EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114426304-59-01/F
Substance name: triethoxy(phenyl)silane
EC number: 212-305-8
CAS number: 780-69-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26.06.2017
Registered tonnage band: 100-1000T

DECISION A 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.

While your originally proposed test for

- **a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a rat, oral route using the analogue substance trimethoxy(phenyl)silane (CAS no 2996-92-1, EC no 221-066-9)**

is rejected, you are requested to perform:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route 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 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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

The decision of ECHA is based on the examination of the testing proposal submitted by you for the registered substance triethoxy(phenyl)silane, CAS No 780-69-8 (EC No 212-305-8) (hereafter referred to as "target substance"), taking into account the updated dossier with the submission number [redacted].

In relation to the testing proposal subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirement for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.). In your testing strategy you propose to test the analogue substance trimethoxy(phenyl)silane (CAS no 2996-92-1, EC no 221-066-9; hereafter referred to as "source substance") and to use the results to adapt this standard information requirement 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 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 at 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

In your former registration dossier with the submission number [redacted], which was the basis for the initial draft decision, you have provided the following arguments to justify the read-across approach:

"Within the aryl alkoxysilanes analogue group, in which triethoxy(phenyl)silane belongs, trimethoxy(phenyl)silane (CAS 2996-92-1) has been selected as the most appropriate and representative member of the analogue group because of its structural features or chemical functional groups (alkoxysilane moiety and aryl moiety), and will therefore be used for the

proposed test (For Details refer to the testing proposal justification attached to this study record)."
"Read-across hypothesis
After oral and inhalative application, both triethoxy(phenyl)silane (CAS 780-69-8) and trimethoxy(phenyl)silane (CAS 2996-92-1) hydrolyse rapidly to the same silanol hydrolysis product, phenylsilanetriol. The non-silanol hydrolysis products, ethanol and methanol, are not expected to contribute to any adverse effects for systemic or reproductive toxicity at the relevant dose levels. This is discussed further below.
The predicted half-lives of triethoxy(phenyl)silane (CAS 780-69-8) and trimethoxy(phenyl)silane (CAS 2996-92-1) at 20-25°C and at pH 7 are 1.5 and 0.4 h, respectively, (see Section 5.1.2). As the hydrolysis reaction may be acid or base catalysed, the rate of reaction is expected to be slowest at pH 7 and increase as the pH is raised or lowered.
Reaction rate increases with temperature therefore hydrolysis will be faster at physiologically relevant temperatures compared to standard laboratory conditions. Under ideal conditions, hydrolysis rate can be recalculated according to the equation:
DT50(X°C) = DT50(T) x e(0.08 (T-X))
Where T = temperature for which data are available and X = target temperature.
Thus, for triethoxy(phenyl)silane (CAS 780-69-8) the hydrolysis half-life at 37.5°C and pH 7 (relevant for lungs and blood) is 22.2 min.
For the read-across substance, trimethoxy(phenyl)silane (CAS 2996-92-1), the corresponding half-life is approximately 5.9 min."

and

"The basis of the read across is the hydrolytic stability and relevance of the silanetriol hydrolysis products".

In your updated registration with the submission number [redacted] you have restructured your arguments, however the main hypothesis remains (in the updated CSR document in chapter 1.4):

"The basis of the read across is the hydrolytic stability and relevance of the silanetriol hydrolysis products".

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

In your updated registration dossier you have provided as separate attachments in IUCLID, Section 13, updated versions of the initially submitted documents, relevant to the testing proposed:

[redacted]

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.

The attachments [redacted] do not provide information on the read-across approach used for the endpoint subject of the current decision.

Apart from the above general information you have provided the substance specific read-across hypothesis and justification, in the Chemical Safety Report (CSR) in section 5. This information includes the read-across hypothesis and justification, the identification of the source and target substances; discussion on the repeated systemic toxicity of the non-silanol hydrolysis products and a conclusion on your read-across approach.

In addition you have provided in the technical dossier of the target substance the following toxicological studies.

For the target substance:

- Ames test (OECD 471, GLP, [redacted] (2002));
- *In vitro* mammalian chromose aberration test (OECD 473, GLP, [redacted] (2012));
- an acute oral toxicity study (Carpenter C.P, Weil C.S & Smyth H.F. (1974) and Smyth H.F, Carpenter C.P, Weil C.S & Pozzani U.C (1954));
- an acute dermal toxicity study (OECD 402, [redacted] (1972) and Carpenter CP; Weil CS; Smyth HF Jr (1974)).

For the source substance:

- results of a combined repeated dose toxicity with reproduction / developmental toxicity screening test via oral route (OECD 422, GLP, [redacted] 2009);
- results of a repeated dose inhalation toxicity study, 28/14-Day (OECD 412; [redacted] (1980));
- results of a repeated dose inhalation toxicity study, 28/14-Day (OECD 412; [redacted] (1981)).

No new information has been provided in your updated dossier.

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 aryl 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 trimethoxy(phenyl)silane (CAS no 2996-92-1, EC no 221-066-9) as a source substance.

According to ECHA's understanding in your initial read-across hypothesis as per dossier with the submission number [redacted] you suggest that based on their structural similarities target and source substances have similar properties:

- target and source substances undergo similar hydrolysis process and as a result the same silanol hydrolysis product is formed;
- 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;
- and hence the toxicological properties of the substances would be similar.

ECHA also understands that the basis of your hypothesis is the postulation

- that the hydrolysis of the parent substances is both rapid and complete, leading to the formation of the proposed same silanol hydrolysis product (phenylsilanetriol);
- and that the formed silanol substance is exclusively relevant in terms of bioavailability and hence would drive the systemic toxicity.

In addition, you claim that the non-silanol hydrolysis products do not contribute to any adverse effects for the systemic or reproductive toxicity.

In your updated dossier with the submission number [redacted] you updated your read-across and grouping approach. According to ECHA's understanding now you claim that based on their structural similarities and physico-chemical properties,target and source substances would have similar toxicological properties relevant to pre-natal developmental toxicity, and the source substance would represent a conservative estimate of the possible hazard.

ECHA observes also that you have removed from the pre-natal developmental toxicity endpoint your hypothesis on fast and complete hydrolysis. However, still your read-across hypothesis relies on *"the hydrolytic stability and relevance of the silanetriol hydrolysis products".*
Moreover from your documentation it appears that your assumption of a fast and complete hydrolysis is still part of your overall assessment of the registered substance's properties, as it is still part of your consideration describing the intrinsic properties of the target substance *i.e.* description of the hydrolysis properties of the target substance.
Additionally ECHA notes that the hypothesis of a fast and complete hydrolysis is still part of your read-across approach for other endpoints such as irritation and repeated dose toxicity.

In the following, ECHA examines whether the substances have indeed similar properties or that they would follow a regular pattern in their properties, before assessing the scientific validity of your postulation regarding the formation, relevance and exclusivity of the proposed silanol hydrolysis products as the driver for the systemic toxicity of the parent substances.

(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 the source substance has solely been characterised by its chemical name and CAS No and no information on the composition or impurities has been provided in the technical dossier of the target substance.
In the read-across justification document [redacted] you state *that "Detailed information on the purity/impurity profiles of substances in the analogue group is not described in detail in this report for reasons of commercial confidentiality. Substance-specific Substance Identity Profiles are available for all registered substances and these are included in the appropriate technical dossiers. In general, the substances in this group are typically monoconstituent substances of high purity (>90%) and typical impurities are other alkoxysilanes, alcohols or closely related substances. The specific identity of any impurities would not impact upon the approaches or conclusions for the endpoints covered by this report. In any case where a classified impurity is identified, the implications of this will be described in the individual Chemical Safety Report(s)."*

ECHA notes that the above presented information is not sufficient, for the following reasons. Firstly, it is not supported by substance specific analysis of the possible differences in the composition and impurity profiles of the source and target substances and the impact they may have on the proposed prediction.

Secondly, ECHA notes that you have not clearly identified to which 'appropriate technical dossiers' you are referring to, in case of the source substance, which prevents ECHA from assessing the relevant data contained therein.

Finally, as already indicated by you, commercial confidentiality is at stake – which may also prevent ECHA from discussing with you the implications of potential substances' differences if it would be based solely on the data present in another registrant's dossier.

ECHA considers that currently the composition and the impurity profile of the source and target substances cannot be compared using the information provided in the registration dossier. Therefore, ECHA cannot reach conclusion whether the source substance can be used to predict properties for the registered substance.

(ii) Structural (dis)similarities and their impact on prediction

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.

In your initial read-across and grouping approach you have described the structural similarities between target and source substances by indicating that they both contain *"a silicon moiety and three alkoxy (-OX) groups"*. ECHA notes that in addition to the structural similarities, structural difference can be observed in the size of the alkoxy group. Whereas the source substance contains three methoxy (-OMe) groups, the target substance contains three ethoxy (-OEt) groups bound to the Si (silicon) atom.

ECHA observed, that you have clearly identified the structural basis for the prediction, *i.e.* you postulate that both the source substance and the target substance hydrolyse, forming the same silanol hydrolysis product, phenylsilanetriol. However, ECHA noted that you have not provided any information on how the structural similarities and differences in the parent 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.

In your updated read-across and grouping approach as presented in the current CSR document you have described the structural similarities between target and source substances by indicating that they both have *"all relevant structural features or chemical functional groups serving as analogue substance"*. ECHA notes that in addition to the structural similarities, structural difference can be observed in the size of the alkoxy group. Whereas the source substance contains three methoxy (-OMe) groups, the target substance contains three ethoxy (-OEt) groups bound to the Si (silicon) atom.

You propose to base your prediction on the structural similarity of the target and source substances, however ECHA notes that you do not elaborate on how the structural similarities and differences in the parent 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.

ECHA notes that structural similarity alone is not sufficient for predicting toxicological properties related to human health. The provided explanation is therefore not sufficient to establish a scientifically credible link between the structural similarity and the prediction.

(iii) Similar 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.

In your initial read-across justification you state that physico-chemical parameters/properties of target and source substances are *"in the same range"*. You have proposed that the similar physico-chemical properties of the target and source substances support the structural similarity and enable the read-across between the substances.

ECHA observed that the physico-chemical properties of target and source substances are in the same range except the water solubility of the parent substances. Comparison of the water solubility of the parent (source and target) compounds reveals that the water solubility of the source substance is approximately 30 fold higher as that of the target substance. ECHA notes that you have not explained how the presented difference affects the prediction.

In your updated, endpoint specific read-across justification for pre-natal developmental toxicity, you do not provide comparison of the physico-chemical parameters/properties of the target and source substances. ECHA notes that in the CSR document in section 5.6.3, the endpoint specific read-across justification for repeated dose toxicity and the IUCLID

dossier of the target substance contains comparison of the physico-chemical parameters/properties of target and source substances and ECHA took this into account.

ECHA observes that the physico-chemical properties of target and source substances are broadly in the same range, however the water solubility and the vapour pressure of the parent substances are diverging. Comparison of the water solubility and the vapour pressure of the parent (source and target) compounds reveals that the water solubility of the source substance is approximately 30 fold higher as that of the target substance and the vapour pressure of the source substance is about 100 fold higher than of the target substance, using the values reported for the target substance, in the target substance's IUCLID dossier. ECHA notes that you have not explained how the presented difference affects the prediction.

In your initial read-across justification, under the point *"Similar toxicokinetics"* you claim that *"Given the low vapour pressures of both triethoxy(phenyl)silane (CAS 780-69-8) and trimethoxy(phenyl)silane (CAS 2996-92-1), significant inhalation exposure would be expected to neither one. It is therefore considered appropriate to read-across the repeated inhalation toxicity data from"* source substance to the target substance and *"In view of the rapid hydrolysis following oral dosing and based on the fact that the same silanol-containing product of hydrolysis is formed by both triethoxy(phenyl)silane (CAS 780-69-8) and trimethoxy(phenyl)silane (CAS 2996-92-1), it is considered appropriate to read-across the available oral data from trimethoxy(phenyl)silane (CAS 2996-92-1) to triethoxy(phenyl)silane (CAS 780-69-8)."* ECHA notes that in the absence of toxicokinetics studies for the target and source substances, you have provided toxicokinetic predictions/assessments which are based on the physico-chemical properties of the substances themselves and/or their hydrolysis products. ECHA observes that your toxicokinetic predictions rely upon the assumed rapid and complete hydrolysis of the target and source substances to the proposed silanol hydrolysis product phenylsilanetriol. However, as pointed out in the (iv) section of the current decision, there is no evidence supporting your assumption of the formation, presence and stability of the proposed silanol hydrolysis products. Hence the predicted toxicokinetic profile of the target and source substance cannot be considered as valid, as it is based on scientifically unconfirmed assumptions.

ECHA considers that your initial claim of similar toxicity profiles of the source and target substances as a result of similar toxicokinetic profile is not substantiated and as such does not hold.

In your updated, endpoint specific read-across justification for pre-natal developmental toxicity you do not provide consideration on the toxicokinetic profile of the substances.

In addition, ECHA notes that in your initial read-across justification there is no information on whether other metabolic pathways of the parent substances and/or its hydrolysis products would occur and thus play a role in the systemic toxicity of the substances. Therefore, it is not possible to verify your assumption that only the proposed silanol hydrolysis products are relevant to drive the toxicity profiles of source and target substances.
In your updated CSR in chapter 5.1.3 you propose that due to the fast hydrolysis of the parent substance and *"Due to the high water solubility no further metabolism is expected."* ECHA observes that your hypothesis of a fast hydrolysis is still not substantiated, as explained in details in Section 0, title d, heading (iv), below. In addition it is not clear

whether your statement as cited above refers to the parent substance or the hydrolysis products, hence it cannot be interpreted.

Therefore, it is not possible to verify your assumption that *"read-across of long-term mammalian toxicity data between the phenylsilanes could be robustly supported using RAAF scenario 2".*

ECHA notes that the dossier contains an acute oral toxicity study (Carpenter C.P, Weil C.S & Smyth H.F. (1974) and Smyth H.F, Carpenter C.P, Weil C.S & Pozzani U.C (1954)) and an acute demal toxicity study (OECD 402, [redacted] (1972) and Carpenter CP; Weil CS; Smyth HF Jr (1974)) with the target substance as well as the results of an acute oral toxicity study, results of repeated dose toxicity studies (OECD 412) via inhalation and a combined repeated dose toxicity with reproduction / developmental toxicity screening test via oral route (OECD 422, GLP, [redacted] 2009) for the source substance.
No new toxicological studies, relevant for human health has been provided in the updated dossier.

ECHA notes that acute toxicity data alone is not sufficient to establish the toxicological profile of a substance with regard to reproductive toxicity. As a higher tier study, e.g. screening study, is still not available for the target substance comparison of toxicological profiles of the substances is still not possible.

ECHA also notes that due to these lacking information your claim that the source substance would represent *"the worst-case in respect of the effects observed in available studies"* or *"can be seen as a conservative estimate"* is not substantiated by data and hence cannot be confirmed.

Therefore ECHA concludes that based on the presented information it is not possible to confirm that the substances would have similar properties or they would follow a regular pattern in their properties. In the absence of such information there is not an adequate basis for predicting the properties of the target substance from the data obtained with the source substance.

(iv) Hypothesis on formation, relevance and "exclusivity" of the silanol hydrolysis products, driving the toxicity

ECHA understands that your initial hypothesis as per dossier with submission number [redacted] relies on the assumption that both target and source substances undergo rapid and complete hydrolysis at pH 2 (within seconds) and they form the same silanol hydrolysis product phenylsilanetriol. You propose that based on the formation and relevance of the same silanol hydrolysis product, properties of the source substance can be used to predict the properties of the target substance and: *"The basis of the read across is the hydrolytic stability and relevance of the silanetriol hydrolysis products".*

Firstly, ECHA observes that hydrolysis half-life rate at pH 2 is based on assumptions which are not substantiated by data. You postulate that for the target substance *"the calculated half-life at pH 2 and 37.5 °C is 5 s"* and for the source substance *"a calculated half-life of 5 sec."* under the same conditions. ECHA notes that there is no hydrolysis data available in the registration dossier for pH 2 (neither for the target nor for the source substance) but instead 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, ECHA considers that the formation of the proposed silanol hydrolysis products which are the basis of the hypothesis is not supported by data. Specifically, ECHA notes that the formation of the proposed silanol hydrolysis product from both the source and target substances would involve three hydrolysis steps. In the hydrolysis studies provided in the registration dossier there is no evidence of the formation of the proposed silanol hydrolysis product so it is not possible to verify that ultimate hydrolysis of both target and source substances has indeed occurred within the timeframe of the test.

Furthermore, you have not substantiated your assumption of a complete hydrolysis. In fact, the hydrolysis process which involves several steps may produce also other substances, which possible presence and effects on your hypothesis you have not addressed.

Thirdly, your assumption that the silanols are exclusively relevant in terms of bioavailability and hence would drive the systemic toxicity is not supported by data. In fact you acknowledge the occurrence of condensation reaction following the hydrolysis of the parent substances but you did not consider the implication of such reaction on the prediction.

You explain that the silanol hydrolysis products may undergo condensation reactions leading to the formation of siloxane dimers, oligomers and polymers and state that:
"A highly cross-linked gel may form. The degree of condensation that will occur may vary with:

- *Concentration of the silanol; the greater the initial concentration, the greater the degree of condensation. Significant condensation is not expected at concentrations less than approximately 100 mg/l, but is dependent on specific conditions.*
- *pH;the condensation reaction may be either acid or base catalysed.*
- *Temperature".*

Moreover, ECHA observes that the degree of condensation also depends on the:

- Timescale;
- The nature of the R-group; and
- The number of Si-OH groups will have impact on the condensation reaction; (e.g. silanetriols condense more rapidly than silanediols).

ECHA notes that you have not specified the conditions, neither for the target nor for the source substance, under which the condensation occurs. In particular, substance specific concentration limit, specific pH, temperature and impact of the groups bound to the Si atom are not defined. In consequence, the nature of the condensation products and their rate offormation under conditions relevant to the proposed test(s) are not clear. Thus exposure to condensation products cannot be ruled out following administration of the source and target substances but you have not addressed how and in which manner the condensation products of the source and target substances would affect the systemic toxicity.

Finally, ECHA notes that you have not addressed adequately how the formation of the non-silanol hydrolysis products influences the prediction. As a result of the hydrolysis reaction non-silanol hydrolysis products are also formed: i.e. ethanol from the target substance and methanol from the source substance. You claim that the non-silanol hydrolysis products play

no significant role in the systemic toxicity of the substances as "*The non-silanol hydrolysis products, ethanol and methanol, are not expected to contribute to any adverse effects for systemic or reproductive toxicity at the relevant dose levels.*".

ECHA notes that in your read across justification you have not provided sufficient information on the "relevant dose levels". In addition, your proposal did not address the possible interactions between the parent substances and their hydrolysis products and you have not taken into consideration the implication of such reaction on the prediction.

In summary, ECHA considers that given the lacking evidence on the formation, and relevance of the proposed silanol hydrolysis products your hypothesis that only the silanols are relevant in terms of bioavailability and hence would drive the systemic toxicity cannot be confirmed.

As already noted above, in the updated dossier you still rely on the assumption of "*the hydrolytic stability and relevance of the silanetriol hydrolysis products" and* fast and complete hydrolysis. In addition, we note that you have not provided any new measured data which would support your assumption. Therefore, the shortcomings observed above are still valid.

Consequently, there is not an adequate basis for predicting the human health properties of the target substance 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.
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. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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 pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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 pre-natal developmental toxicity study according to EU B.31./OECD TG 414 in rat, via the oral route with the analogue substance trimethoxy(phenyl)silane (CAS no 2996-92-1, EC no 221-066-9).

ECHA notes that in the updated dossier you provided your considerations for alternative methods to fulfil the information requirement for Pre-natal developmental toxicity, in a first

species. 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 taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance. 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.

In addition to the testing proposal you have also submitted an intention to test the registered substance in a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test according to OECD TG 422 and to use the results for your read-across testing strategy. ECHA acknowledges your intention to perform OECD TG 422 with the registered substance. Studies conducted according to OECD TG 422 may strengthen the overall read-across approach for the endpoint under consideration as long as comparison of toxicological profiles between target and source substances is possible. However, the results may or may not confirm your hypothesis. ECHA considers that it is at your discretion to perform an OECD TG 422, as mentioned above.

ECHA considers that a pre-natal developmental toxicity study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species

You proposed testing by the oral route.

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.

In your comments to the draft decision you did not provide considerations to the specific endpoint, subject to the current decision.

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: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414) while your originally proposed test for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a rat, oral route using the analogue substance trimethoxy(phenyl)silane (CAS no 2996-92-1, EC no 221-066-9) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

ECHA notes that a revised version of OECD TG 414 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).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 30 April 2015.

ECHA held a third party consultation for the testing proposal from 25 June 2015 until 10 August 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:

ECHA notified you of the draft decision and invited you to provide comments. In your comments to the draft decision you did not provide specific considerations to the endpoint subject to the current decision.

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.

You updated your registration on 26 June 2017. ECHA took the information in the updated registration into account, and modified the draft decision.

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

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

Appendix 3: Further information, observations and technical guidance

1. This 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.