EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114347448-41-01/F Helsinki, 28 November 2016

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 3-(trimethoxysilyl)propylamine, CAS No 13822-56-5 (EC No 237-511-5), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for 3-(trimethoxysilyl)propylamine, CAS No 13822-56-5 (EC No 237-511-5), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after the deadline for updating (15 March 2015) communicated to the Registrant by ECHA on 06 February 2015.
This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

The compliance check was initiated on 12 November 2013.

On 7 February 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 10 March 2014 ECHA received comments from the Registrant on the draft decision.

On 12 May 2014 the Registrant updated his registration dossier with the submission number [redacted].

The compliance check request to submit information to meet the information requirement for Annex X, Section 8.7.3 was removed from the draft decision due to the legislative amendment of this provision by virtue of Commission Regulation (EU) 2015/282 of 20 February 2015. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning this information requirement. ECHA may, in accordance with Article 41 of the REACH Regulation, initiate a further compliance check of the registration dossier with respect to this information requirement.

However, ECHA Secretariat did consider further the Registrant's comments and update concerning the information requirements of Annex VI, Section 2.3.5.; Annex VII, Sections 7.2.; 7.3.; 7.4.; 7.5.; 7.7.; 7.8.; and 7.9.; Annex VIII, Sections 8.4.2. ; and Annex IX, Sections 7.16.; 7.17.; 8.6.2.; 8.7.2. and 9.2.2.1. Section II and III was changed accordingly.

On 21 July 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposal(s) for amendment to the draft decision were submitted.

On 26 August 2016 ECHA notified the Registrant of the proposal(s) for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal(s) for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal(s) for amendment received and did not amend the draft decision.

On 5 September 2016 ECHA referred the draft decision to the Member State Committee.

By 26 September 2016, in accordance to Article 51(5), the Registrant provided comments on the proposal for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision was reached on 10 October 2016 in a written procedure launched on 29 September 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Information in the technical dossier related to the identity of the substance

Pursuant to Articles 41(1), 41(3), 10(a)(ii) and Annex VI, Section 2 of the REACH Regulation the Registrant shall submit the following information for the registered substance subject to the present decision:

1. Spectral data (nuclear magnetic resonance or mass spectrum) (Annex VI, 2.3.5).

B. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and (vii), 12(1)(e), 13 and Annexes VII, VIII, IX and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. Melting/freezing point (Annex VII, Section 7.2.; test method: EU A.1./OECD 102);

2. Flash-point (Annex VII, Section 7.9.; test method: as specified in Section III);

3. *In vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2., test method: OECD 473) or *in vitro* micronucleus study (Annex VIII, 8.4.2., test method: OECD 487);

4. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats; and

5. Pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **5 December 2018**. The timeline has been set to allow for sequential testing as appropriate.

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier related to the identity of the substance

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

1. Spectral data (nuclear magnetic resonance or mass spectrum) (Annex VI, 2.3.5)

ECHA notes that the registration does not contain the nuclear magnetic resonance (NMR) spectrum or Mass spectrum (MS) which are required according to Annex VI Section 2.3.5. of the REACH Regulation to support the identity of the registered substance. ECHA points out that the identity of the substance cannot be confirmed based exclusively on the infra-red spectrum which the Registrant included in section 1.4 of the IUCLID dossier.

ECHA regards this required information scientifically necessary for the identification of the registered substance as NMR spectroscopic analyses such as a ^{1}H-NMR or a ^{13}C-NMR are powerful tools for structure characterisation and elucidation due to characteristic chemical shifts and spin-spin coupling that also reflects the relative abundance of individual atoms. Alternatively, a mass spectrum, which is an appropriate analytical method to characterise the substance and determine its elemental composition, can be provided.

Accordingly, the Registrant is requested to provide the missing NMR spectrum, such as a ^{1}H-NMR or a ^{13}C-NMR or, alternatively, a mass spectrum including the corresponding interpretation of the fragmentation scheme.

As for the reporting of the spectral data in the registration dossier, the information should be included in IUCLID section 1.4. The Registrant shall ensure that the description of the analytical method(s) used for the recording of the spectra is specified in the dossier, in line with the requirements under Annex VI section 2.3.7.

B. Information in the technical dossier derived from the application of Annexes VII to X

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

The decision of ECHA is based on the examination of the updated registration submitted by the Registrant for the registered substance 3-(trimethoxysilyl)propylamine, CAS No 13822-56-5 (EC No 237-511-5); hereafter referred to as 'target substance'.
In the updated registration, the Registrant has revised his read-across and grouping adaptation for the standard information requirements for *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: EU B.10./OECD 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD 487); Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD 408) in rats; and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route. In the read-across and grouping approach, the Registrant is using studies conducted with the analogue substance 3-aminopropyltriethoxysilane, CAS No 919-30-2; hereafter referred to as 'source substance' to adapt the standard information requirements for the endpoints listed above.

ECHA has considered first the scientific validity of the proposed read-across and grouping approach in the section below, and thereafter addressed the information requests (Sections 3, 4 and 5).

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents the Registrant's justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

The Registrant puts forward the following read-across hypothesis for systemic and reproductive toxicity:
"The hypothesis is that source (read-across) and target (registration) substances have similar toxicological properties because they hydrolyse to a common silicon-containing hydrolysis product, and after reaching the stomach following oral adminsitration, 3-(trimethoxysilyl)propylamine and 3-aminopropyltriethoxysilane hydrolyse very rapidly (half-life in the order of a few seconds) to the same silanol hydrolysis products. The non-silanol hydrolysis products, methanol and ethanol, do not contribute to any adverse effects for systemic or reproductive toxicity at the relevant dose levels based on publicly available information. [...]"

The Registrant puts forward the following read-across hypothesis for genetic toxicity:
"3-aminopropyltriethoxysilane is a close structural analogue of 3-(trimethoxysilyl)propylamine; both substances are trialkoxysilanes with an aminopropyl group, and both hydrolyse to aminopropylsilanetriol. Hydrolysis is likely to occur under the conditions of the studies and also in vivo. The non-silanol products of hydrolysis are ethanol and methanol, which are not expected to contribute to genetic toxicity, [...]"

ECHA understands this as the hypothesis under which the Registrant make predictions for the properties listed above.

b. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

The Registrant has provided a read-across justification for systemic and reproductive toxicity in Section 3.5.6.2. of the CSR and for genetic toxicity in Section 3.5.7.5. of the CSR. The Registrant brings forward the following arguments to support the read-across approach:

- Structural similarity: Both the source and target substance contains a silicon atom which is attached to an identical aminopropyl side chain. In addition, both the source and target substances also have three alkoxy groups bound to the silicon atom. The only difference is that these three alkoxy groups are ethoxy- for the source substance and methoxy- groups for the target substance.

- Similar physicochemical characteristics: *"Both parent substances are very soluble in water, have low log Kow and low vapour pressure; they are of similar molecular weight."*

- Similar hydrolysis: Both the source and the target substances hydrolyse rapidly to produce the same silicon-containing hydrolysis product, *i.e.* 3-aminopropylsilanetriol, and either ethanol or methanol.
  For systemic and reproductive toxicity the Registrant presents the following arguments:
  "The predicted half-lives at 20-25°C of the registered substance, 3-(trimethoxysilyl)propylamine, are 2.6 hours at pH 7, 5 seconds at pH 2, 0.2 hours at pH 4 and 0.1 hours at pH 9. At 37.5°C and pH 2 (relevant for conditions in the stomach following oral exposure), the calculated half-life is approximately 5 seconds. The products of hydrolysis are 3-aminopropylsilanetriol and methanol."
  The source *"substance, 3-aminopropyltriethoxysilane, has a measured hydrolysis half-life of 8.5 hours at pH 7. At 37.5ºC and pH 2 (relevant for conditions in the stomach following oral exposure), the calculated half-life is approximately 5 seconds. The products of hydrolysis are 3-aminopropylsilanetriol and ethanol."*

For genetic toxicity the Registrant presents the following arguments:
"The rates of hydrolysis that are relevant to in vitro conditions and intraperitoneal exposure of pH and temperature have been calculated.
3-(Trimethoxysilyl)propylamine hydrolyses rapidly, with an estimated hydrolysis half-life of 1 h at pH7 and 37.5°C.
3-Aminopropyltriethoxysilane hydrolyses rapidly, with a hydrolysis half-life, calculated from measured values at 20°C, of 3 h at pH7 and 37.5°C."

- Similar toxicokinetics: *"Given the low vapour pressure of 3-(trimethoxysilyl) propylamine, significant inhalation exposure is not expected and any repeated dose testing with the parent substance would therefore most appropriately be performed by the oral route. In view of the rapid hydrolysis following oral dosing, it is therefore appropriate to read-across the available oral data for the read-across substance 3-aminopropyltriethoxysilane, which produces the same silicon-containing hydrolysis product, to address the potential for systemic organ toxicity, therefore further comparison of the toxicokinetics is not considered necessary."*
- *Similar acute toxicity:* *"Acute oral and dermal toxicity studies are available for the registered substance and 3-aminopropyltriethoxysilane. Dermal LD50 values were above classification cut-offs as was the oral LD50 for the registered substance. Although the read-across substance is classified as Acute Tox oral Cat 4, the LD50 for male animals was comparable for the two substances."*

- The non-silanol hydrolysis products do not contribute to systemic or reproductive toxicity.

- No structural alerts for genotoxicity for the source and target substances. In addition, the non-silanol hydrolysis products are not genotoxic.

The following information has been provided with the target substance:
- QSAR prediction of hydrolysis;
- Acute oral toxicity study (Reliability 2 (reliable with restrictions); non-GLP; similar to OECD 401; 1980);
- Acute inhalation toxicity study (Reliability 4 (not assessable); non-GLP; non-Guideline; 1980);
- Acute dermal toxicity study (Reliability 2 (reliable with restrictions); non-GLP; similar to OECD 401; 1980); and
- Bacterial reverse mutation assay (Reliability 1 (reliable without restrictions); OECD 471; 1997; *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvr)

The following information has been provided with the source substance;
- Hydrolysis as a function of pH (Reliability 2 (reliable with restrictions); OECD 111; 2001);
- QSAR prediction of hydrolysis;
- Acute oral toxicity study (Reliability 2 (reliable with restrictions); non-GLP; according to EPA OTS 798.1175; 1989);
- Acute inhalation toxicity study (Reliability 2 (reliable with restrictions); non-GLP; OECD 403; 1982);
- Acute dermal toxicity study (Reliability 2 (reliable with restrictions); non-GLP; according to EPA OTS 798.1000; 1989);
- *In Vitro* Mammalian Chromosome Aberration Test (Reliability 2 (reliable with restrictions); OECD 473; GLP; 1999);
- *In Vitro* Mammalian Cell Gene Mutation Test (Reliability 2 (reliable with restrictions); OECD 476; GLP; 1997);

- Mammalian Erythrocyte Micronucleus Test (Reliability 2 (reliable with restrictions); mouse; OECD 474; GLP; 1988)
- Sub-chronic oral toxicity study (Reliability 2 (reliable with restrictions); rat; 90-days; GLP; OECD 408; 2001);
- Sub-acute inhalation study (Reliability 2 (reliable with restrictions); rat; 28-days; GLP; OECD 412; 1991);
- Dermal carcinogenicity study (Reliability 2 (reliable with restrictions); mouse; 24-months; non-GLP; non-Guideline; 1987)
- Pre-natal developmental toxicity study (Reliability 2 (reliable with restrictions); rats; GLP; similar to OECD 414; 1998).

The following information has been provided with a substance other than the source or target substance:

- Hydrolysis study (reliability 4 (not assignable); non-guideline; non-GLP; conducted with 3-Trimethoxysilylpropan-1-amine, CAS No13822-56-5, EC No 237-511-5)

c. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

Based on the read-across approach and supporting information provided, ECHA understands that the prediction is based on an analogue approach which uses 3-aminopropyltriethoxysilane as a source substance to predict the properties of the target (registered) substance of 3-(trimethoxysilyl)propylamine.

According to ECHA's understanding the Registrant suggests that based on their structural similarities target and source substances have similar properties:

- both target and source substances undergo hydrolysis which results in that the same silanol hydrolysis product is formed;
- the target and source substances have similar physico-chemical characteristic and are assumed to have a similar toxicokinetics- and acute toxicity- profile;

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

- that the hydrolysis of the parent substances is both rapid and complete, leading to the formation of the same silanol hydrolysis products (3-aminopropylsilanetriol); and
- that the ultimate hydrolysis product would drive genetic, systemic, and reproductive toxicity.

In addition, the Registrant claims that the non-silanol hydrolysis products do not contribute to any adverse effects with regard to genetic, systemic, and reproductive 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 the claim regarding the formation, relevance and exclusivity of the proposed silanol hydrolysis product 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.

The Registrant has clearly identified the structural basis for the prediction, *i.e.* he postulates that both the source substance and the target substance hydrolyse to form a common ultimate hydrolysis product. Furthermore, the source and the target substances differ in that the source substance have three ethoxy- groups attached to the silicon atom whereas the target substance has three methoxy- groups attached to the silicon atom. This will at each step of the hydrolysis result in that different non-silanol hydrolysis products are formed; i.e. ethanol for the source substance and methanol for the target substance. ECHA notes that the ultimate hydrolysis product is the same for both the source and the target substances. However, ECHA notes that the Registrant has not provided any information on how the structural differences in the parent substances and consequently in the intermediate silanol hydrolysis products formed before the ultimate common hydrolysis product may impact the toxicokinetic properties (in particular hydrolysis) and 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.

In the read-across justification the Registrant states that physico-chemical parameters/properties of target and source substances are similar. He has proposed that the similar physico-chemical properties of the target and source substances support the read across between the substances. ECHA observes that the physico-chemical properties of target and source substances are in the same/similar range.

ECHA considers that the fact that physico-chemical parameters are in the same range may support a similar toxicokinetic and toxicity profile, but cannot be used alone to justify a prediction of properties related to human health.

The Registrant has provided information on acute toxicity with both substances, and genetic toxicity, repeated dosed toxicity and prenatal developmental toxicity with the source substance to support the read-across approach.

ECHA notes that only for acute toxicity there are studies available on both the source and target substances. However, the Registrant have not explained how similar acute toxicity can be used to predict the properties of the target substance following repeated does administration. ECHA notes that acute toxicity alone is not sufficient to establish the toxicological profiles of the substances and support the prediction of genetic toxicity, repeated dose toxicity and prenatal developmental toxicity of the target substance from the source substance.

Furthermore, ECHA notes that for genetic toxicity, repeated dose toxicity and toxicity to reproduction information has only been provided for either the source or the target substance, but not for both for the same endpoint. There are no studies which allow a side-by-side comparison of the results for source and target substances for the same property. Moreover, ECHA notes that no information has been provided on the ultimate hydrolysis product which is claimed to drive toxicity. ECHA considers that the available information does not support a claim of similar toxicity, with regard to genetic toxicity, repeated dose toxicity and toxicity to reproduction, because there is no information available which would allow comparison of the toxicity profiles between source substance and the target substance.

ECHA notes that the Registrant has 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 the target substance and ethanol from the source substance. The Registrant claims that the non-silanol hydrolysis products play no significant role for genetic toxicity, repeated dose toxicity and toxicity to reproduction as the non-silanol hydrolysis products are not expected to contribute to any adverse effects for these endpoints at the relevant dose levels.
ECHA notes that in read-across justification no information have been provided on the "relevant dose levels". In addition, the read-across justification do not address the possible interactions between the parent substances and their (intermediate) hydrolysis products and do not take into consideration the implication of such reaction on the prediction.

ECHA concludes that the presented evidence does not support a similar or regular pattern of toxicity for the properties under consideration as a result of structural similarity. 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.

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

ECHA understands that the read-across hypothesis relies on the assumption that both target and source substances undergo rapid and complete hydrolysis at pH 2 (within seconds) and form the same silanol hydrolysis product (3-aminopropylsilanetriol). The Registrant proposes that, based on the formation of the same ultimate hydrolysis product, the properties of the source substance can be used to predict the properties of the target substance.

Firstly, ECHA observes that hydrolysis half-life rate 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 it has been assumed 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 ultimate common silanol hydrolysis product 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 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 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, the Registrant has not substantiated his assumption of a complete hydrolysis. In fact, the hydrolysis process which involves three steps may produce also other substances, which possible presence and effects have not addressed. Moreover, ECHA notes that the Registrant claims that the k1, k2, k3 values for the different steps of hydrolysis reaction are for the source substance. In fact these values are for a different substance, 3-Trimethoxysilylpropan-1-amine, CAS No13822-56-5, EC No 237-511-5), which is not part of the current read-across approach.

Thirdly, the Registrant's assumption that the common ultimate silanol hydrolysis product are exclusively relevant in terms of bioavailability and hence would drive the systemic toxicity is not supported by data. In fact he acknowledges the occurrence of condensation reaction following the hydrolysis of the parent substances but he did not consider the implication of such reaction on the prediction. The Registrant explains that the silanol hydrolysis product may undergo condensation reactions leading to the formation of siloxane dimers, oligomers and polymers and state that: "*In chemical terms the organochloro- and organoalkoxysilanes initially undergo hydrolysis by reaction with water to produce silanols(s) and it is the silanols which are the true monomers and subsequently undergo condensation reactions to form oligomers and then silicone polymers and resins (*[redacted]*).*" However, the Registrant do not explain how these condensation reactions may influence the prediction.

In addition, with regard to the *in vitro* mutagenicity studies, ECHA notes that the hydrolysis rate at neutral pH is rather slow and differ between the substances (target substance 2.6 hours at pH 7, 5; and source substance 8.5 hours at pH 7), therefore, the presence of the common hydrolysis product during *in vitro* testing might be low compared to the concentration of parent substances. Furthermore, the Registrant did not consider the presence of intermediate hydrolysis products (di-substituted 3-aminopropylsilanol and mono-subtituted 3-aminopropylsilanediol derivatives) in his read-across justification. ECHA concludes that the Registrant has not considered that the levels of parent substances, intermediate hydrolysis products and common hydrolysis product may vary significantly because the source substance is expected to hydrolyse more slowly than the target substance.

In summary, ECHA considers that given the lacking evidence to support the read-across hypothesis, that due to complete and rapid hydrolyis only the common ultimate silanol hydrolysis product is 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

(iv) Similar toxicokinetics

The Registrant claims that oral route is the most appropriate route of administration and that "*in view of the rapid hydrolysis following oral dosing, it is therefore appropriate to read-across the available oral data for the read-across substance 3-aminopropyltriethoxysilane, which produces the same silicon-containing hydrolysis product, to address the potential for systemic organ toxicity, therefore further comparison of the toxicokinetics is not considered necessary.*"

ECHA notes that there are no toxicokinetics studies for the target or source substances. The Registrant predicts toxicokinetic behaviour based on the physico-chemical properties of the parent substances. ECHA observes that the toxicokinetic prediction rely upon an assumed rapid and complete hydrolysis of the target and source substances to a common hydrolysis product. However, as pointed out in the (iii) section above, there is not sufficient evidence to support the assumption of rapid and complete hydrolysis of the parent substances. Hence the toxicokinetic behaviour of the parent substances and intermediate hydrolysis products needs to be considered in the prediction.

ECHA considers that the claim of similar toxicity profiles of the source and target substances as a result of similar toxicokinetic profile is not substantiated and it is based on scientifically unconfirmed assumptions.

Therefore, it is not possible to verify the assumption that only the proposed silanol hydrolysis products are relevant to drive the toxicity profiles of source and target substances.

d. Conclusion on the read-across approach

ECHA notes that in the Registrant's comments to the Member State Competent Authority's proposal for amendment the Registrant agrees that there are elements of the read-across strategy missing.

ECHA reminds the Registrant that as per the note for consideration in Section IIB above, the Registrant may adapt the testing requested above. Any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.); Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.); and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects these adaptations in the technical dossier that are based on Annex XI, Section 1.5.

1. Melting/freezing point (Annex VII, Section 7.2.)

"Melting/freezing point" is a standard information requirement as laid down in Annex VII, Section 7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The registrant has sought to adapt the information requirement for this endpoint using the justification : *"A melting point of <-60°C is reported in secondary literature; the reliability could not be assigned. However, it is sufficient to indicate that the melting point is well below the cut-off of -20°C identified in Column 2 of REACH Annex VII."*

The technical dossier contains data for this standard information requirement, which according to the information provided by the Registrant meets Klimisch criterion 4 only and is therefore not assignable. The Klimisch criterion is a system to assess the reliability of data as laid out in the Guidance on information requirements and chemical safety assessment Chapter R.4: Evaluation of available information, Section R.4.2. (Version of December 2011).

ECHA concludes that the Registrant has not provided any reliable data and has therefore not fulfilled the standard information requirement of Section 7.8. of Annex VII of the REACH Regulation.

The Registrant sought further to adapt the information requirement, as he provided a justification based on data with unassignable reliability. The adaptation is therefore neither sufficiently justified nor supported by factual evidence. The Registrant is therefore requested to submit the information for this endpoint using an appropriate test method on the registered substance.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Melting/freezing temperature (test method: EU A.1.) or Melting point / melting range (test method: OECD 102).

2. Flash-point (Annex VII, Section 7.9.)

"Flash-point" is a standard information requirement as laid down in Annex VII, Section 7.9. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant provided two values for flash point sourced from SDSs with neither further information (i.e. study summary) nor justification supporting the information.

The use of information from safety data sheets to address information requirements creates a circular reference when preparing safety data sheets for communicating to downstream users the conditions of safe use of the substance subject to this decision. Information on the original study, i.e. the study summary, must be available in the registration dossier to enable the assessment of the reliability of the information provided for this endpoint.

As no study summary was provided, the data neither fulfils the standard information requirement nor the conditions for adapting the standard information requirement in accordance with Section 1.1.1. of Annex XI.

As consequence, the technical dossier contains data for this standard information requirement, which is not assignable (Klimisch 4). The Klimisch criterion is a system to assess the reliability of data as laid out in the Guidance on information requirements and chemical safety assessment Chapter R.4: Evaluation of available information, Section R.4.2. (Version of December 2011).

ECHA concludes that the Registrant has not provided any reliable data and has therefore not fulfilled the standard information requirement of Annex VII, Section 7.9. of the REACH Regulation. He has neither made an adaptation to the standard information requirement.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Flash-point. Appropriate test methods are listed in Regulation (EC) No 1272/2008 (the CLP Regulation), Annex I, Section 2.6.4.4.

3. *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2.)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has sought to adapt this information requirement by applying read-across according to Annex XI, 1.5. In this respect, the Registrant has provided a study record of an *in vitro* cytogenicity study in mammalian cells according to OECD 473/ EU Method B.10. (*In vitro* Mammalian Chromosome Aberration Test) using the reference-substance 3-aminopropyltriethoxysilane, CAS No 919-30-2 (EC No 213-048-41983).

In their comments on the draft decision and their subsequent update, the Registrant has provided a revised read-across and grouping adaptation. ECHA has assessed the new information and concludes that information provided does not meet the general rules for adaptation of Annex XI, Section 1.5., as explained in Section Section III.B.0. above.

The Registrant has also provided a read-across study record of an *in vivo* mammalian erythrocyte micronucleus test equivalent or similar to OECD 474 (Mammalian Erythrocyte Micronucleus Test) with deviations using the reference substance 3-aminopropyltriethoxysilane, CAS No 919-30-2 (EC No 213-048-4).

The Registrant has not explicitly claimed the adaptation according to Annex VIII, Column 2 of Section 8.4.2. However, ECHA understands that the Registrant provided this *in vivo* read-across study record to adapt the standard information requirement of Annex VIII, 8.4.2 according to Annex VIII, Column 2 of Section 8.4.2; i.e. "*the study does not need to be conducted if adequate data from an in vivo cytogenicity test are available*".

In order to assess whether the *in vivo* study provides adequate data for said Column 2 adaptation, it is necessary to evaluate the underlying read-across according to Annex XI, 1.5. first. However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, 1.5. for the reasons set out inSection III.B.0. above.

Therefore, the adaptations of the information requirement suggested by the Registrant cannot be accepted because the in vivo study done on the read-across substance does not provide adequate data to meet the requirements of Annex VIII, Column 2 of Section 8.4.2. for the registered substance.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* cytogenicity study in mammalian cells (test method: OECD 473) or *in vitro* mammalian cell micronucleus study (test method: OECD 487).

4. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.)

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

The Registrant has sought to adapt this information requirement by applying read-across according to Annex XI, 1.5. In this respect, the Registrant has provided a study record of a sub-chronic toxicity study according to OECD 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) using the reference substance 3-aminopropyltriethoxysilane, CAS No 919-30-2 (EC No 213-048-4).

In their comments on the draft decision and their subsequent update, the Registrant has provided a revised read-across and grouping adaptation. ECHA has assessed the new information and concludes that information provided does not meet the general rules for adaptation of Annex XI, Section 1.5., as explained in Section Section III.B.0. above.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In light of the properties of the substance (i.e., liquid with low vapour pressure and systemic effects seen after oral exposure) and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD 408) in rats.

5. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

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

The Registrant has sought to adapt this information requirement by applying read-across according to Annex XI, 1.5. In this respect, the Registrant has provided a study record of a pre-natal developmental toxicity study according to EPA OTS 798.4900 (similar to OECD 414) using the reference substance 3-aminopropyltriethoxysilane, CAS No 919-30-2 (EC No 213-048-4).

In their comments on the draft decision and their subsequent update, the Registrant has provided a revised read-across and grouping adaptation. ECHA has assessed the new information and concludes that information provided does not meet the general rules for adaptation of Annex XI, Section 1.5., as explained in Section Section III.B.0. above.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rats or rabbits by the oral route.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight of evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

IV. Deadline

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study or an extended one-generation reproductive toxicity study (Annex X, 8.7.3.).

As the request for this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID6 dossier is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

V. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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.