EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114425318-51-01/F
Substance name: (3-chloropropyl)dimethoxymethylsilane
EC number: 242-056-0
CAS number: 18171-19-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15.07.2015
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(s) and decided as follows.

While your originally proposed test for a Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species using the analogue substance (3-chloropropyl)triethoxysilane (CAS no 5089-70-3, EC no 225-805-6) 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(s) submitted by you for the registered substance (3-chloropropyl)dimethoxymethylsilane, CAS No 18171-19-2 (EC No 242-056-0) (hereafter referred to as "target substance").

In relation to the testing proposals subject to the present decision, you propose a testing strategy intending to fulfil the standard information 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 (3-chloropropyl)triethoxysilane (CAS no 5089-70-3, EC no 225-805-6); hereafter referred to as "source substance"). 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 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

You have provided the following arguments to justify the read-across approach:

"*Read-across is based on the presence of a common functional group (3-chloropropyl) in the registered and read-across substances, and the rapid hydrolysis of both substances to produce silanols containing this group. Read-across substances have been selected as the most appropriate based on chemical structure for which data were available.*"

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

You have provided several documents as separate attachments in IUCLID, Section 13:

[redacted]

Analogue grouping report: Dissociation Constant of Hydrolysis Products of Organosilicon Substances document outlines the approach to analogue grouping of organosilicon substances with a half-life of <12 hours and which are known to generate silanol hydrolysis product.

Analogue Grouping Report: [redacted] discusses the semi-quantitative approaches in order to fill gaps in the data set for some substances for the purpose of REACH registration. The objective of the proposed method is only to identify, without testing, substances which are expected to have melting point <-20°C.

[redacted] "outlines the approach" to mammalian toxicity of alkyl alkoxysilanes and silanols. The report groups substances "which contain one or more alkoxy groups (-OR') or hydroxyl groups (-OH) attached directly to silicon, with general formula R(4-x)-SiOR'x and R(4-x)-Si(OH)x, where R can be one of more of": -H -alkyl group (linear, branched or cyclic; saturated or unsaturated) and and R' can be one or more of: -CH3 (methoxy) and -CH2CH3 (ethoxy). Individual substances have been assigned to substance "Groups" and assigned an internal code (e.g. I-2-C, II-1 etc).

A data matrix and results of physico-chemical and toxiciological properties is provided. According to the report, this data "*are also used for read-across to address potential systemic toxicity from silanols for chlorosilanes*".

[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] : Main analogue group, [redacted] : Main analogue group do not provide information on the read-across approach used for the endpoint subject of the current decision.

In the Chemical Safety Report (CSR) section 5.9.2 (Developmental toxicity) and in the technical dossier section 7.8., you refer to a substance-specific read-across justification provided in section 5.6.3. of the CSR and section 7.5 of the technical dossier. However, in the provided justification you compare the target substance and 3-chloropropyl-

trimethoxysilane (CAS 2530-87-2), which is the source substance used to adapt the sub-chronic toxicity (90-day) study.

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

For the target substance:
- Acute oral toxicity study (OECD 423, GLP, [redacted] 2002);
- Skin and eye irritation studies ([redacted] 2002);
- Ames test ([redacted] 2002);

For the source substance the dossier contains no information on toxicological studies.

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 alkyl silanes 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 (3-chloropropyl)triethoxysilane (CAS: 5089-70-3, EC: 225-805-6)as a source substance.

ECHA considers that due to limited information provided for the actual source substance (3-chloropropyl)triethoxysilane, only partial analysis of your read across hypothesis is possible.

According to ECHA's understanding 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 structurally similar silanol hydrolysis products are formed;
- 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 structurally similar silanol hydrolysis products (3-chloropropyl) methylsilanediol, and (3-chloropropyl) silanetriol) and either methanol or ethanol;
- and that the formed silanol substances are exclusively relevant in terms of bioavailability and systemic toxicity.

In addition, you claim that the non-silanol hydrolysis products do not contribute to any adverse effects for the systemic 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 silananol hydrolysis products as the driver for the systemic toxicity of the parent substances.

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

Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. It has to be justified why such prediction is possible in view of the identified structural

differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You have described the structural similarities between target and source substances by indicating that they both have *"common functional group (3-chloropropyl) in the registered and read-across substances, and the rapid hydrolysis of both substances to produce silanols containing this group."*. ECHA notes that in addition to the structural similarities, structural differences can be observed. Whereas the source substance contains three alkoxy (-OEt, ethoxy) groups and a chloropropyl group bound to the Si (silicon) atom, the target substance contains two methoxy groups, one methyl (-Me) group and one chloropropyl group bound to the Si (silicon) atom.

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 structurally similar silanol hydrolysis products, (3-chloropropyl) silanetriol and (3-chloropropyl) methylsilanediol, respectively.

However, ECHA observes that due to the described structural differences of target and source substances the silanol hydrolysis products formed from the parent substances are different. ECHA notes that the (3-chloropropyl) methylsilanediol - formed form the target substance - and (3-chloropropyl) silanetriol – formed from the source substance - differ in the number of the hydroxyl groups and in the presence of a methyl group bound to the silicon atom in case of the target substance.

In the CSR (p. 48 Read-across hypothesis) you acknowledged a structural difference between the parent substances. However your claim that *"the fact that one methoxy group is replaced by a toxicologically inert methyl group"* results in *"reducing reactivity of the parent substance."* does not explain what is the consequence of such structural difference on the possibility to predict.

ECHA notes that you have not provided any information on how the structural differences in the parent substances and consequently in the silanol hydrolysis products may impact the toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substance.

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

(ii) 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.

Toxicokinetics

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 itself and/or its 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 products, (3-chloropropyl)methylsilanediol, and (3-chloropropyl)silanetriol, respectively.

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.

Moreover, you have not provided toxicokinetics information for the intended source (3-chloropropyl)dimethoxymethylsilane but rather (3-chloropropyl)dimethoxymethylsilane. ECHA considers that your 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.

Toxicological information

You further propose that the results of the acute toxicity data *"indicate that acute systemic toxicity for the oral route is similar for the two silanol hydrolysis products, although there is no specific information on mode of action".* ECHA notes that the dossier contains an acute oral toxicity study (OECD 423, GLP, [redacted] 2002), eye/skin irritation studies, or an Ames test ([redacted] 2002) with the target substance but there is no information for the source substance.

ECHA notes that acute toxicity data alone is not sufficient to establish the toxicological profile of a substance with regard prenatal developmental toxicity. As no higher tier study, e.g., reproduction/developmental toxicity screening test, is available for the target or the source substance comparison of toxicological profiles of the substances is not possible.

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.

In addition, ECHA notes that 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.

Hydrolysis

ECHA understands that the hypothesis relies on the assumption that both target and source substances undergo rapid and complete hydrolysis at pH 2 (within seconds) and they form structurally similar silanol hydrolysis products (3-chloropropyl) methylsilanediol, and (3-chloropropyl), respectively. You propose that based on the formation and relevance of the similar silanol hydrolysis products, 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 silanediol hydrolysis products".*

Firstly, ECHA observes that hydrolysis half-life rate at pH2 is based on assumptions which are not substantiated by data. You postulate that *"Thus, for (3-*

chloropropyl)dimethoxymethylsilane the hydrolysis half-life at 37.5ºC and pH 7 (relevant for lungs and blood) is 0.37 hours (1330 seconds). At 37.5ºC and pH 2 (relevant for conditions in the stomach following oral exposure), it is not appropriate to apply any further correction for temperature to the limit value and the hydrolysis half -life is therefore approximately 5 seconds." You have not estimated the hydrolysis rate of the source substance, but you have given an estimate of the hydrolysis rate of the closely related substance (3-chloropropyl)diethoxymethylsilane (CAS 13501-76-3) for which you conclude: *"As a worst-case it can therefore be considered that the half-life for the substance at pH 2 and 37.5°C is approximately 5 seconds."*

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 the target substance would involve two hydrolysis steps. The formation of the proposed silanol hydrolysis product from the source substance would involve three hydrolysis steps. In the hydrolysis studies/QSAR/read-across data provided in the registration dossier there is no evidence of the formation of the proposed silanol hydrolysis products 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, whose possible presence and effects on your hypothesis you have not addressed.

Condensation

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:

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. A significant degree of condensation is expected at concentrations above 200 mg/l, but is dependent on specific conditions.*
- *pH;the condensation reaction may be either acid or base catalysed.*
- *Temperature. Other species present.*

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; 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 of formation 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.

Non-silanol substances
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., methanol from the target substance and ethanol from the source substance. You claim that the non-silanol hydrolysis products play no significant role in the systemic toxicity of the substances as *"Generally effects noted include nasal irritation in rats (but not monkeys), CNS depression, effects on body and organ weight and in some cases effects on clinical chemistry parameters. Studies were conducted up to significant doses and generally effects when noted, are considered adverse only at upper end of the dose ranges studied e. g 650 mg/m3 in monkeys, 13000 mg/m3 in rats.*
Methanol is not classified for repeated dose toxicity in Annex VI of Regulation (EC) No 1272/2008."

Your hypothesis did not discuss the impact of the different alcohol between the source and the target, i.e., ethanol and methanol.

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. Therefore, 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 with the analogue substance (3-chloropropyl)triethoxysilane (EC No 225-805-6).

ECHA has evaluated your proposal to perform the test with the analogue substance chloropropyl)triethoxysilane (EC No 225-805-6). 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.

ECHA considers that the proposed 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 this basis, ECHA considers testing should be performed with rats or rabbits as a first species.

You proposed testing by the oral route. ECHA agrees 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) 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 this specific endpoint.

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 (test method: EU B.31./OECD TG 414) using the analogue substance (3-chloropropyl)triethoxysilane (CAS no 5089-70-3, EC no 225-805-6) 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* R.7a, chapter R.7.6.2.3.2 (July 2017).

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 this testing proposal for examination pursuant to Article 40(1) on 18 February 2013 under a different lead registrant in registration [redacted].

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

Subsequently, you as the new lead registrant updated the registration by submission number [redacted], and you maintained the testing proposal on 15 July 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation: 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 08 July 2016, 30 calendar days after the end of the commenting period. 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 of the IUCLID dossier.

You did not update the dossier by the given deadline.

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.