[If applicable: MSC identifiers]

Helsinki, 13 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453648-38-01/F
Substance name: 2,4,6,8,10-pentamethylcyclopentasiloxane
EC number: 228-204-7
CAS number: 6166-86-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17/09/2018
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

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

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) in rats, using the analogue substance 2,4,6,8-tetramethylcyclotetrasiloxane, CAS No 2370-88-9 (EC No 219-137-4 is rejected, you are requested to perform:

Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the registered substance (purity higher than 95%).

You have to submit the requested information in an updated registration dossier by ***20 December 2019***. You also have to update the chemical safety report, where relevant.

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

This decision does not address the information requirement of the Extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. of the REACH Regulation. The results of the Sub-chronic toxicity study (90-day) will be used, among other relevant information, to decide on the study design of the Extended one generation reproductive toxicity study. Therefore, your testing proposal for Extended one-generation reproductive toxicity study will be addressed after having received the results of the Sub-chronic toxicity study (90-day).

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Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance 2,4,6,8,10-pentamethylcyclopentasiloxane (CAS: 6166-86-5), hereafter referred to as 'HD5' or 'target substance'.

In relation to the testing proposal subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirements for a 90-day repeated dose toxicity study (Annex IX, Section 8.6.2.) by testing the analogue substance 2,4,6,8-tetramethyl-cyclotetrasiloxane (CAS No 2370-88-9, EC No 219-137-4) hereafter referred to as 'HD4' or 'source substance') and to use the results to adapt the standard information requirements for your registered substance by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation.

ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the 90-day subchronic toxicity endpoint.

Grouping of substances and read-across approach

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether programmes of testing proposed by you are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

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

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

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

You have proposed to cover the standard information requirement for a sub-chronic toxicity study (90-days, Annex IX, Section 8.6.2) by performing the test with the source substance.

You have provided the following hypothesis: "*The read-across hypothesis is that the systemic toxicity of the registered and read-across substances results from exposure to the ultimate products of hydrolysis, which are the same for the both substances*". You further state "*The basis of the read across is the hydrolytic stability and relevance of the silanol hydrolysis products. The hydrolysis half-life of the substance has been measured using an accepted method. HD5 hydrolyses very rapidly (half-life 4.2 min at pH 7 and 22.5°C, see Section 4.1.1.1), with the ultimate hydrolysis product being methylsilanetriol. The half-life*

refers to degradation of the parent substance (ring-opening); full hydrolysis takes longer (approximately 1 day). The analogue methodology takes into account the properties of all hydrolysis products and the choice of read-across substance is described on a case-by-case basis for individual endpoints".

You have provided a more detailed read-across justification in the CSR, Section 5.6.3., regarding the sub-chronic toxicity study. You state that "*the read-across substance is predictive for the toxicological profile of the registered substance as structure and key physical chemical parameters are very similar and predict similar toxicokinetic behaviour. Both substances react rapidly both in vivo and ex vivo to common hydrolysis products. Rapid excretion of the hydrolysis product via urine can be expected for both substances".*

You further explain why the read-across approach is considered acceptable for the properties under consideration:

Structural similarity

- *HD5 is a cyclic siloxane with five silicon atoms linked by five oxygen atoms; each silicon atom is substituted by a methyl group and a hydrogen atom. HD4 is the equivalent methyl/hydrogen substituted siloxane with four silicons and four oxygens in the ring.*

Hydrolysis

- Based on in vitro hydrolysis investigations and QSAR predictions you conclude: "*Both HD4 and HD5 hydrolyse rapidly (both have calculated half-lives of ≤5 s at pH 2 and 37.5°C, the conditions relevant to oral exposure). The intermediate hydrolysis products in both cases are a series of linear silanediols, H4L4-diol, H3L3-diol and H2L2-diol, followed by methylsilanediol; HD5 produces in addition H5L5-diol as the first hydrolysis product. The final hydrolysis product is methylsilanetriol and hydrogen gas is produced as a by-product of the reaction."*

Toxicokinetics

- You have further compared the predicted half-lives of the parent compounds and their intermediate hydrolysis products to the gastric emptying half-life and conclude that the hydrolysis will be almost complete in the stomach under *in vivo* conditions.

Overall you conclude that "*Based on the similar chemical structure and similar toxicokinetic behaviour it is appropriate to read across long-term mammalian toxicity data for 2,4,6,8-tetramethylcycloterasiloxane to 2,4,6,8,10-pentamethylcyclopentasiloxane in order to minimise the number of animal tests performed".*

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

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

You have provided a read-across documentation in the CSR focussing on HD4 and HD5 hydrolysis. You have provided a data matrix with the key physicochemical parameters

(attached in Section 13 of the IUCLID dossier, and summarised in Table 5.5.3. of the CSR). To further support the read-across approach, you have provided a data matrix summarising the information on physico-chemical, toxicological and ecotoxicological properties.

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

Structural similarity and dissimilarity

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

ECHA notes that you have sufficiently described in your read-across justification document the structural similarities and differences between the target and source substances and their breakdown hydrolysis products.

Hydrolysis to common breakdown products

ECHA understands that the read-across approach is based on the hydrolysis of the registered and source substances resulting in the same hydrolysis products. Therefore, below, ECHA analyses the hydrolysis data.
You propose that the first step is ring opening of the parent cyclic siloxanes HD4 and HD5. This results in a methylsiloxanediol chain, i.e. $H[OSi(H)(Me)]_4OH$ (H4L4-diol) and $H[OSi(H)(Me)]_5OH$ (H5L5-diol), respectively. You propose that H4L4-diol and H5L5-diol are further hydrolysed resulting in methylsilanediol and in a methylsiloxanediol chain, which is one methylsiloxane unit shorter, i.e. H5L5 results in H4L4-diol. Once this stage is reached, the hydrolysis pathways for HD4 and HD5 merge and progress further until the chain has been completely hydrolysed to methylsilandiol. You claim that methylsilanetriol is the final hydrolysis product.

The half-life of the substances in this pathways was measured in a non-guideline, non-GLP study in vitro [redacted] 2010), using head-space vessels. An imidazole buffer system at pH 7 with 20 % acetonitrile as co-solvent was used at 25°C. The disappearance of the parent compounds was measured, the disappearance of the intermediate products was not measured. Furthermore, the appearance of H-gas was measured.

The measured half-lives for HD5 and HD4 were 4.3 and 2.2 minutes respectively. The half-life for breakdown of the Si-H bonds was determined to be 6 – 8 hours. The results show that the initial ring opening of HD4 and HD5 is the main pathway and occurs rather rapid. In comparison the further hydrolysis of the H5L5-diol and H4L4-diol to the final product methylsilanetriol appears to be slower, as indicated by the kinetics of the appearance of H-gas.
You have pointed out that the critical question with regard of the proposed read-across between HD4 and HD5 is, whether significant amounts of non-common substances, i.e. HD5 and H5L5-diol are systemically available.

In order to address this question, you have provided predictions for the half-lives of the intermediates at pH 7 and 25°C obtained with a validated QSAR method. The predicted half-lives are 4.2, 10, 26 and 63 minutes for H5L5-diol, H4L4-diol, H3L3-diol, and H2L2-diol, respectively. The half-lives of parent HD5 and the intermediates were used to plot the percentages of the individual substance versus time at pH 7. H5L5-diol reaches about 38 % of the initial amount of HD5 after 7 minutes and then declines to reach about 4 % after 30 minutes. H4L4-diol, the first common intermediate of both pathways reaches about 28 % after 13 minutes and then declines to about 10 % after 30 minutes. In can be expected that a similar plot for HD4 results in different time profiles for H4L4-diol, since the half live of HD4 is shorter than the one for H5L5-diol and the half live for H4L4-diol is longer than for H5L5-diol.

In order to derive a prediction of half-lives at lower pH (such as in the stomach) and at higher temperature (such as 37°C) you recalculated the values and derived half-lives for the individual intermediates of <5 seconds. Then you compare the half-lives of the substances in the stomach with the typical gastric emtying half-life for liquids of 77 minutes in the rat. Using these data you plot the concentration-time profiles for HD5 and intermediates in the stomach and conclude that HD5 and HD4 both hydrolyse very rapidly in the stomach and that almost no HD5 nor H5L5-diol escapes the stomach. The formation of methylsilanetriol is then thought to be more slow.

You address the uncertainties of your predictions, i.e. shortening of the linear methylsiloxanediol via cleavage in the centre of the chain and the breaking of the Si-H bond earlier in the process. You conclude that relative to the gastric emptying time, such alternative pathways would still lead to a full hydrolysis to methylsilanediol or methylsilanetriol.

ECHA considers your calculations and predictions based on the used QSAR models as acceptable and concludes that you have demonstrated that the registered and analogue substances hydrolyse in a similar way to form the final hydrolysis product, methylsilanetriol.

Support of a similar or regular pattern as a result of common breakdown products

One important aspect in establishing predictions based on common breakdown products 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.

ECHA has evaluated the toxicological information for the different endpoints, provided for the target and the source substances and has the following observations based on your reporting:

- The physicochemical properties of the source and the target substance are within the same range.
- For repeated dose toxicity, ECHA notes that you have not provided any data, obtained with the registered substance but you provided the following information:
  - With the source substance (HD4) you have provided one screening study (OECD TG 422) in rats, via inhalation. You have identified a NOAEC for systemic toxicity of 100 ppm (equivalent to [redacted] mg/m^3), based on toxicity in the urinary tract in

both sexes (injury, inflammation and dilation of urethra, urinary bladder, ureter or kidney) and on toxicity in the thyroid gland (amorphous material in the colloid of the gland) observed in males at 1000 ppm (equivalent to [redacted] mg/m^3).

- ECHA further notes that you also have provided a 28-day oral-gavage study in rats conducted with trimethoxy(methyl)silane (CAS 1185-55-3). ECHA understands that you provided this information, because you claim that this substance is hydrolysing to the same common breakdown product as the source and target substances. Under the conditions of this study, the exposure to trimethoxy(methyl)silane was associated with dose-dependent "*organ weight and/or histomorphological changes in males (liver, thymus, thyroid, duodenum, jejunum, and red blood cell) and females (liver, thyroid, duodenum, jejunum, and adrenal gland) at dose levels at or above 250 mg/kg bw/day*". The identified NOAEL was 50 mg/kg bw/day.

ECHA notes that comparison of the toxicity profiles between source and target substance is not possible, since no information is available for the target substance.

However, the information allows to compare the results obtained with the source substance and trimethoxy(methyl)silane, which you claim to result in common breakdown products. ECHA, therefore, compared the results of the two studies above. The detected systemic effects for the source and the trimethoxy(methyl)silane are different. While the main target organs for HD4 are the urinary tract and thyroid gland, the *trimethoxy(methyl)silane* affects the liver, thymus, thyroid, duodenum, jejunum, red blood cell (in male) and adrenal gland (in female). This appears to contradict your hypothesis that the same breakdown products derived from different parent compounds would cause the same type of effects.

In your comments to the draft decision you expressed your intention to "*update the existing dossier by September 19, 2018, enclosing additional information to support the proposed read across from 2,4,6,8-tetramethylcyclotetrasiloxane (CAS 2370-88-9, EC No 219-137-4".*

ECHA notes that you have updated your dossier (submission number: [redacted] from 17 September 2018) by providing a 90-day inhalation study in rats (OECD TG 413, GLP compliant) with the supporting source substance trimethoxy(methyl)silane (CAS 1185-55-3) and you have updated your read-across justification. Based on the results of this study you concluded that both HD4 and trimethoxy(methyl)silane "*inhalation studies primarily target the urinary tract (although with a marked difference in potency)*". You further state that the difference in toxicity effects observed in the oral study with trimethoxy(methyl)silane and in the inhalation study with HD4 "*may be route-specific*" and "[....] *do not contradict the hypothesis that the same breakdown products derived from different parent compounds would cause the same type of effects.*"

ECHA analysed the new data and compared them with the data from the inhalation study with the source substance HD4. ECHA has the following observations:

- ECHA agrees that kidney and urinary bladder are one of the target organs for both substances. However, the detected effects are at different concentration levels: HD4 shows these effects at 1000 ppm (ca. 9.8 mg/L), while trimethoxy(methyl)silane – at 400 ppm (ca. 2.2 mg/L). ECHA notes that you have acknowledged the different potency of the effects, however you did not explain what would be the possible reason for this difference. You did also not explain how those differences would

influence the prediction from the source substance (HD4) to the target substance (HD5).

- ECHA further notes that the two substances also affect different organs:
  - HD4 affects: the thyroid gland: *"amorphous material in the colloid of the gland were observed in males of all treatment groups with dose-dependency in its severity and incidence"*; the brain: *"a dose-dependent and statistically significant reduction of absolute weights of brain"* in males without body weight reduction at 1000 ppm. Even if no further findings related to possible neurotoxicity of the test item were noted, you state that *"because of the dose dependency and statistical significance of this effect, its relation to the treatment could not be excluded"*.

  - trimethoxy(methyl)silane affects: the adrenal gland: in females - absolute weight increased at 400 ppm (by 18%) and at 1600 ppm (by 25 %); relative to body weight increased at 1600 ppm (by 27%); testes: *"decreased soft testes"* is reported as *"test article-related gross necropsy finding"* observed at the two highest tested concentrations (400 and 1600 ppm) and weights of testes and epididymides were decreased in high exposure level (1600 ppm) recovery group male rats

You did not comment on these results and did not provide any explanation what would be the possible cause of these differences, observed after the same route of administration (inhalation) of the two tested compounds. Hence, ECHA considers that your claim "[...] *the same breakdown products derived from different parent compounds would cause the same type of effects by the same route of exposure"* is not supported.

Therefore ECHA concludes that based on the presented information it is not possible to confirm that the source and target substances would have similar properties or they would follow a regular pattern in their properties. In the absence of such information, there is not an adequate basis for predicting the properties of the target substance from the data obtained with the source substance.

Outcome

ECHA concludes that you have not provided adequate and reliable information to demonstrate that the criteria of Annex XI, 1.5. are met and that testing carried out with the source substance would allow to predict the relevant toxicological property of the target substance.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to

meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the analogue substance HD4.

As explained in the section "Grouping of substances and read-across approach" above, this adaptation is rejected. Hence, there is a need to test the registered substance.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route is low (maximum [redacted] mg/m^3). Hence, the test shall be performed by the oral route using the test method OECD TG 408.

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

ECHA notes that you have registered your substance as theoretical monoconstituent with greater than 99% purity with the following remark "*This substance is registered as single substance although part of a* [redacted] *multiconstituent substance to take advantage of the join submission.* [redacted] *Analytical characterisation data are only available for the multiconsituent substance. Therefore this composition only reflects virtually what could be the composition of the pure substance based on the analytical characterisation data of the multiconstituent substance.*"

ECHA further notes that no composition is provided for the multiconstituent substance in the IUCLID dossier. However, in the CSR you provide the following concentration ranges for the main constituents: for [redacted]% (w/w) and for [redacted] (w/w).

ECHA further notes that several of the tests in your dossier have been performed with the registered substance with a purity of 99.889% (w/w).

ECHA understands that you intend to use data obtained in studies with the mono-constituent HD4 and HD5, respectively, to cover the hazard properties for the multi-constituent substance.
To ensure that the relevant hazard property of the registered substance is appropriately identified ECHA therefore requests that the study is conducted with the registered substance with purity higher than 95%, as registered within the joint registration.

ECHA emphasises that Appendix 3 requests that adequate information on substance identity for the sample tested must be available. ECHA considers that the test material information is an integral part of the robust study summary to be submitted in the update IUCLID dossier.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance (purity higher than 95%): Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) while your originally proposed test for sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) *with the analogue substance* 2,4,6,8-tetramethyl-cyclotetrasiloxane (EC No 219-137-4) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your considerations:

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (Annex X, 8.7.3.). However, this testing proposal is not addressed in this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the Extended one-generation reproductive toxicity study. Therefore, you are required to perform the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your testing proposal for the Extended one-generation reproductive toxicity study. The updated testing proposal should include a justification for the design of the Extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the Sub-chronic toxicity study (90-day).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 1 October 2015.

ECHA held a third party consultation for the testing proposals from 31 January 2018 until 19 March 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **19 September 2018**, 30 calendar days after the end of the commenting period.

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

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s).

You updated your registration on 17 September 2018. ECHA took the information in the updated registration into account, and did not amend the draft decision. The updated information is reflected in the Reasons (Appendix 1).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

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

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

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

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