EUROPEAN CHEMICALS AGENCY

Helsinki, 10 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465874-35-01/F
Substance name: Triethoxy(vinyl)silane
EC number: 201-081-7
CAS number: 78-08-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30 October 2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed tests for Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats), inhalation route and Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, inhalation route with an analogue substance trimethoxy(vinyl)silane, EC No 220-449-8 are rejected, you are requested to perform:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**
2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohort 3 (Developmental immunotoxicity)**

You are additionally requested to perform:

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

You have to submit the requested information in an updated registration dossier by **18 October 2021**. You also have to update the chemical safety report, where relevant.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment C4

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance triethoxy(vinyl)silane (EC: 201-081-7; CAS: 78-08-0), hereafter referred to as HD5 or "target substance".

In relation to the testing proposals subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirements for pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) and for an extended one-generation reproductive toxicity study (Anne X, Section 8.7.3.). For both information requirements you propose to test the analogue substance trimethoxy(vinyl)silane, (EC: 220-449-8; CAS: 2768-02-7) hereafter referred to as "source substance") and to use the results to adapt the standard information requirements for your registered substance by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach before assessing the individual endpoints in sections 1 and 2.

Grouping of substances and read-across approach

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*".

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

a. Description of the grouping and read-across approach proposed by you

You have proposed to cover the standard information requirements for a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) and an extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) by performing the tests with the source substance: trimethoxy(vinyl)silane (EC: 220-449-8; CAS: 2768-02-7).

You have provided a read-across justification in the Chemical Safety Report (CSR), Section 5.6.3. and a Testing Proposal Justification ([redacted] as a separate attachment in Section 13 of the IUCLID dossier. To further support your read-across approach you have provided the following documents as separate attachments in IUCLID, Section 13:

- [redacted] document, summarising the information on the

physicochemical and toxicological properties of substances in the alkyl alkoxysilanes and silanols analogue group.

- [redacted] document which 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.

You state that "*The source substance was selected as the most appropriate based on chemical structure and also reflects the worst-case in respect of the effects observed in available studies*". You further say that after oral and inhalation application the target and the source substances "*hydrolyse rapidly to the same silanol hydrolysis product, vinylsilanetriol".*

You use the following arguments to support the prediction of properties of the target substance from data of the source substance:

- Structural similarity: you explain that the two substances contain a silicon moiety and three alkoxy groups. The target and source substance differ in the type of the alkoxy groups: ethoxy- and methoxy-, respectively.

- Similar physicochemical properties: "*endpoints demonstration similarity include: water solubility (soluble), boiling point (123-169 °C), density (0.92-0.97 g/cm^3), vapour pressure (low to medium volatility), partition coefficient (log Pow between 1.1 and 3.0), flammability (flammable), surface tension (not surface active), viscosity (low viscosity)*"

- Similar hydrolysis: you provide QSAR data on the hydrolysis of the target and the source substances and state that they are "*hydrolysing rapidly at pH 7*" to a common final product vinylsilanetriol and the predicted half-life is 0.9 h for the target and 0.2 h for the source substance. You further state that "*at acidic pH the reaction is very rapid; the calculated half-life at pH 2 and 37.5 °C is 5 s*".

- Similar toxicological properties: you state that "*the analogue group of vinyl alkoxysilanes is based on similarities in physicochemical and toxicological properties*".

As an integral part of this prediction, you propose that the target and source substances have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

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

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

(i) Structural (dis)similarities

Structural similarity is a prerequisite for applying the grouping and read-across approach, however, ECHA does not accept in general or in this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA notes that you have sufficiently described in your read-across justification document the structural similarities between the target and source substances. However, you have not explained how the structural dissimilarities (ethoxy and methoxy groups) would impact the hydrolysis rates of the parent substances as well as the formation of the intermediate hydrolysis products, and consequently the toxicity profiles of the substances.

(ii) Support of a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.*" One prerequisite for a prediction based on read-across therefore is that the substances involved are structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

Physicochemical properties

ECHA notes that the physicochemical properties of the target and source substances are within the same range. You acknowledge the differences in the water solubility and the four time difference in the vapour pressure: 304 Pa at 25°C (target substance) vs 1190 Pa at 25°C (source substance) and "*considered appropriate to read-across the mammalian toxicity data from trimethoxy(vinyl)silane to triethoxy(vinyl)silane as a worst case approach*". This information suggests that exposure via inhalation may occur for the target and the source substance. However, ECHA notes that you did not provide any data on the absorption of the target and the source substances to substantiate this "*worst case*" approach as well as you did not explain how these differences will impact the concentration and the distribution of both the parent substances and the hydrolysis products.

Hydrolysis

ECHA notes that there are no measured hydrolysis data for the target and source substances under conditions relevant for oral exposure. In your read-across justification you provided QSAR predictions for hydrolysis half-lives of the target and source substances. You predicted an initial hydrolysis half-life at pH 7, 20°C for the target substance of 54 min (0.9 h) and for the source substance - 12 min (0.2 h). In addition, you have provided an extrapolated hydrolysis half-life of 5 seconds, for pH 2 at 37°C for both substances. ECHA notes that you have postulated that the rate of the hydrolysis reaction is dependent on hydronium ion concentration and that there will be a 100-fold increase in hydrolysis rate on going from pH 4 to pH 2. ECHA accepts that the hydrolysis is catalysed by the hydronium ion, however there is no evidence provided to suggest such a dependence on the hydronium ion concentration and consequently ECHA considers the assumption of a 100 fold increase in hydrolysis rate on going from pH 4 to pH 2 as not supported by scientific evidence.

The QSAR predictions suggest that exposure to the parent compounds may occur, however, ECHA notes that you did not explain why the difference in the initial hydrolysis would not lead to differences in the toxicity profile of target and source substances.

Further, ECHA notes that the hydrolysis of the target and source substances is a step-wise process. However, in the CSR and in the IUCLID dossier, you only address the first hydrolysis step and did not provide any information on the type of the intermediate hydrolysis products formed and on their hydrolysis rates. ECHA points out that differences in the hydrolysis kinetics could lead to qualitative and quantitative differences in the systemic availability of the parent substances and their hydrolysis products and, consequently, to influence differently the toxicity of the target and source substances.

In addition, ECHA notes that in the Chemical Safety Report (1.3.) you say that silanetriols "*may undergo condensation reactions to give siloxane dimers, oligomers and polymers*". Further, ECHA observes that your dossier does not contain information, neither for the target nor for the source substance, about the conditions under which the condensation reaction occurs. In particular, substance specific concentration limit, specific pH, temperature and impact of the groups bound to the Si atom are not defined. Most importantly, the nature of the condensation products (e.g. size distribution) and their rate of formation under conditions relevant to the proposed test(s) are not clear.

In summary, from the presented information it is not clear whether the parent substances, the monomer form of the silanol hydrolysis products or the condensation products will be predominant in terms of bioavailability and hence would drive the toxicity of target and source substances

Toxicity profile

You postulate that target and source substances have similar toxicological profile. Based on the data submitted for acute toxicity, irritation, sensitization and genetic toxicity, the source and target substances show similar toxicity profiles, i.e. no effects were observed. Further, for the repeated-dose toxicity you say that for the target and the source substances "*the main effects were also observed in kidney and urinary bladder. It is therefore considered appropriate to read-across the toxicity data from trimethoxy(vinyl) silane (CAS 2768-02-7) to triethoxy(vinyl) silane (CAS 78-08-0) as a worst-case approach*".

In regard to the systemic toxicity, you have submitted the following repeated-dose toxicity studies, relevant for this endpoint:

with the target substance:

1. Range finding short-term (9-day) repeated-dose toxicity inhalation study (GLP compliant, comparable to OECD 413, reliability 2) at concentrations of 100, 500 and 1000 ppm (*Repeated dose toxicity: inhalation* [redacted], *1994*). Target organs: kidney and urinary. NOAEC = 100 ppm (equivalent to 775 mg/m^3).
2. Key Repeated dose toxicity study (90-day) via inhalation route (OECD TG 413; reliability 2) at concentrations of 5, 15, 50 ppm (*Key Repeated dose toxicity: inhalation* [redacted], *1994*). NOAEC = 50 ppm (equivalent to 388.3 mg/m^3).
3. 28-day inhalation toxicity study (GLP compliant, OECD TG 412, reliability 4) in male rats, at 145 mg/m^3 (*Repeated dose toxicity: inhalation* [redacted] *1991*). No effects observed.

and with the source substance:

4. Repeated dose toxicity study (90-day) via inhalation route (OECD TG 413) in rats, at concentrations of 10, 100, 400 ppm). Target organs: kidney and urinary bladder. NOAEC = 100 ppm (equivalent to 606 mg/m^3).
5. Key Reproduction/Developmental Toxicity Screening Test (OECD TG 422; reliability 1) via oral route, doses of 0, 62.5, 250, 1000 mg/kg bw/day. ([redacted], 2005). LOAEL = 250 mg/kg bw/day was set, based on histopathological changes in kidney and urinary bladder.

In addition, a 9-day range-finding inhalation study with the source substance is reported in the ECHA dissemination website:

6. Range finding short-term (9-day) repeated dose toxicity inhalation study (GLP compliant, comparable to OECD 413, reliability 2) at concentrations 150, 750, or 1500 ppm). Target organ: kidney. NOAEC = 150 ppm (equivalent to 908 mg/m^3)

Taking into account the presented information, ECHA understands that you based your "worst case" approach on the toxicological information from inhalation toxicity studies, available for the target and the source substances. Therefore, ECHA has analysed the studies in light of your hypothesis of *"a worst-case approach"* and has the following observations:

With regards to the similar target organs:

- Based on the information for the target substance, ECHA notes that in the range-finding study (1), effects in kidney and urinary tract are reported at concentration levels of 500 ppm and above. ECHA further observes that no such effects are reported neither at the highest tested concentration of 50 ppm in the 90-day study (2) nor at the only concentration of [redacted] mg/m^3 tested in the 28-day study (3). ECHA considers that the toxicity of the registered substance cannot be verified, due to too low concentrations used in the 90-day and the 28-day toxicity studies.

- For the source substance, ECHA notes that kidney and urinary bladder are reported as the main target organs both after 9-day (6) and 90-day (4) of administration via inhalation. These effects are also supported by the 28-day oral-gavage study (5) in rats.

- Based on the analysis of the available information, ECHA considers that despite the lack of reliable sub-chronic toxicity study with the target substance, the target and the source substance seem to have the same target organ toxicity after repeated-dose administration.

With regard to your statement that the source substance can be regarded as a worst case:

- Firstly, ECHA notes that the NOAEC values for the target and the source substance, set from the two range-finding studies (1 and 6) are at comparable level: $NOAEC_{target\ substance}$ = 100 ppm (775 mg/m^3) vs $NOAEC_{source\ substance}$ = 150 ppm (908 mg/m^3). Since the substances have NOAEC values at comparable concentrations, ECHA considers that it cannot be concluded that the source substance presents the worst case.

- Secondly, the lack of effects in the 90-day toxicity study with the target substance, due to too low tested concentrations, does not allow the comparison of the toxicity profiles of the target and the source substances after sub-chronic administration.

- Thirdly, ECHA points out that information from repeated dose toxicity studies does not constitute, on its own, relevant supporting information to establish a worst-case for reproductive and developmental toxicity properties. ECHA acknowledges that for the source substance you have provided a screening for reproduction and developmental toxicity study (OECD TG 422). However, you have not provided such study for the target substance. Therefore, ECHA considers that comparison of the toxicological profile regarding reproductive/developmental toxicity of the target and the source substances is not possible.

In your comments to the draft decision, you proposed that ECHA postpones the decision making for one year. During this year, you intend to refine and improve the argumentation regarding the lack of information on hydrolysis behaviour between the source and target substances. In addition, you intend to conduct an OECD TG 422 study on the target substance in order to compare the toxicological profiles of the source and target substances. You proposed to update the dossier and requested an intermediate evaluation by ECHA after one year to either confirm or reject the updated read-across adaptation. You also proposed that ECHA would take a decision on the acceptance of the updated read-across adaptation.

ECHA does not have a policy of postponing the decision making process nor performing any interim evaluations on an ongoing decision making process. It is fully at your own discretion to perform any additional studies outside the Annex IX and X information requirements, and/or to gather additional information to support and refine the rejected read-across adaptation. Any new data will be evaluated by ECHA once the deadline in the decision has expired.

Outcome

Based on the above presented analysis, ECHA considers that you did not provide enough arguments to support the proposed "worst-case" read-across approach for the properties reproductive and developmental toxicity.

Conclusion on the read-across approach

Based on the data submitted by you, ECHA concludes that you have not provided adequate and reliable information to demonstrate that the criteria of Annex XI, 1.5. are met and that read-across approach is plausible to meet the information requirements for pre-natal developmental toxicity (Annex IX, section 8.7.2) and extended one-generation reproductive toxicity (Annex X, section 8.7.3). Consequently, the testing proposed on the source substance is not appropriate to fulfil the information requirements for 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 in rats according to EU B.31./OECD TG 414 by inhalation with the source substance trimethoxy(vinyl)silane (EC: 220-449-8).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your testing proposal to perform the test with the source substance (EC: 220-449-8; CAS: 2768-02-7). As explained in the section "Grouping of substances and read-across approach" above, your adaptation of this information requirement is rejected.

ECHA considers that a study performed with the target substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: OECD TG 414, while your originally proposed test for Pre-natal developmental toxicity study in a first species (test method: OECD TG 414) with the source substance trimethoxy(vinyl)silane (EC: 220-449-8; CAS: 2768-02-7) via inhalation route is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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.

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the target 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 an extended one-generation reproductive toxicity study in rats by inhalation route according to OECD TG 443 with the source substance trimethoxy(vinyl)silane (EC: 220-449-8; CAS: 2768-02-7).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your testing proposal to perform the test with the source substance (EC: 220-449-8; CAS: 2768-02-7). As explained above in the section "Grouping of substances and read-across approach" your adaptation of the information requirement is rejected. Hence there is a need to test the registered substance.

Adequate information on this endpoint needs to be present in the technical dossier for the target substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the

ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include an extension of Cohort 1B and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA notes that for the target substance, the conditions of column 2, Section 8.7.3., Annex X are not met. Therefore, ECHA agrees that the criteria to extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.
You proposed not to include Cohorts 2A and 2B and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Therefore, ECHA agrees that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

ECHA notes that the existing information on trimethoxy(vinyll)silane (EC: 220-449-8), substance structurally analogous to the target substance, derived from an available Combined Repeated Dose and Reproductive/ Developmental Toxicity Screening Test oral

study (OECD TG 422) *([redacted], 2005)* shows evidence of adverse effects on thymus. You have provided detailed findings in tabular format, showing a statistically significant decrease of absolute thymus weight in females at non-lethal low and mid dose levels. The decrease was by 16.6% and 19.5%, respectively and was not accompanied by body weight reduction. This raises concern and warrant the assessment of developmental immunotoxicity.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study performed with the source substance trimethoxy(vinyl)silane.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohort 3 (Developmental immunotoxicity).

while your originally proposed test for Extended one-generation reproductive toxicity study (test method EU B.56./ OECD TG 443), in rat, inhalation route, with the source substance trimethoxy(vinyl)silane (EC: 220-449-8; CAS: 2768-02-7) is rejected according to Article 40(3)(d) of the REACH Regulation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were

identified. However, you may expand the study by including the extension of Cohort 1B and the Cohorts 2A and 2B if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

3. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance target for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

As outlined above under 1. ECHA has requested a pre-natal developmental toxicity study in a first species according to OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.). Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed in a second species (rabbit or rats), depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid. ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit or rat), oral route (test method: OECD TG 414).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 30 October 2017.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 7 June 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **5 November 2018**, 30 calendar days after the end of the commenting period.

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).

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 requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

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

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

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

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