ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 30 January 2019

Addressee
[redacted]

Decision number: TPE-D-2114455992-37-01/F
Substance name: Trimethoxyoctylsilane
EC number: 221-338-7
CAS number: 3069-40-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27 June 2017
Registered tonnage band: 100-1000

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 test for Pre-natal developmental toxicity study (EU B.31./OECD TG 414) using the analogue substance triethoxyoctylsilane (EC No 220-941-2), is rejected, you are requested to perform:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rats or rabbits), oral route, using the registered substance.**

Your following testing proposal is rejected:

2. **Reproductive toxicity study (Annex IX, Section 8.7.3.).**

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 **6 February 2020**. 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.

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 in rats according to OECD TG 414 by the oral route with the analogue substance triethoxyoctylsilane (EC No 220-941-2).

ECHA requested your considerations for alternative methods to fulfill the information requirement for Reproductive toxicity (pre-natal developmental toxicity). 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 considered first the scientific validity of the read-across hypothesis, before assessing the testing proposed.

a) Read-across and grouping approach

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

(1) Description of the grouping and read-across approach proposed by you

You have proposed to cover the standard information requirement for a pre-natal developmental toxicity study (Annex IX, 8.7.2.) on the registered substance ('target substance') by performing the test with an analogue substance triethoxyoctylsilane (EC No 220-941-2) ('source substance').

In the read-across justification provided in the CSR, Section 5.6.3. you say that the target and source subsatnces are part of the *"trialkoxy(alkyl)silanes containing a single silicon centre with three -OR groups"*. In your hypothesis you state that *"the toxicology of the octyl alkoxysilanes is similar due to the structural similarity"* and that *"the observed effects are expected to be of the same type for all substances".*

In summary, you use the following arguments to support the prediction of properties of the target substance from data of the source substance:

- Structural similarity: you explain that the two substances contain a single silicon centre with three alkoxy groups and one C8-side chain bound to silicon. The target and source substance differ in the type of the alkoxy groups: methoxy- and ethoxy, respectively.

- Physico-chemical properties: are in a comparable range. Regarding different log K_{ow} values you further state that "*this difference might mean that in a repeated dose toxicity study the parent ethoxy substances are eliminated from the tissues at a slower rate than the parent methoxy substances*", thus the data with the source substance could be regarded as "*worst-case data*".

- Data on hydrolysis: you provide QSAR data on the hydrolysis of the target and the source substance and state that they "*are predicted to hydrolyse rapidly at the pH of the stomach thereby forming the hydrolysis products octylsilanetriol [...] and ethanol and methanol*". You also acknowledge, "*The ethoxy-silanes hydrolyse slower than the methoxy-silanes due to the greater electron-donating effect of the ethoxy group".*

You conclude that "*based on the similar chemical structures and physicochemical properties of the parent, hydrolysis products and metabolites, it is possible that the mechanisms of toxicity for the target and source substances are the same and independent of route. Further evidence is needed to confirm this conclusion and this will be provided by the planned further toxicity tests (see Section 2 of this report and the Test Plan document)*".

You have provided several documents 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.

(2) 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 alkoxysilane 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 2943-75-1, EC 220-941-2), as a source substance.

ECHA understands that your read-across approach is based on the structural similarity, similar physico-chemical properties and rapid hydrolysis to a common hydrolysis product octylsilanetriol of the target and the source susbatnces.

(i) 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.

ECHA notes that you have sufficiently described in your read-across justification document the structural similarities between the target and source substances. ECHA further notes that you acknowledged also the structural differences of both substances that result in the lower vapour pressure, lower water solubility and higher log K_{ow} for the source substance.

(ii) Support of a similar 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 structural 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

Firstly, you propose that similar physicochemical properties of the target and source substances support the structural similarity, indicate similar toxicokinetics and enable the read across between the substances. In your read-across justification you state that the physicochemical properties of the target and source substance are "*within a relatively small range*". ECHA notes that you acknowledge the differences in water solubility, partition coefficient (log K_{ow}) and the hydrolysis rate of the target and source subsatnces.
You suggest that the higher log K_{ow} might result in a slower tissue elimination rate than the target substance in a repeated dose toxicity study, therefore you assume that the data with the source substance could be regarded as "the worst case." However, you have not substantiated your assumption with any toxicokinetic or repeated dose toxicity data that could allow such comparision. Therefore, your assumption of "worst case" is not supported by scientific evidence.

Secondly, in your read-across justification you provided QSAR predictions for hydrolysis half-lives of the target and source substance and their hydrolysis products. The exploited model, as stated in the QPRF provided by you, is specifically developed for the prediction of hydrolysis for Si-containing compounds at different pH values ([redacted]).

In particular, the hydrolysis half-life at pH=2, relevant at a gastric level (and pH=7, relevant for lungs and blood) at 37.5 °C is extrapolated and discussed.

Further, you have provided an extrapolated hydrolysis half-life of 5 seconds, for pH 2 at 37°C (Table 4, CSR) for both substances. 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 going from pH 4 to pH 2 as not supported by scientific evidence.

ECHA notes also that the hydrolysis rates of the source and target substances differ significantly. Eventhough, you acknowledge that "*due to the greater electron-donaiting effect of the ethoxy group*" the ethoxy-silanes hydrolyse slower than the methoxy-silanes and that the "*concentration and distribution of the hydrolysis productes could differ due to different rates of hydrolysis*", you did not explain why those differences would not lead to differences in the toxicity profile of target and source substances. 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 and, consequently, to influence differently the toxicity of the target and source substances.

Further, ECHA notes that the data on hydrolysis are based on QSAR estimations and there are no measured hydrolysis data for the target and source substances under conditions relevant for oral exposure. Even though, considering all the evidence, it can be assumed that the target substance is likely to rapidly hydrolyse at very low pHs (stomach conditions). However, according to the extrapolation suggested by you and the uncertainty of the predictions, it is unclear how fast. ECHA points out that while *in silico* (QSAR) studies may increase the robustness of a case, they are not usually sufficient as standalone information. You have also acknowledged this deficiency by expressing both in the CSR and in the Testing strategy document ([redacted]) an intention to provide more data on "*hydrolysis rates under conditions relevant for toxicity studies in the rat*". ECHA considers that generating this additional information is important, however it may or may not support your read-across hypothesis.

Thirdly, you postulate that the toxicity of the substances would be independent from the hydrolysis/condensation kinetics. However, 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.

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.

Fourthly, you postulate that target and source substances have similar toxicological profile. ECHA notes that in the technical dossier you have provided study records with the target substance for:

- Acute oral toxicity study (OECD 401, [redacted] *(1988)*
- Acute inhalation toxicity study (OECD 403, [redacted] *(1990)*

and study records with the source substance for:

- Screening repeated dose/reproductive toxicity study (OECD TG 422, [redacted] *2010*)

No repeated-dose or reproductive toxicity studies are provided with the target substance. ECHA notes that acute toxicity data alone is not sufficient to establish the toxicological profile of a substance with regard to repeated dose toxicity. As no higher tier study, *e.g.* screening study is available for the target substance, comparison of toxicological profiles of the substances is not possible.

ECHA acknowledges your intention "*to conduct an OECD 422 test on trimethoxy(octyl)silane for comparison with the available OECD 422 test* on the analogue subsatnce triethoxyoctylsilane".

ECHA agrees that at this point in time you have not provided the necessary evidence to support your hypothesis and additional studies may strengthen the overall read-across approach.

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.

(3) Conclusion on the read-across approach

Based on the data submitted by you, ECHA concludes that you have not provided adequate and reliable information to demonstrate that the criteria of Annex XI, 1.5. are met and that read-across approach is plausible to meet the information requirements for pre-natal developmental toxicity (Annex IX, section 8.7.2).

b) Test required

As noted above, pre-natal developmental toxicity study is the standard information requirement for your dossier, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that a 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 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 the rat or the rabbit as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment*

(version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 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 (rat or rabbit), oral route (test method: OECD TG 414, while your originally proposed test for Pre-natal developmental toxicity study in a first species (test method: OECD TG 414) *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.

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 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

2. Reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

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 to be performed with the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC No 220-941-2) with the following justification in the IUCLID dossier: "*experimental study planned (based on read-across)"* and study period

According to Annex IX, Section 8.7.3., as amended by Commission Regulation (EU) 2015/282 (entered into force on 13 March 2015), an extended one-generation reproductive toxicity study is only an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD TG 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity.

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 notes further that there are no repeated dose toxicity studies in your dossier that could indicate the need to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation. You have also not included any justification why to perform a reproductive toxicity study at tonnage level 100 – 1000 tonnes per year.

ECHA concludes that at this stage there is no information gap for the information requirement of Annex IX, Section 8.7.3. at the tonnage level you registered.

Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed extended one-generation reproductive toxicity study (OECD TG 443) is rejected.

Notes for your consideration

ECHA is aware that you have also received a draft decision requesting the 90-day study for the target substance (Communication number: TPE-D-2114392825-36-01/D).
Once the results from this study are available, you should reconsider the information requirement of Annex IX, Section 8.7.3. If the sub-chronic toxicity study indicates adverse effects on reproductive organs or tissues, or reveals other concerns in relation with reproductive toxicity, a new testing proposal for the present endpoint would – in accordance with the REACH Regulation – have to be submitted, unless compliance with this information requirement is scientifically justified and documented by means of specific or general rules of adaptation.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 27 June 2017.

ECHA held a third party consultation for the testing proposals from 27 September 2017 until 13 November 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **1 August 2018**, 30 calendar days after the end of the commenting period.

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.

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 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 relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition.

   In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.