EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: CCH-D-2114428794-40-01/F
Substance name: dimethoxydimethylsilane
EC number: 214-189-4
CAS number: 1112-39-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06.05.2015
Registered tonnage band: 100-1000 tonnes per annum

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. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route; with the registered substance according to the following study-design specifications:**
   - **Ten 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) without extension to mate the Cohort 1B animals to produce the F2 generation**
   - **Cohorts 2A and 2B (Developmental neurotoxicity);**
   - **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 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.

The timeline has been set to allow for sequential testing of the requests made in a separate decision of **19 July 2018** (TPE-D-2114428349-43-01/F) on a Testing Proposal on the registered substance and of the requests in this decision.

You are required to submit the requested information in an updated registration dossier by ***26 April 2022***. In the separate decision TPE-D-2114428349-43-01/F you are required to submit the requested sub-chronic toxicity study (90-day) and pre-natal developmental

toxicity study in an updated registration dossier by ***27 January 2020***. You may only commence the extended one-generation reproductive toxicity study as requested under point 2. of this decision after ***27 April 2020***, unless an indication to the contrary is communicated to you by ECHA before that date. 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

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier contains negative results for both these information requirements (namely Section 8.4.1., Annex VII and Section 8.4.2., Annex VIII). Therefore, adequate information on *in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a mouse lymphoma mutagenicity assay (OECD TG 476) with the analogue substances diethoxy(dimethyl)silane (EC number 201-127-6).

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

i. Description of the grouping and read-across approach proposed by the Registrant

You have provided a read-across justification as a separate attachment, in the registration dossier, and in the endpoint summary in the registration. In summary you provide the following arguments to support the read-across approach: *"To reduce animal testing REACH recommends to make use of a read-across approach where appropriate based on the high accordance in properties relevant for the specific endpoint. In the case of genetic toxicity relevant properties are structural similarity as well as physical-chemical and basic toxicological parameters in the same range. Especially functional groups that are associated with genetic toxicity have to be compared. In the following paragraphs the read-across approach for dimethoxydimethylsilane (CAS 1112-39-6) is evaluated point by point" and "This is supported by the fact that neither dimethoxy-dimethylsilane nor the read-across substances have functional groups associated with genotoxicity, which is in accordance with most of the other substances of the group. The substances have the same or similar hydrolysis products and therefore read-across to the analogues is appropriate. The other products of hydrolysis methanol, ethanol, and HCl are not genotoxic."*

You have also provided a data matrix, listing two source substances, namely diethoxy(dimethyl)silane (EC number 201-127-6, CAS RN 78-62-6) and dichloro(dimethyl)silane (EC number 200-901-0, CAS RN 75-78-5) and the registered substance, as part of a bigger category ("*Substances in the analogue group I-2 and I-2C*").

ECHA understands that your hypothesis to justify the read-across approach under which you make predictions for the endpoint listed above, is based on (a) structural similarity as well as (b) comparison of functional groups that are associated with genetic toxicity, (c) similar

physical-chemical and basic toxicological parameters, and (d) similar and common hydrolysis products.

You are predicting that the properties of the source substances (analogues) can be directly read across to the registered substance, i.e. that they have the same properties for genetic toxicity.

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

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 pre-requisite 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.

(a) 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. Hence, elements are missing from your adaptation approach such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

(b) Also, ECHA agrees that the functional side-chains are important and need to be considered when evaluating toxicological properties in general, and in genetic toxicology, as a number of reactive groups and molecular substructures are associated with toxicological properties of chemicals. However ECHA considers that this is not *per se* a basis which is sufficient to predict the human health properties of a substance.

(c) Likewise, ECHA considers that having similar physico-chemical and basic toxicological properties is a prerequisite for the use of the grouping and read-across approach according to Annex XI, Section 1.5., but is not by itself a sufficient basis to be able to predict the properties of the registered substance. Specifically, substances may have similar physico-chemical properties, but entirely different human health properties. Therefore this is not a reliable basis for prediction.

In respect of the comparison of toxicological properties, ECHA considers that substances may have similar toxicological properties for one endpoint, but different toxicological properties for another endpoint. Hence it is necessary to have a basis for predicting the properties of the registered substance. ECHA further notes that multiple substances listed in "*Table 1: Summary of available genotoxicity data for substances in the analogue group I-2 and I-2C*" provided in your technical dossier have positive results in genotoxicity tests.

ECHA considers that there is not an adequate basis for considering that it is possible to predict that the outcome of the test under adaptation will be negative, as opposed to positive.

(d) Finally, you claimed that a common breakdown product (dimethylsilanediol) is generated by the target and the source substance, in addition to non-common products (methanol, ethanol) which have known properties. You have also claimed that the data show no

association between the rate of hydrolysis and genetic toxicity. The hydrolysis rate of the registered substance is moderately fast, with a half-time of <0.6 hour at 25°C and pH7.

ECHA considers that given the exposure time in the OECD TG 476 assay being from 3 to 6 hours, the test substance will have hydrolysed almost completely by the time the exposure time is at its end. ECHA agrees that there is a common breakdown product, however, you have not excluded that there will be exposure to the parent compound. The hypothesis of common breakdown products does not address the differences in effect that could be expected from the parent compound prior to the hydrolysis to the breakdown products. Additionally the rate of hydrolysis of diethoxy(dimethyl)silane (EC number 201-127-6, CAS RN 78-62-6) is found to be 5.5 hours at at 25°C. Hence it cannot be claimed that the OECD TG 476 test system will be exposed exclusively to the common breakdown product (dimethylsilanediol) during the standard time of exposure.

For the reasons set out above, ECHA considers that there is not a reliable basis for predicting the properties of the parent substance prior to hydrolysis on the basis of this argument.

In your comments to the draft decision, you have submitted an updated read-across justification, and indicated an intention to update your dossier. As the principal components of your read-across justification in your comments, you have:

1. identified a category for read-across of the registered substance (the alkyl alkoxysilanes category) which is different from those identified in the registration dossier, and identified members belonging to the alkyl alkoxysilanes category. Simultaneously you have indicated that the substance, dichloro(dimethyl)silane (EC number 200-901-0, CAS RN 75-78-5), "*is a surrogate substance and not part of the alkyl alkoxysilanes analogue group. However, it is considered appropriate to provide relevant information for the endpoint genetic toxicity;*"

2. amended your justification for read-across relying now on (i) "*similar structural features (alkoxysilane moiety and alkyl moiety), (ii) Similar metabolic pathways (alkoxysilanes undergo rapid hydrolysis), distribution and excretion (in urine), (iii) Similar physico-chemical properties, (iv) common toxicological profile*";

3. provided rates of hydrolysis (including at low pH (1.5-2°C) to mimic the GI tract pH), in support of point (2)(ii) above.

4. appl[ied] read-across within the analogue group of alkyl alkoxysilanes and the surrogate substance Dichloro(dimethyl)silane (CAS No 75-78-5).

5. Explained that "*the positive results obtained for* in vitro *mammalian cytogenicity and mammalian mutagenicity tests, with Trimethoxy(methyl)silane (CAS RN 1185-55-3,) have been cleared by the negative result obtained in the in vivo genotoxicity study, indicating that this analogue substance does not display cytogenicity. According to the acute toxicity results, there has been an adequate exposure of the target tissue to the analogue substance (CAS RN 1185-55-3). From the increase in % of the small mutant colonies in the in vitro mammalian mutagenicity test, it can be confirmed that the analogue substance has indeed a clastogenic effect. The absence of cytogenicity was also confirmed, for the ambiguous result obtained with Dichlorodimethylsilane (CAS RN 75-78-5) for the in vitro cytogenicity in mammalian cells, with a negative in vivo study.*"

ECHA considers that points (2) (i), (iii) {except where it deals with hydrolysis, point (ii)}

and (iv) are already addressed by the arguments in the draft decision. ECHA has evaluated the other arguments brought by the registrant below.

1. You have defined a new category for this read-across adaptation, "Alkyl alkoxysilanes", together with a 'surrogate' substance, Dichloro(dimethyl)silane (CAS No 75-78-5), for the endpoint of *in vitro* gene mutation in mammalian cells. This category is different from the categories proposed in the registration dossier (cf. Table 1.4.1 and 1.4.2 of the CSR; Group I-2 in "[redacted]"). ECHA considers that the boundaries of the category do not appear to be scientifically based, insofar as you rely on (at least) three different definitions of the category, and there is limited and inadequate justification for the inclusion/ exclusion of substances within the category. In the absence of a justified basis for category inclusion and exclusion, ECHA cannot establish whether the toxicological properties may be predicted from data for reference substance(s) within the group by interpolation to other substances within the structural domain of the category, because ECHA cannot reliably assess what substances should be in the structural domain of the category.
2. (ii) {apart from hydrolysis rates- see (3) below}. You rely on the general hypothesis of similar metabolic pathways and rapid/ immediate hydrolysis among the category members to support their general read-across hypothesis. This has already been addressed in the decision (see above): you do not discuss specifically the hydrolysis products of the source substances, and how they would not affect the intrinsic properties of the source substance, so that you can reliably predict the potential of the registered substance to (not) induce gene mutation in mammalian cells. Since you do not address the properties of the hydrolysis products and take into account the structural differences between these products, the read-across hypothesis is not an adequate basis for predicting the properties of the substance.
3. You argue that "Under conditions given in the gastrointestinal tract and representing the conditions after oral exposure (pH 2) the alkoxysilane moiety will also hydrolyse immediately." ECHA notes that conditions of pH2 are not present during dermal or inhalation exposure, nor during buccal absorption. Moreover, the specific endpoint concerned, in vitro gene mutation, is also conducted at approximately pH 7. Thus calculated hydrolysis times at pH 2 are not relevant for this endpoint, nor are they informative for all routes of exposure. Thus they cannot be used for predicting the properties of the registered substance under these conditions. ECHA notes substantial predicted half-lives for hydrolysis at pH 7 and 20-25C, according to Table 2, for the registered substance and other "Alkyl alkoxysilanes", which are significantly different from the Chlorosilane analogue, (75-78-5). The difference in hydrolysis rates between the Chlorosilane analogue, (75-78-5) and the "Alkyl alkoxysilanes" means that it is not possible to predict the properties of the "Alkyl alkoxysilanes" from the Chlorosilane analogue, (75-78-5). The comparatively long half-lives of the "Alkyl alkoxysilanes" at pH 7 and 20-25C imply that there will be systemic exposure to the parent substance (i.e. exposure of cells to the parent substance in the in vitro gene mutation assay), and so there must be an acceptable basis for predicting the human health properties of the (parent) registered substance, other than by through its metabolites. As set out in the decision (see above), this is lacking, and so prediction is not possible. ECHA additionally notes that the predictions of the hydrolysis rate were not accompanied by a QMRF or QPRF, and so there is not adequate documentation of the applied QSAR method; thus these predictions cannot be accepted.
4. You do not specify the particular study that will be read-across to address the data gap for the registered substance. Table 3, page 13, indicates that you wish to read across from the substances #2 and #7, while the section on mammalian mutagenicity, page 10, also reads-across to substance #3 and #4, and a testing

proposal for OECD TG 489 on substance #3. In the conclusion, you consider it appropriate to apply read-across within the analogue group of alkyl alkoxysilanes and the surrogate substance Dichloro(dimethyl)silane (CAS No 75-78-5). An endpoint study record is only available (in the registration dossier) for Dimethyldiethoxysilane (78-62-6 / 201-127-6), and adequate information is not available for the other studies cited. You cite multiple relevant studies which should be read-across, including one which is positive for this endpoint, but do not provide all of these, providing data for only one. ECHA is unable to assess these studies to determine if they are of an adequate quality, nor to assess which of these should be used to read-across (which would be necessary for predicting the properties of the registered substance). ECHA also notes the concerns about these studies which were previously raised in the draft decision.

5. ECHA considers this is irrelevant for justifying the proposed read-approach applicable to the endpoint of *in vitro* gene mutation in mammalian cells; rather it is an interpretation of the data which is to be read-across. ECHA further notes that the results of an in vivo cytogenicity study do not address a concern for in vitro gene mutation.

ECHA considers that the updated read-across adaptation, as provided in the registrant comments, fails to provide a reliable basis for predicting the properties of the registered substance, for the reasons as set out above, and so cannot be accepted. Since there is an information gap it is necessary to provide information for this endpoint.

ECHA considers that the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), has not been met.

iii. ECHAs conclusion

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation.However, on the basis of the documentation that provides an explanation of the grouping and read-across approach, ECHA considers that your adaptation does not meet the general rule for adaptation of Annex XI, Section 1.5. because, for the reasons as set out above, and additionally considering the overall weight of all the arguments, ECHA considers that there is not a reliable basis whereby the human health effects may be predicted from data for the reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Therefore, your adaptation of the information requirement is rejected.

As explained above, 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.

ECHA considers that the *in vitro* mammalian cell gene mutation test – *hprt* test (OECD TG 476) and the *in vitro* mammalian cell gene mutation test – Mouse lymphoma assay (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490).

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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 Section 8.7.3., Annex IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

i. The information requirement

You submitted a screening study on the registered substance (50, 250 and 1000 mg/kg bw/day). The study was conducted on the registered substance, according to the OECD TG 422 and in compliance with good laboratory practice (GLP). ECHA considers that adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity are observed. More specifically, at 1000 mg/kg bw/day, you reported an increase in post-implantation loss, an increase in days of gestation, a decrease in live pups, a decrease in the total viable pups/total, a decrease in final litter weight, a decrease in final average pup weight and an increase in the percentage of post-natal loss. In addition, males exhibited testicular seminiferous tubule degeneration with epididymides involvement. Thus both the column 1 conditions of "adverse effects on reproductive organs or tissues" and "reveal other concerns in relation to reproductive toxicity" are met.

Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for the registered substance.

However, you have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.3. Instead you did not consider the information requirement for reproductive toxicity in Annex IX, Section 8.7.3., column 1, because: *"[I]n accordance with Column 1 of REACH Annex IX the 2-generation reproductive toxicity study (required in Section 8.7.3) does not need to be conducted as no adverse effects on reproductive performance was observed in a screening study conducted with the submission substance. Furthermore, a 90-day repeated dose inhalation toxicity study in rats is planned for the registered substance, including detailed investigation of reproductive organs. These could include but are not limited to "Examination of reproductive organs, sperm parameters, and oestrus cycle". The need for further testing for reproductive toxicity will be assessed when the results of that test are available."*

However, ECHA considers that such adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed from the OECD TG 422 screening study provided. As set out above, ECHA considers that there are concerns in relation to reproductive toxicity and in relation to adverse effects on reproductive organs which are observed in the above study.

Hence, an extended one-generation reproductive toxicity study is an information requirement for registrations of the registered substance.

ii. Read-across approach proposed in Registrant's comments

In your comments, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a justification for read-across to the 'alkyl alkoxysilanes' category, which is described in Appendix 1, Section 1, above. In addition to a general proposal for read-across within the category, you have made specific reference to read-across from the analogue substance Trimethoxy(methyl)silane (CAS No 1185-55-3) and that the "dossier for Trimethoxy(methyl)silane includes a testing proposal for an EOGRTS in response to ECHA Draft Decision SEV-D-2114279311-53-01/D." Additionally, you have argued (1) that the results of future testing on the registered substance subject to this decision and Trimethoxy(methyl)silane will strengthen the read-across (2) Article 13 of Regulation (EC) No 1907/2006 states that "In particular for human toxicity, information shall be generated whenever possible [...] from information from structurally related substances (grouping or read-across ...)." Hence, using data from the EOGRTS with Trimethoxy(methyl)silane in addition to the RDT studies to be performed with Dimethoxy(dimethyl)silane will allow us to significantly reduce the number of animals and to effectively implement animal protection measures.

ECHA's evaluation is as follows.

(1) ECHA understands that you have the intention to follow a testing strategy using the results from future studies using an analogue substance. However, a data gap exists for this endpoint, and this is being addressed under this compliance check process. ECHA cannot take into account the results of future tests on an analogue substance and whether these future tests will support a read-across.
(2) ECHA notes that Article 13(1) starts with "Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met.", and ECHA considers that the conditions of Annex XI, 1.5 are not met. Hence grouping and read-across is not possible.

In respect of your general justification for read-across, and the specific use of Trimethoxy(methyl)silane as an analogue substance, the reasons set out for the rejection of read-across in Appendix 1, section 1, both on the read-across as proposed in the dossier, and on the read-across proposed in your comments apply by analogy, with the exception of argument based upon the fact that the genotoxicity test is conducted in vitro at ~pH 7. ECHA further notes that you have not provided any acceptable reason as to why Trimethoxy(methyl)silane has been chosen as a source substance within this category, and why it alone can predict the properties of the registered substance. Thus ECHA considers that the proposed use of read-across does not meet the requirements of Annex XI, 1.5, and cannot be accepted.

iii. Conclusion

As explained above, 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 to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

a) The specifications for the 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 the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the 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 R.7a, chapter R.7.6 (version 4.1, October 2015).

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.

You should note that both the "combined repeated dose toxicity study with the reproduction/ developmental toxicity screening" test (OECD TG 422) and the "repeated dose (90-day) oral toxicity study" in rodents (OECD TG 408) can serve as dose range-finding studies. Furthermore you are reminded that any result from dose range-finding studies performed prior to the extended one-generation reproductive toxicity study are to be reported with the main study. This will support the justifications of the dose level selection and interpretation of the results.

In your comments, you outlined that further information relevant for the EOGRT study design might be obtained after the 90-day repeated dose toxicity and prenatal development toxicity studies have been carried out (requests identified and notified to you in a separate decision of 11 December 2015 - communication number TPE-D-2114312744-54-01/D). ECHA notes that you are expected to make use of these results to confirm the study design of the currently requested study.

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 IX. When there are triggers for developmetal neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on the registered substance and on substances structurally analogous to the registered substance, derived from available *in vivo* studies (OECD TG 422 studies and 28-day repeated dose toxicity (RDT) studies) show evidence of substance-specific findings which cause a particular concern on developmental neurotoxicity justifying inclusion of the Cohorts 2A and 2B: in the thyroid, both after gross pathology "*effects attributable to the test article occurred in the [...] thyroid glands [...] in male and females"* and after histopathology, "*thyroid follicular cell hypertrohpy was observed in the thyroid gland of high-dose rats of both sexes*". In addition, the structurally similar substance trimethoxy(methyl)silane (with EC number 214-685-0) tested in an OECD TG 422 study exhibited similar effects in the thyroid.

In your comments you argued (1) that Dichloro(dimethyl)silane does not have effects on the thyroid, and ECHA has modified the text accordingly. (2) that the effects observed in the thyroid may be secondary to increased thyroid hormone metabolism and that the rat is

a sensitive species. ECHA considers that the Registrant has not established substance-specific evidence and reasoning for concluding that results from rat and the thyroid effects are irrelevant for human risk assessment or that the thyroid effects are secondary to increased thyroid hormone metabolism, and so there is no reason to adapt the information requirement. (3) that "*Further information might be obtained by determining thyroid hormone levels in the 90-d RDT as well as PNDT studies*". ECHA agrees that further information may be obtained separately under the Registrant's responsibility.

However since there are already existing information on the registered substance and on substances structurally analogous to the registered substance that show evidence of substance-specific findings which cause a particular concern on developmental neurotoxicity, Cohorts 2A and 2B need to be conducted. This also includes the addressing that effects observed in thyroid glands which are only one of the triggers for the DNT cohorts.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* studies on the registered substance itself and on substances structurally analogous to the registered substance.

Finally you are reminded that you must justify the study design in the dossier and thus you have to document the existence/ non-existence of the conditions/triggers.

ECHA further notes that this decision does not take into account any updates submitted after the draft decision was sent (11 December 2015). All new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

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 IX.

ECHA notes that existing information on the registered substance itself and on substances structurally analogous to the registered substance, derived from available *in vivo* studies (OECD TG 422 studies or a 28-day RDT study) show evidence of substance-related effects on thymus: "*... statistically-significant differences were observed in males in the thymus (decrease absolute and relative weights) at 1000 mg/kg bw/day*". In addition, the structurally similar substances trimethoxy(methyl)silane (EC number 214-685-0) tested in a OECD TG 422 study and dichlorodimethylsilane (EC number 200-901-0) tested in a 28-day RDT study (inhalation), exhibited similar effects in the thymus.

As supporting evidence, "*statistically-significant differences were observed in females in the spleen (decrease absolute and relative weights) at 1000 mg/kg bw/day*", and you also report that "*statistically significant changes were noted in haematological parameters checked (RBC, MCV, MCH, MCHC, WBC, total and differential, Hgb, Hct and PLT)*" without specifying which ones.

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* studies on the registered substance itself and on substances structurally analogous to the registered substance.

In your comments you argued that ECHA refers to one of the analogues belonging to the category (Trimethoxy(methyl)silane) in its justification for including cohorts 2A, 2B and 3, thereby acknowledging the structural similarity to Dimethoxy(dimethyl)silane. ECHA notes that the Annex IX/X, section 8.7.3. requires an assessment of "*effects caused by substances structurally analogous to the substance being studied*", which is a different legal standard compared to a read-across approach according to Annex XI, section 1.5. Hence if effects are found that can trigger one of the possible cohorts, ECHA has to take these findings into consideration to address a registered substance.

Finally you are reminded that you must justify the study design in the dossier and thus you have to document the existence/ non-existence of the conditions/triggers.

ECHA further notes that this decision does not take into account any updates submitted after the draft decision was sent (11 December 2015). All new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a an organic liquid, with a vapour pressure calculated to be 7.4 hPa at 25°C and boiling point of 81.5°C, ECHA concludes that testing should be performed by the oral route.

b) Outcome

Based on the available information, 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, by 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 some 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;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

Currently, the extension of Cohort 1B is not requested. However, the sub-chronic toxicity study (90-day) and pre-natal developmental toxicity study requested in a separate decision of **19 July 2018** (TPE-D-2114428349-43-01/F) on a Testing Proposal on the registered substance and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) and pre-natal developmental toxicity study are to be conducted first and the study results submitted to ECHA in a dossier update by the 18-month deadline indicated in that decision. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will

inform you within three months after expiry of the 18-month deadline to provide the sub-chronic toxicity study (90-day)), as indicated in the separate decision, of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by the expiry of the three months following the 18-month deadline for providing the results of the sub-chronic toxicity study (90-day), the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) and pre-natal developmental toxicity study you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented.

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 42 months from the date of adoption of the decision. Before notifying the case to the Member State Competent authorities (MSCAs) the deadline was extended to 51 months so as to allow the consideration for the sequential testing, so that you can provide and consider yourself the information requested in the separate decision of **19 July 2018** (TPE-D-2114428349-43-01/F) on a Testing Proposal Evaluation on the registered substance before you initiate the extended one-generation reproductive toxicity study. Following a proposal for amendment from one of the MSCAs, it was proposed to reduce the time to 45 months, as a consequence of the proposal to reduce the deadline of the testing proposal decision (TPE-D-2114428349-43-01/F) from 24 to 18 months. The reduced time is considered as sufficient to perform the studies required. Hence, ECHA has modified the deadline of the TPE decision to 18 months and the deadline of the present decision to 45 months.

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 17 November 2015.

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

On 11 December 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 1 February 2016 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Appendix 1, whereas no amendments to the information requested (page 1) were made.

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

You stated you had no comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-60 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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2020. Note: the start of the evaluation may be postponed upon the evaluating Member State's decision.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. 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 your Member State.

4. 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.