ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114426293-54-01/F
Substance name: trimethoxyoctylsilane
EC number: 221-338-7
CAS number: 3069-40-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27.06.2017
Registered tonnage band: 100-1000T

DECISION ON A 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 Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) using the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC No 220-941-2)

is rejected, you are requested to perform:

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.**

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 **27 January 2020**. 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 trimethoxyoctylsilane (CAS No 3069-40-7, EC No 221-338-7) (hereafter referred to as "target substance"), taking into account the updated dossier.

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 Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.). In your testing strategy you propose to test an analogue substance and to use the results to adapt the standard information requirement by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that in your updated dossier (the submission number [redacted]) you have continued with this general strategy, however you changed the analogue substance which is to be tested and your arguments to justify the read-across approach. In the original dossier you have proposed the analogue substance triethoxy(2,4,4-trimethylpentyl)silane (CAS No 35435-21-3, EC No 252-558-1) while in the updated dossier you are proposing a different analogue substance triethoxy(octyl)silane (CAS 2943-75-1 EC 220-941-2). ECHA has assessed your testing strategy of using this new analogue substance triethoxy(octyl)silane (CAS 2943-75-1 EC 220-941-2), hereafter referred as "source substance").
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 justification document attached in section 7.5.1 of the updated IUCLID dossier and in the updated CSR document in chapter 5.6.3 you present your new read-across hypothesis and justification:

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

However, you also note that:

"There is currently insufficient information to conclude on whether read-across is appropriate ...".

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

You have provided several documents as separate attachments in IUCLID, Section 13 relevant to the testing proposed:

[redacted]

Apart from the above general information you have provided the substance specific read-across hypothesis and justification, in the technical dossier, under the endpoint study summary for repeated dose toxicity, in Section 7.5 and 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; comparison of the structural features, physico-chemical properties, some predicted toxicokinetics properties and the available toxicological data of the source and target substances. In the same place you also discuss the repeated systemic toxicity of the non-silanol hydrolysis products and conclude on your read-across approach.

In addition you have provided in the technical dossier of the target substance the following toxicological studies relevant for the test proposed and subject to the current decision.
For the target substance:

- an acute oral toxicity study (OECD 401, [redacted] (1988));
- an acute inhalation toxicity study (OECD 403, [redacted] (1990)).

For the source substance:

- a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test, via oral route (OECD 422, [redacted] 2010).

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 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.

According to ECHA's understanding you suggest that based on their structural similarities,target and source substances have similar toxicological properties *i.e.* similar sub-chronic repeated dose toxicity, following oral administration.

You use the following arguments to support the prediction of properties of the registered substance from data for the source substances:

- similarity of the physico-chemical properties of the parent substances;
- you also claim that differences in the physico-chemical properties are as expected based on the structural differences;
- due to the similarity of the physico-chemical properties of the parent substances and their silanol hydrolysis products, the substances would not have significant differences in their toxicokinetic profile;
- target and source substances are hydrolytically unstable and undergo similar hydrolysis process
- and as a result structurally similar hydrolysis products are formed.

ECHA also understands that the key supporting element of your hypothesis is the postulation that the parent substances undergo similar fast and "significant" hydrolysis process.

You further postulate that based on this "significant" hydrolysis, due to the absence of other metabolic processes and limited uptake of the parent substances and the formed condensation products, the silanol monomers would mainly drive the toxicity profile of the substances.

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

You also acknowledge that *"Additional data are required before it can be concluded that read-across within this analogue group is appropriate."*

ECHA observes that in your justification document you identify and acknowledge the weaknesses of your supporting information and you propose further investigations to provide experimental evidence supporting your read-across hypothesis *e.g.*

"This is dealt with in two ways in the test plan:

1. *In vitro testing to learn more about the hydrolysis rates of alkoxysilanes under conditions relevant for oral exposure in the rat is ongoing.*
2. *Testing to at least 28-day repeated dose toxicity for all substances. Consistent properties in the available toxicology studies would indicate that differences in the hydrolysis rates and physicochemical properties of the hydrolysis products do not impact the read-across."*

Additionally, your mention your intention to perform a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, according to OECD TG 422 with the registered substance.
ECHA agrees with you that currently there is insufficient information to conclude on whether read-across between the source and target substance is plausible or not.

In particular ECHA notes the following shortcomings of your read-across approach:

Firstly, the hydrolysis rate of the substances under relevant conditions is not proven. ECHA observes that hydrolysis half-life rate of the substances at pH2 is based on assumptions which are not substantiated by data. 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 state that the rate of the hydrolysis is dependent on hydronium ion concentration and t there will be a 100 fold increase in hydrolysis rate 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.

Secondly, your statement that exposure to the parent substances and intermediate hydrolysis products may occur but is limited is not substantiated. The concentration, distribution and characterisation of the hydrolysis products and their corresponding condensation products (*e.g.* size distribution) need to be further investigated to (possibly) support your statement.

ECHA acknowledges your intention to provide more data to substantiate your read-across strategy.

With this regard ECHA notes that knowledge addressing the above mentioned shortcomings, in conjunction with *in vivo* repeated dose toxicity data may help to clarify the validity of your postulation that uptake of the condensation products is negligible and hence does not impact the possibility to read-across. In addition, the toxicokinetic predictions need to be re-evaluated in view of the newly acquired information.
Also, studies conducted according to OECD TG 422 may strengthen the overall read-across approach. However, the results may or may not confirm your hypothesis.

ECHA points out that at this moment you have not provided the necessary evidence to support the likelihood of similar toxicological properties for the Sub-chronic toxicity study (90-day) via oral route toxicity.

The 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 is currently available for the target substance, comparison of toxicological profiles of the substances is not possible.

In summary, your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However, similarity in chemical structure and in some of the physico-chemical properties does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on structural similarity and physico-chemical properties has not established why the prediction is reliable for the human health end-points for which the read across is claimed.

Therefore, ECHA considers that this grouping and read-across approach currently does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach

currently does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

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 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 substances is not appropriate to fulfil the information requirement of the substance subject to the present decision.

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) by the oral route according to EU B.26./OECD TG 408 with the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC No 220-941-2).

ECHA notes that in the updated dossier you provided your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90 day). 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.

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 that 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) and potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

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.

In addition, ECHA notes that in your CSR document you discuss the use of studies performed on other analogue substances trie**t**hoxy(2,4,4-trimethylpentyl)silane (CAS 35435-21-3) and trimethoxy(2,4,4-trimethylpentyl)silane (CAS 34396-03-7) for the purpose of interim hazard and risk assessment for the registered substance.
For that purpose in section 7.5.1 of your IUCLID dossier you have submitted the following information on analogue substance tri**et**hoxy(2,4,4-trimethylpentyl)silane (CAS 35435-21-3):

- a sub-chronic repeated dose toxicity study (90 days), via oral route (OECD 408; [redacted] (2015)) and
- two repeated dose 28-day toxicity studies via oral route (OECD 407, [redacted] (2001) and OECD 407 [redacted] (2001));

and on the tri**m**ethoxy(2,4,4-trimethylpentyl)silane (CAS 34396-03-7):

- a repeated dose 28-day toxicity study via inhalation route (OECD 412; [redacted], 1986).

You also note that *"The data from these tests do not support read-across to the registered substance due to the observed neuromuscular effects observed with the linear registered substance in the OECD 422 test, which were absent in the reliable tests on the branched substances. However, in order to allow interim risk characterisation data on triethoxy(2,4,4-trimethylpentyl)silane (CAS 35435-21-3) have been read across as these provide the lowest NOAEL values."*
ECHA understands that you intend to use the data on the analogue substance triethoxy(2,4,4-trimethylpentyl)silane (CAS 35435-21-3) only as *"an interim risk characterisation"*.

ECHA acknowledges your intention to provide interim risk characterisation for the registered substance and your justification using the same hypothesis, data and justification as set out in Section 0 *'Grouping of substances and read-across approach'* of the present decision. However, as your read-across justification has the same shortcomings as already explained in the Section 0 of this decision it cannot be accepted. Therefore, ECHA agrees with your conclusion, as also cited above, that *"The data from these tests do not support read-across to the registered substance ..."*
On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met. Therefore ECHA concludes that the data provided on the analogue substance triethoxy(2,4,4-trimethylpentyl)silane (CAS 35435-21-3) could not be used to fulfil the current information requirement for the registered substance.

Finally, ECHA considers that by submitting a testing proposals on the analogue substance triethoxy(octyl)silane (CAS No 2943-75-1, EC No 220-941-2) you have deemed it necessary to generate further data on this substance for the purpose of fulfilling relevant information requirement of the registered substance. ECHA agrees that the information present in the technical dossier is currently insufficient.

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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408) while your originally proposed test for a Sub-chronic toxicity study (90-day), oral route (test method:

EU B.26./OECD TG 408) using 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

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).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal for examination pursuant to Article 40(1) on 26 April 2013.

ECHA held a third party consultation for the testing proposal from 7 August 2015 until 22 September 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. ECHA took into account your comments and did not amend the request(s).

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 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 the dossier on the 27 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.