EUROPEAN CHEMICALS AGENCY

Helsinki, 18 May 2018

Addressee: [redacted]

Decision number: CCH-D-2114405896-41-01/F
Substance name: Trimethoxyvinylsilane
EC number: 220-449-8
CAS number: 2768-02-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/03/2016
Registered tonnage band: Over 1000 tonnes

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Spectral data (Annex VI, Section 2.3.5.) on the registered substance;**
   - **Nuclear magnetic resonance or mass spectrum**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least two weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohort 3 (Developmental immunotoxicity).**

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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **25 November 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of 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.

The scope of this compliance check decision is limited to the standard information requirements of Annex IX, Section 8.7.2. and Annex X, Section 8.7.2. and Section 8.7.3. to the REACH Regulation.

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 **Claudio Carlon**, Head of Unit, Evaluation **E2**

[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

IDENTIFICATION OF THE SUBSTANCE

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

1. **Spectral data (Annex VI, Section 2.3.5.) on the registered substance;**

   - **Nuclear magnetic resonance or mass spectrum**

Spectral data is a standard requirement in a registration dossier as laid down in Annex VI Section 2.3.5, of the REACH Regulation. Adequate information is required to be sufficient to enable the identity of the substance to be verified.

The technical dossier does not contain a Ultra-violet (UV) spectrum and/or a Nuclear magnetic resonance (NMR) (or mass (MS) spectrum as alternative) and it does not contain a justification for the non-inclusion of this information.

ECHA regards this required information scientifically necessary to confirm the identification of the registered substance. 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 which also reflect the relative abundance of individual atoms. Alternatively, if an NMR is not available, a mass spectrum can be provided.

ECHA notes that, although the UV spectrum is a REACH requirement, and because the registered substance lacks chromophore in its structure, no significant additional information is expected from this analysis and therefore it can be omitted.

ECHA considers that a request for extension of the commenting deadline submitted on the day of the deadline does not address the request. Therefore ECHA considers that you have not provided any specific comment on the content of the draft decision and the updated dossier you submitted is not taken into account in the decision-making process.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: a NMR spectrum, such as a ^{1}H-NMR and/or a ^{13}C-NMR. As an alternative to an NMR spectrum, a mass spectrum (MS) can be provided.

You shall ensure that the description of the analytical methods used for recording the spectra is specified in the dossier in such detail to allow the methods to be reproduced, in line with the requirements under Annex VI, Section 2.3.7 of the REACH Regulation. You shall ensure that the information is consistent with the information provided throughout the dossier.

As for the reporting of the spectral data in the registration dossier, the information should be included in the IUCLID section 1.4. Further technical details on how to report the requested information are available in the Manual "How to prepare registration and PPORD dossiers" (version: 4.0, May 2017) on the ECHA website.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a)(vi) and/or (vii), and 12(1)(e) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains, for the extended one-generation study endpoint (Annex X, Section 8.7.3.), adaptation arguments in form of a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach in general, before assessing the individual endpoint (request 3).

Grouping and read-across approach for toxicological information

You have sought to adapt the information requirements for an extended one-generation study endpoint (Annex X, Section 8.7.3.) by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments.

However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.
The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common

[2] ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.
[3] ECHA's Read-Across Assessment Framework.

compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

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

You propose to read across between the structurally similar substance, trimethoxy(methyl) silane, EC number 214-685-0 (CAS RN 001185-55-3), as source substance and the substance subject to this decision, trimethoxy(vinyl)silane, EC number 220-449-8 (CAS RN 2768-02-7) as target substance.

In the IUCLID 6, section 7.8.1. of your registration dossier, you provided an argument to adapt the information requirement according to Annex X, Section 8.7.3, as follows: *"In accordance with ECHA Draft Decision number* [redacted]*, the Registrants intend to address the potential hazard related to reproductive toxicity for the registered substance using an extended one-generation reproductive study in the rat (OECD TG 443) via the inhaled route. It is proposed to read-across these data from the structural analogue trimethoxy(methyl) silane (CAS 1185-55-3) for which there is a study proposal to test in an extended one-generation reproductive study in the rat, (OECD TG 443) via the inhaled route. The study will include appropriate cohorts to assess developmental and immunotoxicity and the need for an extension of the 1B cohort to produce an F2 generation will be considered during the study. Full details of the read-across justification, potentially involving the generation and comparison of limited in vivo TK data for the registered and read-across substances, will be provided in the updated dossier with the study results."*

Your dossier contains two documents as a separate attachment in IUCLID, Section 13, relevant to the reproductive toxicity endpoint:

[redacted]

The first document, the [redacted], is an overview of the grouping and read-across methods the [redacted] has relied upon for its REACH submissions. The document provides a description of the general principles applied but does not provide any registered substance-specific information.

You use arguments to support the prediction of properties of the registered substance from data for the reference substance within the group by interpolation to other substances in the group, and argue that the registered substance is part of the class of "[redacted]" (presented as a list in section 8.2.10, Table 8.18), as is the source substance. You add that "[redacted]". You also highlight that "[redacted] *[...] This is a significant part of the explanation of the general lack of metabolism of the substances*" (chapter 2, page 8).

According to you the source and registered substances have "*similar toxicological profiles*" for the above-mentioned information requirements (section 4.8, page 17).

The matrix report you provided (second document) is summarising the available physico-chemical and toxicological data on the analogue group of "[redacted]" to which the registered and source substances belong. You confirm that "*the basis of the read across is the hydrolytic stability and relevance of the [redacted] hydrolysis products. The hydrolysis half-life of the substance has been estimated using weight of evidence from reliable measured data and prediction from a validated QSAR. The estimated half-lives are 0.04 h at pH 4, 0.1 h at pH 7 and 0.004 h at pH 9 and 20-25°C. The analogue methodology takes into account the properties of all hydrolysis products [...].*"

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the reproductive toxicity property of the registered substance from the source substances.

b. ECHA analysis of your grouping and read-across approach

In the following, ECHA examines your basis for predicting the toxicity of the registered substance. According to ECHA's understanding, you suggest that, based on their structural similarities, the target and source substances have similar properties, because:

- the target and source substances undergo similar hydrolysis process and as a result structurally similar silanol hydrolysis products are formed;
- due to the similarity of the physico-chemical properties of the parent substances and their silanol hydrolysis products, the substances would possess similar toxicokinetic profile;
- and hence the toxicological properties of the substances would be similar.

(i) Hydrolysis

ECHA understands that the general hypothesis relies on the assumption that both target and source substances undergo rapid and complete hydrolysis, so there is no systemic exposure to the parent compounds but only to the hydrolysis products, and that they form structurally similar silanol hydrolysis products, namely [redacted], respectively. You propose that, based on the formation and relevance of the similar silanol hydrolysis products, the properties of the source substance can be used to predict the properties of the target substance and that "*[T]the basis of the read across is the hydrolytic stability and relevance of the [redacted] hydrolysis products*".

Firstly, in order to demonstrate that the source and target were appropriately part of the class of "[redacted]", ECHA analysed the information you provided regarding the rate of hydrolysis. You have sought to evaluate this information according to Annex XI, Section 1.2., Weight of evidence.
In the technical dossier you have provided four study records for the registered substance for:

- a hydrolysis study (2001, reliability 2), conducted according to the OECD TG 211 and EU method C.7 (EEC/92/69). However, this study does not provide the information required by Annex VIII, Section 9.2.2.1., because the final results provided were obtained based on calculations derived from a publication ([redacted], 1992) at a different temperature, and were not derived from the hydrolysis study conducted according to OECD TG 211/ EU method C.7. ECHA considers that these results are not reliable.
- a hydrolysis study (2002, reliability 4), relying on a secondary literature source. ECHA concludes that this study does not provide the information required by Annex VIII, Section 9.2.2.1.
- a hydrolysis study (2001, reliability 4), relying on a secondary literature source. ECHA concludes that this study does not provide the information required by Annex VIII, Section 9.2.2.1.

- a hydrolysis study (1991, reliability 4), relying on a secondary literature source. ECHA concludes that this study does not provide the information required by Annex VIII, Section 9.2.2.1.

You have also provided results from a quantitative structure-activity relationship model ((Q)SAR). According to Annex XI, section 1.3. of the REACH Regulation, the conditions for this adaptation are the following:
- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

ECHA notes that the both the registered and the source substances are part of the training set and rely on the above data (2002) for the registered substance and on data which cannot be assessed for the source substance. ECHA therefore considers that the first condition is not met, because the conclusion of the same endpoint study summary cannot be used reliably in a QSAR model if it is considered unreliable in the first place. Consequently the adaptation according to Annex XI, section 1.3 cannot be accepted.

Hence ECHA concludes that the information on hydrolysis half-life at pH 7 is based on assumptions which are not substantiated by data. ECHA considers that there is no reliable hydrolysis data available in the registration dossier for pH 7 for the source substance.

As a consequence you have not excluded that there is systemic exposure to the parent compounds for the source or the target substance. Your read-across hypothesis is based upon rapid hydrolysis and the similarity of the breakdown products, and there is no basis provided for predicting the properties of the parent substances (prior to their hydrolytic breakdown).

For the reason that you have not provided a basis for predicting the properties of systemically available parent compound, the read-across fails to provide a reliable basis for predicting the properties of the registered substance.

Additionally, you have proposed that the properties of the registered substance can be predicted because of the similar properties of the hydrolysis products, such as [redacted] hydrolysis product. However, the [redacted] hydrolysis product from the registered substance is structurally different from the putative hydrolysis products from the source substance, and you have not experimentally identified what this hydrolysis product or products are. You have not provided a reasoning which explains why the properties of the vinyl hydrolysis product from the registered substance can be predicted from the hydrolysis products of the source substance, given that there are structural differences.

For this reason also, you have not provided a reliable basis for predicting the properties of the registered substance.

(ii) Substance characterisation of source and target substances

(iii) The substance characterisation of the source substance needs to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities.

In ECHA's Practical Guide "How to use alternatives to animal testing to fulfil your information requirements for REACH registration" (section 4.4), we recommend to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 2.1, May 2017) 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 and CAS RN and that, no information on the composition or impurities has been provided in the technical dossier of the target substance.

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.

(iv) Similarity based on physico-chemical and/ or structural similarity

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical properties does not necessarily lead to predictable or similar human health properties in other endpoints. For example, effects observed in OECD TG 422 studies (regarding repeated dose toxicity) performed with the source and with the registered substance were more severe with the registered substance. Hence ECHA does not consider that similar physico-chemical properties is a sufficient basis for predicting the human health endpoints, including the extended one-generation reproduction toxicity study endpoint (Annex X, Section 8.7.3.). Therefore your justification based on structural similarity and similar physico-chemical properties has not established why the prediction is reliable for the human health endpoints for which the read across is claimed.

(v) Similar physicochemical properties, toxicokinetics and toxicity

You have proposed that due to similarity of the physico-chemical properties of the parent substances and their silanol hydrolysis products, the substances would possess similar toxicokinetic profile and hence the toxicological properties of the substances would be similar. ECHA notes that you have not provided data showing that the parent substances and their silanol hydrolysis products have similar toxicokinetic profiles, and in the absence of such information, ECHA considers that your speculation about the toxicokinetic profile is not a reliable basis to predict the properties of the registered substance. Additionally, ECHA notes that the toxicokinetic profile of a substance is distinct and independent from the toxicodynamic properties of the substance. Specifically, substances can have similar toxicokinetic profile, but entirely distinct toxicodynamic profile, and so the toxicokinetic profile *per se* does not provide a basis to predict the toxicity of a substance. ECHA therefore finds that your reasoning does not provide a reliable basis for predicting the properties of the registered substance.

c. Conclusion on the read-across approach

ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, for the reasons as set out above, ECHA considers that this grouping and read-across approach does not provide a robust and reliable basis whereby the human health

effects of the registered substance may be predicted from data for the reference substance within the group. Hence this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, 1.5, and these are set out below in the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio) transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered 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). The technical dossier contains information on a pre-natal developmental toxicity study in rats by the inhalation route using the registered substance as test material ([redacted], 1993) (EPA OTS 798.4350) at 3 doses (25, 100 and 300 ppm) .

However, there is no information provided for a pre-natal developmental toxicity study in a second species. Furthermore, the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

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

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second 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.

ECHA considers that a request for extension of the commenting deadline submitted on the day of the deadline does not address the request. Therefore ECHA considers that you have not provided any specific comment on the content of the draft decision and the updated dossier you submitted is not taken into account in the decision-making process. Furthermore ECHA notes that submitting a testing proposal on the registered substance is not addressing the information requirement of the current decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are 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 TG 414) in a second species (rabbit) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI.

ECHA notes that a revised version of OECD TG 414 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that 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.

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

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

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with 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. 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 the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

a) The information provided

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (GLP, test method: OECD TG 422) ([redacted] 2005). However, this study does not provide the information required by Annex X, Section 8.7.3., because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. In addition, the criteria for extension of the Cohort 1B are met for the registered substance. Therefore, your adaptation of the information requirement is rejected.

In the technical dossier you have also provided a study record for a "14-week repeated dose toxicity inhalation study" (GLP, non-guideline) ([redacted] 1990). Similarly, this study does not provide the information required by Annex X, Section 8.7.3., because key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study are not covered. Therefore, your adaptation of the information

requirement is rejected.

As indicated above, you have also sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing reference to an adaptation based on a scheduled extended one-generation reproductive toxicity study (OECD TG 443), with the analogue substance trimethoxymethylsilane (EC number 214-685-0). You provided the following justification: *"In accordance with ECHA Draft Decision number [redacted], the Registrants intend to address the potential hazard related to reproductive toxicity for the registered substance using an extended one-generation reproductive study in the rat (OECD TG 443) via the inhaled route [...] from the structural analogue trimethoxy(methyl) silane (CAS RN 1185-55-3) for which there is a study proposal to test in an extended one-generation reproductive study in the rat, (OECD TG 443) via the inhaled route. The study will include appropriate cohorts to assess developmental and immunotoxicity and the need for an extension of the 1B cohort to produce an F2 generation will be considered during the study. Full details of the read-across justification, potentially involving the generation and comparison of limited in vivo TK data for the registered and read-across substances, will be provided in the updated dossier with the study results."*

As explained, under the section of *Grouping and read-across approach for toxicological information*, of this decision, ECHA has rejected your adaptation of the information requirement. Furthermore ECHA does not accept read-across to a study which has not produced results at the time of use ("study planned"). Hence, the information provided 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.

Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

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 if 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). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of 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 existing relevant data to be used for dose level setting, it is recommended that results from a conducted 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. The extension is *inter alia* required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of section 8.7.3., Annex X) and there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies (column 2, first paragraph, lit. (b), third indent of section 8.7.3., Annex X).

The use of the registered substance in the joint submission, based on information from the joint registration dossier submitted by the lead registrant for a tonnage >1000 tpa, is leading to significant exposure of consumers and professionals because the registered substance is used as sealants, non-metal surface treatment, coatings, as intermediate: PROCs 3, 4, 5, 7, 8a, 8b, 9. 10, 11, 13, 14, 19 in formulations, at industrial sites, by professional workers and consumers.

In their proposal for amendment (PfA), a Member State competent authority considered that the toxicity-triggers described to extend the Cohort 1B were not appropriate, for instance many of them occurring at lethal dose level. ECHA notes that you agreed with the PfA submitted. ECHA has reassessed the available information and has modified the justification for extension of Cohort 1B to include only relevant indications at non-lethal dose levels.

There are indications for one or more relevant mode of action related to endocrine disruption:

(i) In the Combined Repeated Dose and Reproductive / Developmental Toxicity Screening Test oral study (OECD TG 422) ([redacted], 2005) (reliability 2) on the registered substance tested at 3 doses (62.5, 250 and 1000 mg/kg bw/day), the following effects were observed at non-lethal dose levels (250 and 62.5 mg/kg bw/day, respectively):
1) a decrease in absolute pituitary weight in males at mid and low dose levels; and
2) increased absolute and relative weight of uterus at mid (and top) doses, indicating potential hormonal overcompensation during recovery period.

(ii) In the 14-week inhalation study ([redacted], 1990) on the registered substance (reliability 1), *"in the 400 ppm group after 14 weeks exposure the absolute testes weight was statistically significantly lower when compared to control mean values."* The body weight was reduced at this dose level but because it is generally considered that moderately reduced body weight does not affect testis weight (OECD GD 151), this finding is considered relevant.

Therefore, ECHA considers that the findings from the OECD TG 422 study (decreased pituitary weight and compensatory increase in uterus weight at non-lethal dose levels) and from the 14-week inhalation study (reduced testes weight) indicate one or more relevant

mode of action in relation of endocrine disruption. Therefore, the criteria for the extension of Cohort 1B are met.

ECHA concludes that Cohort 1B must be extended to include mating of the Cohort 1B animals and production of the F2 generation because the uses of the registered substance in the joint submission is leading to significant exposure of professionals and consumers and there are indications of modes of action related to endocrine disruption from the two available studies on the registered substance ([redacted] 2005; [redacted], 1990).

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

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 has included the request for Cohort 3 based on proposal for amendments (PfAs) from two Member State competent authories. ECHA does not normally review the content of registration updates, once the decision-making process has started (as specified in the notification letter to the registrant). However as the proposals for amendment are relying on details of studies reported after the draft decision was issued, and are related to one of the requests, ECHA has assessed your latest update (submission number [redacted] of 19 December 2017) in this respect, to come to a view on whether it can agree to the PfAs.

The existing information from an available Combined Repeated Dose and Reproductive/ Developmental Toxicity Screening Test oral study (OECD TG 422) ([redacted], 2005) (reliability 2), on the registered substance tested at three doses (62.5, 250 and 1000 mg/kg bw/day) shows the following evidence: a decrease of absolute thymus weights in females at non-lethal low and mid dose levels.

In your comments to the PfAs, you indicated that the developmental immunotoxicity Cohort 3 should not be added to the request. You argued that based on the oral OECD TG 422 study *"there are an insufficient number of triggers and no effects of sufficient severity that could indicate immunotoxicity to trigger the DIT cohort".* Furthermore you argued that in the 14-week inhalation study there were no effects on spleen and thymus, adding to the overall conclusion that there are no sufficient triggers. ECHA agrees that there are no triggers in the inhalation study, although there is a trigger in the oral study, as detailed above.

ECHA also considers that the results from the inhalation study do not outweigh the findings observed in oral OECD TG 422 study and concerns are still present. There is no information in your registration dossier (e.g. toxicokinetics) that would demonstrate that the inhalation route is the most appropriate route of adminstration to detect hazardous properties on reproduction. Additionally, you have not excluded the possibility that there are route-specific differences in toxicity. Hence, the concern for immunotoxicity via the oral route remains. 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 on the registered substance itself.
The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, 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.

ECHA considers that a request for extension of the commenting deadline submitted on the day of the deadline does not address the request. Therefore ECHA considers that you have not provided any specific comment on the content of the draft decision and the updated dossier you submitted is not taken into account in the decision-making process. Furthermore ECHA notes that submitting a testing proposal on the registered substance is not addressing the information requirement of the current decision.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation, and
- Cohort 3 (Developmental immunotoxicity).

Notes for your consideration

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were yet identified. However, you may expand the study by including the Cohorts 2A and 2B if information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if 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. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 18 November 2016.

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 requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-59 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present 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 your Member State.

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.