extended one-generation reproductive toxicity study (premating exposure duration, dose level setting, extension of Cohort 1B (Reproductive toxicity), and on the inclusion of the Cohorts 2A and 2B (Developmental neurotoxicity). ECHA has taken these considerations into account and these are shortly addressed under the related sections/paragraphs.

Information from studies to be conducted before the extended-one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among to other

relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6, July 2017).
The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6, July 2017). In this specific case ten weeks exposure duration is supported by the lipophilicity of the substance (Log Kow: 6.41) to ensure that the steady state in parental animals has been reached before mating.

In your comments to the draft decision 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.

In your opinion, although the substance has high log Kow (Log Kow=6.41) due to its hydrolytic instability *i.e.* rapid hydrolysis under physiological condition, exposure mainly to the less lipophilic silanol hydrolysis product (predicted log Kow of 1.1) will occur. ECHA observes that the hydrolysis studies (according to OECD TG 111) were not conducted on the registered substance but on a fast hydrolyzing chlorosilane (trichloro(methyl)silane CAS No 75-79-6, EC No 200-902-6). Furthermore, the predicted hydrolysis properties under acidic conditions of the gastric environment are based on an unsubstantiated postulation of dependence of hydronium ion concentration as no evidence was 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.

ECHA considers that the available information support the lipophilicity of the substance and ten weeks premating exposure duration is needed to ensure that the steady state is reached before the mating of the P0 generation adults.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

In your comments to the draft decision you consider that *"dose setting for the EOGRTS*

should not be driven by toxicity, but by toxicokinetic behavior if such information is available and indicates nonlinearity, and if the inflection point is well above human exposure levels." You refer to the OECD TG 443, scientific literature (Slikkers 2004b, Creton 2012), ECHA guidance documents on REACH (R7a and R7c) and the CLP regulation.

As explained in ECHA *Guidance on information requirements and chemical safety assessments* R.7a, chapter 7.6, the dose level setting for the EOGRTS should be based on toxicity. Only if the dose level selection is based on toxicity, it is possible to conclude whether the systemic toxicity or the reproductive toxicity occurs at lower dose levels (which one is more sensitive). This is necessary to understand the relationship between the reproductive toxicity and systemic toxicity in order to get adequate information for hazard classification.

Furthermore, toxicokinetics in rats may not adequately reflect the toxicokinetics in humans. The inflection point may be different in humans vs rats due to different causes and may occur at different dose levels. However, ECHA considers that toxicokinetic information is useful in interpreting the results but should not be used in setting the dose levels in reproductive toxicity studies.

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.

ECHA observes that the use of the registered substance is leading to significant exposure of consumers and professionals because the registered substance is used by professionals as masonry treatment products, for coating and sealing, in dry mix applications and as laboratory chemicals (PROCs 7, 10 and 15); the registered substance is used by consumers as masonry treatment products, for coating and sealing and in dry mix applications, leading to wide dispersive indoor and outdoor use resulting in inclusion into or onto a matrix.

Furthermore, there are indications for endocrine-disrupting modes of action in the available toxicological studies. In the provided combined repeated dose toxicity with reproduction developmental toxicity screening test via oral route (OECD TG 422, [redacted] (2010)) *"Increased post-implantation loss, prolonged gestation duration and dystocia"* were observed. Dystocia linked to prolonged gestation duration indicates (a) mode(s) of action related to endocrine disruption. This is also supported by increased post-implantation loss which may be linked to endocrine disrupting mechanisms.In addition, a statistically significantly decrease in the absolute ovarian weight in the middle dose and the high dose group females further points towards endocrine disrupting modes of action.

In your comments on the draft decision you consider the above findings as secondary to overt toxicity or within historical control data. You refer to the 29% reduction of body weight gain over gestation, severe clinical/neurological signs and signs of stress. However, ECHA considers that you do not provide convincing justification why and how postimplantation loss, prolonged gestation duration and dystocia are secondary to systemic toxicity and these findings and decreased ovarisn weight do not represent indications of modes of action related to endocrine dusruption.

Furthermore, the properties of the registered substance indicate a (bio)accumulative potential, as the substance is lipophilic (Log Kow: 6.41).

ECHA responded to your comments regarding lipophilicity already in the context of premating exposure duration.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and there are indications of one or more relevant modes of action related to endocrine disruption in an *in vivo* study (OECD TG 422, [redacted] (2010)). Furthermore, there are indications that the internal dose for the registered substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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.

ECHA notes that existing information on the registered substance itself derived from available *in vivo* studies (OECD TG 422, [redacted] (2010)) show 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".*

You agree to add Cohorts 2A and 2B. ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56./ 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./ 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 some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;
  Cohorts 2A and 2B (Developmental neurotoxicity).

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.

Currently, the inclusion of Cohort 3 (developmental immunotoxicity) is not requested. However, the sub-chronic toxicity study (90-day) requested in this decision and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by the 12-month deadline indicated in this decision. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)), as indicated in this decision, of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by the expiry of three months following the 12-month deadline for providing the results of the sub-chronic toxicity study (90-day), the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision.

Note for your considerations:

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017)).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented.

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

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

"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 endpoint study records under IUCLID section 6.1.4 on analogue substances Triethoxy(2,4,4-trimethylpentyl)silane (EC No 252-558-1, CAS No 35435-21-3) and trichloro(2,4,4-trimethylpentyl)silane (EC No 242-262-0, CAS No 18379-25-4), and QSAR data for the registered substance. Under the endpoint summary in section 6.1.4 of IUCLID technical dossier you provide the following discussion about the current endpoint: "*The read-across to the registered substance is considered scientifically justified;. It is likely that the test organisms in the above studies were predominantly exposed to the hydrolysis products of the substances. These results indicate that the silanol hydrolysis product of the registered substance has low long-term toxicity to aquatic invertebrates and would not cause toxic effects at concentrations that correspond with the solubility limit of the registered substance.*

An estimated ChV value of 0.005 mg/l with triethoxysilane has been derived using the neutral organics predictions in ECOSAR (v.1.11) for the long-term effects of the substance to invertebrates. The data represent an indicative assessment because the QSAR is not fully validated."

Furthermore, ECHA notes that you consider the read-across data to indicate that the "*silanol hydrolysis product of the registered substance has low long-term toxicity to aquatic invertebrates and would not cause toxic effects at concentrations that correspond with the solubility limit of the registered substance".* At the same time you indicate that in the study on Triethoxy(2,4,4-trimethylpentyl)silane (EC No 252-558-1, CAS No 35435-21-3) "*the hydrolysis product was not analysed for in solution and it is not possible to determine whether the observed effects are due to the parent compound, the hydrolysis product or the presence of undissolved test material*". You state further that "*the results of the study should be treated with caution but have nevertheless been used for risk characterisation purposes*." For the study on trichloro(2,4,4-trimethylpentyl)silane (EC No 242-262-0, CAS No 18379-25-4), you note that "*it cannot be excluded that the effects of the test item were at least partly caused by undissolved test item, which could not be removed by the preparation method used during the test period*". Hence, ECHA understands that, as indicated by you, both read-across studies have some stated inconsistencies and should be treated with caution.

Finally, for this endpoint an estimated ChV value of 0.005 mg/l has been derived using the neutral organics predictions in ECOSAR (v.1.11). About this QSAR prediction you state that

"*The data represent an indicative assessment because the QSAR is not fully validated*". ECHA notes that the QSAR prediction does not fulfil the requirements of REACH Annex XI, 1.3 because the substance does not fall within the applicability domain of the QSAR model. The "ECOSAR neutral organics Daphnid ChV" model has been developed with a small dataset and the closest analogue to Triethoxyoctylsilane available in this dataset is Octamethylcyclotetrasiloxane, which is still significantly different from the registered substance.

On the above basis ECHA concludes that you provided the mentioned study reports only for completeness reasons and that there is no adequate information present in the technical dossier on long-term toxicity to *Daphnia* of the registered substance.

Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates *Daphnia magna* reproduction test, OECD TG 211 with the following justification: "*Long-term toxicity testing with Daphnia magna is proposed, in order to assess the aquatic ecotoxicity hazard and derive reliable PNECaquatic values for the registered substance*".

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

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 more sensitive than aquatic invertebrates. ECHA notes that in the short-term aquatic studies no effects were observed. However, 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 <0.13 - 0.79 mg/l. ECHA hence considers that 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)(a) of the REACH Regulation, you are requested to carry out the proposed 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).

4. 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 other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"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: "*In accordance with Column 2 of REACH Annex IX, the long-term aquatic toxicity to fish study (required in Section 9.1.6 of REACH Annex IX) does not need to be conducted as the chemical safety assessment according to Annex I indicates that this is not necessary.*"

Under the endpoint summary in section 6.1.2 of IUCLID technical dossier you provide the following discussion about the current endpoint: "*No data are available describing the long-term toxicity of the registered substance to fish. Testing is not considered necessary for the following reasons:*

In accordance with Column 2 of REACH Annex X, 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 below 1 and therefore the risk is already adequately controlled and further testing is not justifiable.

Based on the short-term aquatic data set, no effects were seen in any trophic level at the limit of solubility of the substance.

Long-term invertebrate toxicity tests have been read across from structural analogues. The results from these tests have been used to derive PNECs. Due to uncertainties with these tests, a long-term toxicity to invertebrate test has been proposed with the registered substance. Results from this test will be used to derive reliable aquatic PNECs because there is no indication that fish would be significantly more sensitive than invertebrates, as indicated by the short-term data and the long-term QSARs.

An estimated ChV value of 0.004 mg/l with triethoxyoctylsilane has been derived using the neutral organics predictions in ECOSAR (v.1.11) for the long-term effects of the substance on fish. The data represent an indicative assessment because the QSAR is not fully validated."

Firstly, you argue that no risks are indicated in the chemical safety assessment as all the RCR's are below 1 and no effects were observed in the available short-term studies. However, according to the ECHA Guidance on information requirements and chemical safety assessment (Version 4., June 2017), Chapter R.7b, 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.

Secondly, you argue that the OECD 211 Daphnia long-term study to be conducted will provide further evidence on chronic toxicity. 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 $PNEC_{aquatic}$, 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. 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.

Lastly, similarly to long-term toxicity testing on aquatic invertebrates (request 3. above), you have also submitted an ECOSAR (v.1.11) QSAR prediction for this endpoint. For the same reasons as set out in request 3. above the QSAR made for this endpoint can not be accepted.

In your comments on the Member State Competent Authority Proposal for Amendment (PfA) you indicated that based on analysis of results of the long-term *Daphnia* study already completed you would determine whether it is necessary to conduct a long-term fish study. However, ECHA points out that as fully discussed above the aquatic ITS given in ECHA Guidance is not applicable in this case as based on the acute aquatic studies it is not possible to assess the relative sensitivities of invertebrates and fish. Long-term testing of both invertebarets and fish is hence required as fully reasoned in the paragraphs above.

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

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 proposed 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 3. and 4.

In the endpoint study record of the testing proposal of long-term toxicity testing on aquatic invertebrates you have discussed that the registered substance is difficult to test due to its low water solubility and "*moderate rate of hydrolysis in aqueous media (t1/2 30 h at pH 7 at 25°C) with a weakly surface active silanetriol hydrolysis product*". Furthermore, you have indicated that the "*preparation of test media and conduct of the study must be done appropriately, observing the guidance for testing of difficult substances, and must be well-supported by robust analytical verification techniques*". 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 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. Furthermore, ECHA notes that if the registered substance is likely to be unstable, a decision to test the parent substance and/or its possibly identified degradation products should be based on a consideration of the half-life of the substance under test and real-world conditions. It is your responsibility to design the test in such a way that the effects on aquatic invertebrates are adequately assessed.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination pursuant to Article 40(1) on 26 May 2014.

ECHA held a third party consultation for the testing proposals from 17 April 2015 until 4 June 2015. ECHA did not receive information from third parties.

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

You were notified that the draft decision does not take into account any updates after 06 July 2016. However, following your request and justification provided (including interlinked read-across testing strategy on several supposedly related registered substances) ECHA has exceptionally granted you additional time until 30 June 2017 for the update for the update of the IUCLID dossier.

You updated your registration on 26 June 2017. Additionally, you updated the dossier after the time given for updating the dossier has elapsed, hence ECHA did not take this update into account. ECHA took into account the information in the updated registration, submitted on 26 June 2017 with submission number [redacted], and amended the draft decision.

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.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-60 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 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

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