EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114424725-49-01/F
Substance name: 2,4,6,8-tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane
EC number: 219-863-1
CAS number: 2554-06-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10.07.2017
Registered tonnage band: 10-100T

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), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats using the registered substance

is rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance.**

Your testing proposals are accepted and you are requested to carry out:

2. **In vivo mammalian erythrocyte micronucleus test (Annex VIII, Section 8.4., column 2; test method: EU B.12./OECD TG 474) in mice or rats, oral route**
3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), using the registered substance.**
4. **Long-term toxicity testing on aquatic invertebrates (test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) using the registered substance.**
5. **Long-term toxicity testing on fish (test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) using the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **27 July 2020**. You shall also update the chemical safety report, where relevant.

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

Appeal

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

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

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

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) (TP) submitted by you for the registered substance 2,4,6,8-tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane (CAS No 2554-06-5, EC No 219-863-1), taking into account the updated dossier, including the updated tonnage band for the joint submission (change from 10-100 tpa to 100-1000 tpa).

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 for the tonnage band of 100 to 1000 tonnes per year 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 inhalation route according to EU B.26./ OECD TG 413 with the registered substance.

ECHA notes that in the updated dossier you provided your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90 day): inhalation. You concluded that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

You proposed testing by the inhalation route without providing any substance-specific explanations justifying the proposed route of administration. It is noted that the inhalation route of administration could be relevant for testing. The registered substance is a liquid which is of low volatility (93.5 Pa) at ambient temperature. In the technical dossier and/or chemical safety report uses with spray application that may generate aerosols of inhalable size are reported, thus human exposure to the registered substance by the inhalation route is likely. However, based on the data provided in the registration dossier, there is no concern for severe local effects following inhalation exposure. Furthermore, ECHA points out that no repeated dose toxicity study conducted via oral route is available and the substance is not classified.

Therefore, ECHA considers that the oral route is the most appropriate route of administration for testing to further investigate systemic toxicity. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

You proposed testing in rats. According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408)

while your originally proposed study, sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD TG 413) using the registered substance is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

2. In vivo mammalian erythrocyte micronucleus test (Annex VIII, Section 8.4., column 2)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X of the REACH Regulation. Column 2 of Annex VIII, Section 8.4. provides that "Appropriate in vivo mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII." Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro mammalian chromosome aberration test* performed according to OECD 473 with the registered substance that shows positive results with metabolic activation. The positive result indicate that the substance is inducing chromosomal aberrations under the conditions of the test.

An appropriate *in vivo* genotoxicity study to follow up the concern on chromosomal aberrations is not available An appropriate *in vivo* genotoxicity study to follow up the concern on gene mutations / chromosomal aberrations is not available for the registered substance. Consequently, there is an information gap and you considered it necessary to generate information for this endpoint.

Hence, you have submitted a testing proposal for a OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test).

ECHA notes that in the updated dossier you provided your considerations for alternative methods to fulfil the information requirement for Genetic toxicity in vivo. You concluded that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA notes that the proposed test is an appropriate test to investigate effects on chromosomal aberrations *in vivo* as described in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.7.1. and figure

R.7.7-1 (version 6.0, July 2017) if the test substance or its metabolite(s) will reach the target tissue as specified in the respective test method (OECD TG 474).

You did not specify the species or route of administration for testing. According to the test method OECD TG 474, the test shall be performed in mice or rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision:
In vivo mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice or rats, oral oute.

Note for your consideration

According to paragraph 10 of the OECD TG 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*". Additionally, according to paragraph 48 (d) of the OECD TG 474, a negative test result can be considered reliable if "*Bone marrow exposure to the test substance(s) occurred*". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

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

a) Examination of a testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out a proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement for the tonnage band of 100 to 1000 tonnes per year as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 with the registered substance.

ECHA notes that in the updated dossier you provided your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). You concluded that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

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

You proposed testing with the rat as a first species. According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You did not specify the route for testing. 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.

b) Consideration of the information received during third party consultation

The third party has indicated (summary): *A sequential testing process is recommended which gives priority to the additionally proposed test on genetic toxicity in vivo. If a positive result will be obtained, the substance self classified as a germ cell mutagen, and appropriate risk measurements be implemented a prenatal developmental toxicity study will not be required (REACH Guidance R.7.6.6.3).*

ECHA notes that it is your responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex IX, Section 8.7., column 2, second indent. This adaptation specifies that in case the substance is known to be a germ cell mutagen (which correspond to a classification as germ cell mutagen category 1A or 1B) and appropriate risk management measures are implemented, the pre-natal developmental toxicity study does not need to be conducted.

However, ECHA notes that results of a positive genetic toxicity *in vivo* assay may contribute to a classification as germ cell mutagen, but this test is usually not sufficient on its own for classification as germ cell mutagen category 1B.

c) Outcome

Therefore, pursuant to Article 40(3) (a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414).

Notes for your consideration

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

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

4. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed tests. "Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Additionally, Column 2 of Annex VII, Section 9.1.1., and ECHA Guidance on information requirements and chemical safety assessment (Chapter R7b Version 4.0, June 2017), indicate that long-term test shall be considered for a poorly water soluble substance such as the registered substance with water solubility of 0.007 mg/L.

You have submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates (*Daphnia magna* reproduction test, EU C.20/OECD TG 211) with the following justification submitted in the respective Endpoint Summary in IUCLID section 6.1.4.: "*There are no reliable long-term invertebrate toxicity data available for the registration substance, therefore good quality data for an appropriate structural analogue, octamethylcyclotetrasiloxane (D4, CAS: 556-67-2), have been read across.*

A 21-d NOEC of 0.0079 mg/l has been determined for the effects of octamethylcyclotetrasiloxane (D4, CAS: 556-67-2) on survival and reproduction of Daphnia magna. A 21-d EC50 of > 0.015 mg/l has been determined in the same test for effects on mortality.

Because D4 has a higher water solubility than the registration substance (0.056 mg/l and 0.0073 – 0.0088 mg/l respectively) and the long-term no observed effect concentration (0.0079 mg/l) for D4 is very close to the limit of water solubility for the registration substance, it is not possible to conclude with confidence whether the NOECs from the study with D4 will be above or below the limit of solubility for the registration substance. Therefore, toxicity may or may not be expressed in long-term studies for the registration substance. This is key for concluding on classification and labelling; therefore, testing proposals are put forward."

ECHA notes that you have submitted an endpoint study record for OECD Guideline 211 (Daphnia magna Reproduction Test) study on analogue substance octamethylcyclotetrasiloxane (D4; CAS No 556-67-2, EC No 209-136-7)but you consider that it is not sufficient to predict the relevant property of the registered substance and therefore you submitted a testing proposal.

In addition to the testing proposal and data on analogue substance D4, in the updated dossier (submission number: [redacted]) you have submitted an ESR for an OECD Guideline 211 study on analogue substance decamethylcyclopentasiloxane (D5; CAS No 541-02-6, EC No 208-764-9). In your updated dossier you have added the following boundary composition for the joint submission "*The registration substance has an average purity of >80% Vi4-D4, with <15% 2,4,6,8,10-pentamethyl-2,4,6,8,10-pentavinylcyclopentasiloxane Vi5-D5 (CAS 17704-22-2; Impurity 1) and <10% 2,4,6-trimethyl-2,4,6-trivinylcyclotrisiloxane Vi3-D3 (CAS 3901-77-7; Impurity 2) present as impurities*" (as given in your CSR)." In your CSR you indicate that the data on D4 "*are supported by read-across evidence relevant to the impurities*" and that the data on D5 is read-across to impurity 1 Vi5-D5, while you note that "*Effects are not anticipated at the limit of solubility and the available data for the main data set are conservative in respect of Impurity 2".* Overall, you consider that "*After due consideration of the properties, the*

presence of these impurities is not expected to affect the overall hazard profile of the substance."

While ECHA acknowledges your approach of considering the registered substance Vi4-D4 and its impurities separately, ECHA considers that you have not provided sufficient explanation and read-across justification on how the data provided would cover the substance as registered. ECHA also notes that further information on how the sample tested needs to be representative of the joint submission is given in Appendix 3. Below.

ECHA concludes that there is no adequate information present in the technical dossier on the toxicity of the registered substance to *Daphnia* and further data needs to be generated, as also indicated by you.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, the Registrant is required to carry out the Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211) study using the registered substance.

5. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed tests.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Additionally, Column 2 of Annex VIII, Section 9.1.3., and ECHA Guidance on information requirements and chemical safety assessment (Chapter R7b Version 4.0, June 2017), indicate that long-term test shall be considered for a poorly water soluble substance such as the registered substance with water solubility of 0.007 mg/L.

You have submitted a testing proposal for testing the registered substance for long-term toxicity testing on fish Fish, early-life stage toxicity test, OECD TG 210 with the following justification submitted under IUCLID section 6.1. Aquatic toxicity: *"There are no reliable long-term fish toxicity data available for 2,4,6,8-Tetramethyl-2,4,6,8-tetravinyltetrasiloxane (Vi4-D4) (CAS 2554 -06 -5), therefore good quality data for an appropriate structural analogue, octamethylcyclotetrasiloxane (D4, CAS: 556-67-2), have been read across."*... *"Because D4 has a higher water solubility than the registration substance (0.056 mg/l and 0.0073 – 0.0088 mg/l respectively) and the long-term no observed effect concentration (≥0.0044 mg/l) for D4 is very close to the limit of water solubility for the registration substance, it is not possible to conclude with confidence whether the NOECs from the study with D4 will be above or below the limit of solubility for the registration substance. Therefore, toxicity may or may not be expressed in long-term studies for the registration substance. This is key for concluding on classification and labelling; therefore, testing proposals are put forward."*

ECHA notes that in your dossier under IUCLID section 6.1.4 you have submitted endpoint study record for a study on analogue substance octamethylcyclotetrasiloxane (D4; CAS No 556-67-2, EC No 209-136-7) ([redacted]) but you consider that it is

not sufficient to predict the relevant property of the registered substance and therefore you submitted a testing proposal.

In addition to the testing proposal and data on analogue substance D4, in the updated dossier (submission number: [redacted]) you have submitted an ESR for an OECD Guideline 210 (Fish, Early-Life Stage Toxicity Test) study on analogue substance decamethylcyclopentasiloxane (D5; CAS No 541-02-6, EC No 208-764-9).

As discussed above in request 4, in your updated dossier you have added a boundary composition for the joint submission indicating Vi5-D5 and Vi3-D3 as the main impurities. In your CSR you indicate that the data on D5 is read-across to Impurity 1 Vi5-D5, while you consider that lack of data for Vi3-D3 is of no concern. Overall you consider that the impurities do not affect the toxicity of the registered substance.

While ECHA acknowledges your approach of considering the registered substance Vi4-D4 and its impurities separately, ECHA considers that you have not provided sufficient explanation and read-across justification on how the data provided would cover the substance as registered. ECHA also notes that further information on how the sample tested needs to be representative of the joint submission is given in Appendix 3. below.

ECHA concludes that there is no adequate information present in the technical dossier on the toxicity of the registered substance to fish and further data needs to be generated, as also indicated by you.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.6 of the REACH Regulation.

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: Fish, early-life stage toxicity test, OECD TG 210).

Notes for your consideration in relation to sections 4 and 5

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

Furthermore, ECHA notes that if the registered substance is likely to be unstable in the aquatic environment, a decision to test the registered substance, relevant constituents of the registered substance and/or its possibly identified degradation product(s), should be based on a consideration of the half-life of the registered substance under test and real-world conditions. It is your responsibilty to design the test in such a way that the effects on aquatic organisms are adequately assessed.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 16 April 2013.

ECHA held a third party consultation for the testing proposal(s) from 3 March 2014 until 17 April 2014. ECHA received information from third parties (see Appendix 1).

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

You were notified that the draft decision does not take into account any updates after 11 July 2016.

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

You submitted an updated dossier on 29 June 2017, which failed the completeness check, and was successfully resubmitted on 10 July 2017 (submission number: [redacted]). You also updated the tonnage band for the joint submission.

ECHA took information in the updated dossier into account and modified the draft decision. The requests for long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4.1. Column 2) and long-term toxicity testing on plants (Annex IX, Section 9.4.3., Column 2) were removed.

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

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

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Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades.

4. Finally there must be adequate information on substance identity for the substance tested to enable the assessment of its suitability, i.e., the tested substance 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.