EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114426301-65-01/F
Substance name: methylsilanetriyl triacetate
EC number: 224-221-9
CAS number: 4253-34-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30.06.2017
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

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

While your originally proposed test for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species rat, using the analogue substance trimethoxy(methyl)silane (CAS No 1185-55-0, EC No 214-685-0)

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 submitted by you for the registered substance triethoxy(methyl)silane CAS No 2031-67-6 (EC No 217-983-9) (hereafter referred to as "target substance").

In relation to the testing proposal subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirement for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.). In your testing strategy you propose to test the analogue substance trimethoxy(methyl)silane, CAS No 1185-55-3 (EC No 214-685-0; hereafter referred to as "source substance"). The results from the structural analogues 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).

In your comments to the draft decision you did not provide considerations to the specific endpoint, subject to the current decision.

After receiving the draft decision you updated your registration with the submission number [redacted]. Therein you have changed your strategy and provided an argument, based on existing data, why you consider that testing is not needed to fulfil the standard information requirement for a pre-natal developmental toxicity study. ECHA has addressed your argument in 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 hypothesis
Methylsilanetriyl triacetate hydrolyses very rapidly in contact with water (half-life <12 seconds at pH 7), generating acetic acid and methylsilanetriol (see Section 5.2.1). Trimethoxy(methyl)silane (CAS 1185-55-3) hydrolyses more slowly at pH 7 (half-life ca. 2.2 hours), at pH 2 and 37.5 °C, such as in the stomach following ingestion, hydrolysis is much more rapid (predicted half-life ca. 5 seconds), and at pH 7 and 37.5 °C (i. e. blood temperature) the hydrolysis half-life is approximately 0.8 hours. The relevant hydrolysis products are methanol and methylsilanetriol. Both parent materials therefore generate the same silanol hydrolysis product and read-across of data is directly relevant. Regarding systemic exposure the toxicity of trimethoxy(methyl)silane is seen as predictive (worst case) for methylsilanetriyl triacetate.
The non-silanol hydrolysis product, methanol, is not expected to contribute to any adverse effects for systemic or reproductive toxicity at the relevant dose levels. This is discussed further below.
Local corrosive effects of methylsilanetriyl triacetate can be assessed qualitatively or quantitatively by considering the amount of acetic acid produced by hydrolysis."

"The registration and read-across substances belong to an analogue group of trialkoxy and triacetoxysilanes containing non-functional alkyl groups."

"The basis of the read across is the hydrolytic stability and relevance of the silanetriol hydrolysis products."

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

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

[redacted]

The document [redacted] is summarising the available physico-chemical and toxicological data on related substances.

The document [redacted] 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, "*each CSR needs to describe clearly whether Category, Analogue or QSAR methods have been applied, and which endpoints they are applied to, and the IUCLID entries must be consistent with this*". Based on this document, ECHA understands that you intend to apply analogue approach as a basis for data gap filling which are further justified in each registration dossier and CSR.

The document [redacted] "*outlines the approach*" to mammalian toxicity of alkyl alkoxysilanes and silanols. It is explained that individual substances have been grouped for

the "*purposes of strategy and read-across approaches*". A summary of mammalian toxicity and data matrix is provided. It is stated that "*where there are data gaps, read-across will be performed from the closest available structurally related substance*". The document does not provide information on the (read-across) approach used for individual substances, but states that "*Details of test proposals and justification of read-across are given in individual Chemical Safety Reports*".

Apart from the above general information you have provided the substance specific read-across hypothesis and justification, in the technical dossier, under the endpoint study summary for repeated dose toxicity, in Section 7.5 and in the Chemical Safety Report (CSR) in section 5.

This information includes the read-across hypothesis and justification, the identification of the source and target substances; comparison of the structural features, physico-chemical properties, predicted toxicokinetics properties and acute dose toxicity of the source and target substances. In the same place you also discuss the repeated systemic toxicity and the local toxicity of the non-silanol hydrolysis products and conclude on your read-across approach.

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

For the target substance:
- an acute inhalation toxicity study (non-guideline, non GLP, [redacted] 1961).

For the source substance:
- a combined repeated dose toxicity with reproduction developmental toxicity screening test via oral route (OECD 422, [redacted] (2005));
- a sub-chronic repeated dose toxicity study via inhalation (OECD 413, [redacted] (2007));

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 trialkoxy and triacetoxysilanes 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 trimethoxy(methyl)silane, CAS No 1185-55-3 (EC No 214-685-0) as a source substance.
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 the same silanol hydrolysis product is formed;
- due to the similarity of the physico-chemical properties of the parent substances and their silanol hydrolysis product the substances would possess similar toxicokinetic profile;
- and hence the toxicological properties of the substances would be similar.

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 silanol hydrolysis product (methylsilanetriol);
- and that the formed silanol substance is exclusively relevant in terms of bioavailability via oral route and hence would drive the systemic toxicity.

In addition, you claim that the non-silanol hydrolysis product methanol 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 silanol hydrolysis products as the driver for the systemic toxicity of the parent substances.

(i) Substance characterisation of source and target substances

The substance characterisation of the source substances need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 "How to report on Read-Across" it is recommended to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

ECHA notes that the source substance has solely been characterised by its chemical name CAS No and EC No and no information on the composition or impurities has been provided in the technical dossier of the target substance.

In the read-across justification document you state *that "Detailed information on the purity/impurity profiles of substances in the analogue group is not described in detail in this report for reasons of commercial confidentiality. Substance-specific Substance Identity Profiles are available for all registered substances and these are included in the appropriate technical dossiers. In general, the substances in this group are typically monoconstituent substances of high purity (>90%) and typical impurities are other alkoxysilanes, alcohols or closely related substances. The specific identity of any impurities would not impact upon the approaches or conclusions for the endpoints covered by this report. In any case where a classified impurity is identified, the implications of this will be described in the individual Chemical Safety Report(s)."*

ECHA notes that the above general statement is not sufficient, for the following reasons.

Firstly, it is not supported by substance specific analysis of the possible differences in the composition and impurity profiles of the source and target substances and the impact they may have on the proposed prediction.

Secondly, ECHA notes that you have not clearly identified to which 'appropriate technical dossiers' you are referring to, which prevents ECHA from assessing the relevant data contained therein.

Finally, as already indicated by you, commercial confidentiality is at stake – which may also prevent ECHA from discussing with you the implications of potential substances' differences if it would be based solely on the data present in another registrant's dossier.

ECHA considers that currently the composition and the impurity profile of the source and target substances cannot be compared using the information provided in the registration dossier. Therefore, ECHA cannot reach conclusion whether the source substance can be used to predict properties for the registered substance.

(ii) 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 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.

You have described the structural similarities between target and source substances by indicating that they both *"belong to an analogue group of trialkoxy and triacetoxysilanes containing non-functional alkyl groups"*. ECHA notes that in addition to the structural similarities, structural differences can be observed. Whereas the source substance contains three alkoxy (-OMe, methoxy) groups, the target substance is an acetoxysilane, containing three carboxylate groups (i.e. acetoxy groups) 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 the same silanol hydrolysis product methylsilanetriol.

ECHA notes that you have not provided any information on how the structural differences 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.

(iii) 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 your read-across justification you state that physico-chemical parameters/properties of target and source substances are *"in the same range"*. You have proposed that the similar physico-chemical properties of the target and source substances support the structural similarity and enable the read across between the substances. ECHA observes that the

physico-chemical properties of target and source substances are in the same range except the vapour pressure of the parent (source and target) substances. Comparison of the vapour pressure of the parent compounds reveals that the vapour pressure of the source substance is approximately 400 fold higher as that of the target substance.

ECHA notes that you have not explained how the presented difference affects the prediction.

You claim under "Similar toxicokinetics" that *"any absorption in the intestine would almost exclusively relate to hydrolysis products. For the oral route, the read-across is therefore directly relevant ..."* and *"with respect to volatility, the read-across substance represents a worst case in terms of potential inhalation exposure..."*
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 product methylsilanetriol.

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 product. Hence the predicted toxicokinetic profile of the target and source substance cannot be considered as valid, as it is based on scientifically unconfirmed assumptions.

ECHA further observes and as pointed out above, the volatility of the (parent) source substance is approximately 400 fold higher as that of the target substance which may represent a worst case scenario in terms of bioavailability of the parent substances. However, you did not explain why the source substance would represent a worst case in terms of toxicity. In addition you have not explained how the bioavailability of the parent substances is connected to your hypothesis which emphasises the relevance of the silanol hydrolysis product *"Both parent materials therefore generate the same silanol hydrolysis product and read-across of data is directly relevant."*.

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.

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 product is relevant to drive the toxicity profiles of source and target substances.

You further propose that *"In the case of repeated dose toxicity and reproductive toxicity relevant properties are structural similarity as well as physical-chemical and basic toxicological parameters in the same range"*. ECHA notes that the dossier contains several acute oral toxicity studies (OECD 401, [redacted] (2001); OECD 401, [redacted] (1979); OECD 401, [redacted] (1981a); OECD 401, [redacted] (1981b) and a non-guideline study, [redacted] (1970a)) and an acute inhalation toxicity study (non-guideline, non GLP, [redacted] 1961) with the target

substance. For the source substance a sub-chronic repeated dose toxicity study via inhalation (OECD 413, [redacted] (2007)), and a combined repeated dose toxicity with reproduction developmental toxicity screening test via oral route (OECD 422, [redacted] (2005)) is provided in the dossier.
ECHA notes that acute toxicity data alone is not sufficient to establish the toxicological profile of a substance with regard to toxicity to reproduction and/or pre-natal development. As no higher tier study, e.g. a screening study, is available for the target 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.

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

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 the same silanol hydrolysis products methylsilanetriol. 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 silanetriol hydrolysis products".*

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 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 product which is 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 and source substance would involve three hydrolysis steps. In the hydrolysis studies 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, you have not substantiated your assumption of a complete hydrolysis. In fact, the hydrolysis process which involves several steps may produce also other substances, which possible presence and effects on your hypothesis you have not addressed.

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 product may undergo condensation reactions leading to the formation of siloxane dimers, oligomers and polymers and state that:
"A highly cross-linked gel may form. 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. Significant condensation is not expected at concentrations less than approximately 100 mg/l, but is dependent on specific conditions.*
- *pH;the condensation reaction may be either acid or base catalysed.*
- *Temperature.*
- *Other species present.*
- *Timescale.*
- *The nature of the R-group.*
- *The number of Si-OH groups; 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 tests 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.

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. acetic acid from the target substance and methanol from the source substance. You claim that the non-silanol hydrolysis product methanol play no significant role in the systemic toxicity of the substances as *"The non-silanol hydrolysis product, methanol, is not expected to contribute to any adverse effects for systemic or reproductive toxicity at the relevant dose levels."* and the *"Local corrosive effects of methylsilanetriyl triacetate can be assessed qualitatively or quantitatively by considering the amount of acetic acid produced by hydrolysis.".*

ECHA notes that in your read across justification you have not provided information on the *"relevant dose levels".* ECHA observes that you report on systemic effects, such as muscle imbalance, increase in blood cholinesterase activity, decrease in albumins and decreased growth, caused by prolonged inhalation exposure to acetic acid. However you did not address adequately whether and how the presence of the acetic acid influences the prenatal developmental toxicity of the target substance and how the presence of different non-silanol hydrolysis products affects the prediction.

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 endpoints 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 in rats according to EU B.31./OECD TG 414 with the analogue substance trimethoxy(methyl)silane (CAS No 1185-55-0, EC No 214-685-0).

ECHA has evaluated your proposal to perform the test with the analogue substance. As explained in Section 0 *'Grouping of substances and read-across approach'* of this decision, your adaptation of the information requirements cannot be accepted. Hence there is a need to test the registered substance.

In your updated dossier you have attempted to adapt the current information requirements using a new strategy, based on existing information.

In your justification document attached to section 7.8.2 of your updated registration dossier you state that:
"Therefore, data from the hydrolysis product acetic acid are used to assess the potential general systemic and local toxicity of methylsilanetriyl triacetate. This is consistent with the Column 2 adaptation for short-term repeat dose toxicity which states studies do not need to be conducted "where a substance undergoes immediate disintegration and there are sufficient data on the cleavage products"

In addition in your IUCLID dossier you state that *"In accordance with Section 2 of REACH Annex XI testing for developmental toxicity (required in Section 8.7.2) will be omitted because it is technically not feasible. The known corrosive effects of methylsilanetriyl*

triacetate mean that testing via all routes at suitable dose levels would lead to severe local effects and significant distress in the test species."

ECHA has assessed your arguments and notes the following shortcomings:

(a) In your first line of argument you attempt to waive the information requirement subject to the current decision based on a column 2 adaption for short-term repeat dose toxicity, due to the immediate disintegration of the registered substance.

ECHA considers that the above mentioned provision (column 2, Section 8.6. of Annex VIII) is not a valid adaptation rule for reproductive toxicity studies (Section 8.7. of Annex IX) according to REACH regulation.

(b) In your second-line of argument you intend to waive the information requirements subject to the current decision, because according to you the registered substance is corrosive and hence it is technically not feasible to conduct a pre-natal developmental toxicity study.

ECHA considers that corrosivity or classification as corrosive *per se* is not an adaptation rule for reproductive toxicity studies.

Eventually, ECHA points out that the following experimental data used to support your claim that the registered substance is corrosive in the gastrointestinal tract and referred to in your waiver document was generated by testing substances unchanged, without vehicles:
(i) an acute dose toxicity study with the registered substance ([redacted] 2001) and,
(ii) a 7 days dose range finding study via oral route with triacetoxy(ethyl)silane (CAS 17689-77-9) ([redacted] 2004).
You also argue that in order to conclude on the corrosivity of a substance thorough macroscopic examinations and clinical observations are essential. ECHA observes however that you acknowledge the absence of such investigation in the above mentioned (i) acute dose toxicity study with the registered substance. Consequently, this study does not allow to conclude on the presence of signs of corrosion in the gastrointestinal tract.

ECHA considers that even for corrosive substances there are provisions that require testing and allow conditions that are adequate to achieve results. In accordance with the ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) when testing corrosive or highly irritating substances in reproductive toxicity studies *"The vehicle should be chosen to minimise gastrointestinal irritation."*
In addition the guidance document also explains that *"For some substances dietary administration may allow adequate dosing without irritation compared with oral gavage dosing. In certain cases, testing of neutral salts of alkaline or acidic substances may be appropriate and allows investigation of intrinsic properties at adequate dose levels"*

ECHA notes that your dossier does not contain records of any attempt to apply a testing strategy which would allow to investigate the intrinsic properties of these substances at adequate dose levels. Hence, ECHA concludes that you have not demonstrated that the registered substance could not be successfully tested with the application of an appropriate testing strategy *e.g.* by the use of an appropriate vehicle or via dietary administration or in form of a neutral salt.

Additionally, ECHA notes that the registered substance hydrolyses, producing acetic acid and a silanol hydrolysis product methylsilanetriol. ECHA observes that you provide a brief summary on the toxicological properties of the hydrolysis/cleavage product acetic acid. On the contrary, you do not provide any information on the silanol hydrolyis product, methylsilanetriol. ECHA considers that your new arguments do not take into consideration the potential systemic toxicity effects of methylsilanetriol.

In summary, ECHA concludes that your new arguments do not provide any valid information to fulfil or waive the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

ECHA considers that a pre-natal developmental study performed with the registered substance is necessary and 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 the basis of this default consideration, ECHA considers testing should be performed with the rat or 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 4.1, October 2015) 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.

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 in rats according to EU B.31./OECD TG 414 with the analogue substance trimethoxy(methyl)silane (CAS No 1185-55-0, EC No 214-685-0) 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 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

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 your registration containing the testing proposals for examination pursuant to Article 40(1) on 13 March 2013.

ECHA held a third party consultation for the testing proposals from 16 March 2015 until 30 April 2015. ECHA did not receive information from third parties.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments. In your comments to the draft decision you did not provide specific considerations to the endpoint subject to the current decision.

You were notified that the draft decision does not take into account any updates after 06 July 2016.

However, following your request and justification provided (including interlinked read-across testing strategy on several supposedly related registered substances) ECHA has exceptionally granted you additional time until 30 June 2017 for the update.

You updated your registration on 30 June 2017 ECHA exceptionally took the information in the updated registration into account, and did not amend the request.

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.