ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114425138-53-01/F
Substance name: 1,1,3,3-tetramethyl-1,3-divinyldisiloxane
EC number: 220-099-6
CAS number: 2627-95-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19.06.2017
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

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

Your testing proposal is accepted and you are requested to carry out:

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.**
2. **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), oral route using the registered substance.**

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

You are required to submit the requested information in an updated registration dossier by **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) submitted by you for the registered substance 1,1,3,3-tetramethyl-1,3-divinyldisiloxane, CAS No 2627-95-4 (EC No 220-099-6) (hereafter referred to as "target substance" or Vi2-L2) taking into account the updated dossier (submission number [redacted]).

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

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

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.

In your dossier with submission number [redacted], based on which the initial draft decision was prepared, you have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route to be performed on the registered substance, according to EU B.26/OECD TG 408. ECHA has accepted this testing proposal.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees 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, potential inhalation-specific effects are already addressed by providing a sub-acute toxicity study by the inhalation route. 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.

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

After receiving the draft decision you have updated your registration dossier with the submission number [redacted].

In your updated dossier you have attempted to adapt the current information requirements using new arguments, all based on existing information. More specifically, you consider to achieve compliance with the relevant REACH information requirement for the registered substance (referred to also as the "target substance") using a 90-day inhalation toxicity study performed on analogue substance hexamethyldisiloxane (EC No 203-492-7; or L2) (hereafter the 'source substance').

You state that:

"Overall, it is concluded that based on the similar chemical structures of the parent, hydrolysis products and metabolites, similar physicochemical properties of the parent substances and consistent findings for all toxicity endpoints, it is likely that the mechanisms of toxicity for the target and source substances are the same and independent of route. Therefore, reading across results of a 90-day inhalation test and a prenatal developmental test (when available) from L2 to Vi-L2 is scientifically justified".

In the technical dossier you have provided the following higher tier studies conducted with the target substance relevant for the read-across approach and justification:

- Key *in vivo* mouse micronucleus assay (OECD 474, GLP, [redacted] 2012);
- Supporting repeated dose 14-day oral dose range finding study (no guideline, GLP, [redacted] 2011);
- Supporting repeated dose 14-day inhalation toxicity study (deviating from OECD 412, GLP, [redacted] 1993);
- Key Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422, GLP, [redacted] (2011a);

and studies conducted with the source substance:

- Key study, toxicokinetics *in vivo* (OECD 417, GLP, [redacted] (2006);
- Key study, toxicokinetics *in vivo* (OECD 417, GLP, [redacted] (2008);
- Supporting study, toxicokinetics *in vivo* (single dose, no guideline, non GLP, [redacted] (2001);
- Supporting sub-acute toxicity inhalation study to investigate alpha 2u-globulin nephropathy induction and the reversible binding of alpha 2u-globulin to L2 (no guideline, non GLP, [redacted] (2002);
- Supporting repeated dose 14-day inhalation Toxicity Study (following OECD 412, GLP, [redacted] 1992);
- Supporting sub-acute inhalation study (OECD TG 412, GLP, [redacted] 1997);
- Key study, sub-chronic 90-day inhalation study (OECD TG 413, GLP, [redacted] 1998);
- Supporting sub-chronic inhalation study with recovery period (OECD TG 413, GLP, [redacted] 1997);
- Supporting 2-year inhalation study (OECD TG 453, GLP, [redacted] 2005);
- Key two-generation reproductive toxicity study, inhalation route (OECD 416, GLP, [redacted] 2006).

ECHA notes that all of the above studies are existing data i.e. they have been conducted before the decision making process has started.

ECHA has analysed your adaptation attempt in order to conclude whether it conforms with the conditions set out in Annex XI, Section 1.5. In accordance with Annex XI, Section 1.5., there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

(i) Structural (dis)similarities and their impact on prediction

In your read-across justification document you have provided substance identity data and explained that "*both substances are disiloxanes with the general structural formula*

Me2Si(R)-O-Si(R)Me2, where R may be methyl or vinyl". You have also explained the differences in the structures: two methyl groups and one vinyl group on each silicon in the target substance and three methyl groups on each silicon in the source substance.

You have further explained the structural differences between the non-common hydrolysis products formed from the parent substances: *"one of the three methyl groups bound to silicon in the source substance hydrolysis product is replaced with a vinyl group in the target substance hydrolysis product".* You have also provided a list of potential metabolites of the target and source substances predicted with OECD QSAR Toolbox. You explain that the metabolites formed from the target and source substances are structurally similar, and some differences in structures are not considered significant.

You further state that "*The exception to this is that the vinyl groups present in Vi2-L2 may undergo oxidation to give an epoxide followed by further reaction to a diol or alpha-hydroxy aldehyde. Epoxides have structural alerts for genotoxicity and sensitisation. However, a complete set of measured data is available for these endpoints for Vi2-L2 and all results are negative. The consistency in existing repeated dose toxicity data for Vi2-L2 and L2 also does not support the generation of different metabolites for Vi2-L2. The prediction of these metabolites is based on vinyl groups in organic compounds; there are no experimental metabolism data for Si-C=C containing compounds to verify that these reactions can occur for this compound type*".

Based on the experimental data available for the target and source substances you conclude that "*there is a consistent profile of toxicity presented for L2 and Vi2-L2, which supports the conclusion that the structural difference (one of the three methyl groups at each of two silicons in L2 is replaced by a vinyl group in Vi2-L2) between the substances does not impact on the toxicokinetics, in vitro or in vivo toxicity. It is therefore reasonable to assume that toxicity data generated on the source substance, L2, is predictive of the toxicity data for the target substance, Vi2-L2 for all endpoints, including eye irritation, repeated dose toxicity and reproductive and developmental toxicity endpoints*".

ECHA notes that you acknowledge the structural differences but you consider that they do not impact the toxicity of the substances. However, ECHA considers that this assumption is not confirmed by the scientific data. To the contrary, as analysed in detail below, in point (ii) and in section 2, there are toxicological differences between the target and source substances. Given the structural differences, in particular the predicted epoxy and diol metabolites, between the target and source substances and their hydrolysis products, ECHA considers that there is a not sufficient basis for predicting the properties of the target substance from source substance.

(ii) Similar properties or regular pattern as a result of structural similarity

Based on the data provided, ECHA agrees with you that the target and source substances have similar toxicity profiles regarding the lower tier endpoints. Similar findings were also reported with regard to general systemic toxicity in the 28-day oral study with the source substance and the oral OECD 422 study with the target substance: reduced body weight gains, alpha-2u globulin nephropathy, brown liver pigmentation, haematology findings (relating to MCHC) and liver hypertrophy (serum chemistry, liver weight changes and microscopic findings).

However, ECHA stresses that in the oral OECD 422 study the target substance showed the following effects in males that had not been observed with the source substance: relative and absolute decreased brain and adrenal weight, adrenal cortical atrophy and vacuolation

of pituitary. You claim that these effects regarding adrenal cortex and pituitary were non-adverse.

ECHA notes the effects of the target substance on the pituitary cannot be considered non-adverse based on the information provided in the endpoint study record that shows a dose-response relationship (0/0, 4/10, 6/10, 8/10 for control, 50, 150 and 600 mg/kg bw/day, respectively). ECHA further notes that it cannot be excluded that the effects on adrenal cortex are adverse as a dose-response, although lower than for pituitary effects, were observed (0/10, 1/10, 2/10, 6/10 for control, 50, 150 and 600 mg/kg bw/day, respectively). In addition, the study duration is not equivalent to a sub-chronic toxicity (90-day) study and the severity of such effects in a longer duration cannot be excluded.

(iii) Conclusion on the read-across approach

ECHA concludes that that the criteria of Annex XI, Section 1.5, are not met, as presented above. Due to the structural differences of the parent compounds and metabolites, and in the light of dissimilar toxicological profiles of the target and source substances there is not an adequate basis for predicting the properties of the target substance from the data obtained with the source substance. Dissimilar toxicological profiles of the target and source substances is further supported by reproductive effects observed with the target substance as described in section 2 below.

ECHA concludes that your new arguments do not provide valid information to fulfil or waive the information requirement of "a sub-chronic toxicity study (90 day)" for the registered substance and it is necessary to provide information for this endpoint.

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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD TG 408),

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

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

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

In your dossier with submission number [redacted], based on which the initial draft decision was prepared, you have submitted a testing proposal for a pre-natal developmental

toxicity study to be performed on the registered substance, according to OECD TG 414. ECHA has accepted this testing proposal.

You did not specify the species to be used for testing. 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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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

After receiving the draft decision you have updated your registration dossier with the submission number [redacted] and changed the testing strategy. You intend to adapt the standard information requirement for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) of the registered substance by referring to data being generated for the source substance hexamethyldisiloxane (EC No 203-492-7; or L2).

More specifically, you have provided the following consideration:

"A study is being conducted on analogue substance hexamethyldisiloxane (107-46-0) based on the decision SEV-D-2114308444-56-01/F. See read-across justification. Once the results are available, the dossier will be updated with the read-across approach."

ECHA examines in the context of the testing proposal examination any intention of testing, including testing of an analogue substance, to ensure that the proposed strategy of generation of data is tailored to the relevant information needs for the endpoint and the dossier under the assessment. Therefore, ECHA has considered the scientific validity of the newly proposed read-across and grouping approach to ascertain whether a prediction of the relevant properties of the registered/target substance by using the results of the proposed test on the source substance is plausible based on the currently available information.

As outlined in the section 1 of this draft decision, in the updated dossier you have provided a read-across justification and available studies conducted with the target and source substances. The analysis of the structural (dis)similarities and their impact on the prediction, as provided in the section 1 above is also fully relevant for the current endpoint.

Regarding reproductive toxicity, you conclude that, based on available data, both substances have not demonstrated adverse effects on fertility: *"neither substance had an effect on fertility in the inhalation two-generation reproductive toxicity study (L2; [redacted] 2006) or in an oral Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (Vi2-L2; [redacted] 2011). These same studies also showed that both substances affected pup body weight gain. In addition, Vi2-L2 appeared to affect pup survival in two litters of the highest dose group. The mechanism of this effect and whether it was directly related to systemic toxicity of Vi2-L2 is not known. However, based on the fact that the OECD 422 study is a screening study, total litter loss was observed in the high dose group only, that there are consistent*

findings across all toxicity endpoints for Vi2-L2 and L2 and there were no route-specific findings, it is concluded that the more comprehensive guideline two-generation study on the source substance provides reassurance that this effect is not a concern for humans".

Regarding the OECD 422 study conducted with the target substance, ECHA notes that the decreased postnatal survival was due to 2 total litter losses. Based on the study results, 19 pups were found dead and 7 pups were missing. In addition, increased number of pups with cool and pale bodies were observed. ECHA considers that due to low maternal toxicity it is likely that these effects are test-substance related. ECHA also notes that the current information provided in the technical dossier does not allow to conclude if there is potential for the substance to cause malformations (e.g. a high number of missing pups could be due to cannibalism as a result of malformations).

ECHA notes that you consider these effects "*not a concern for humans*" and you have provided the following statements to which ECHA provides its responses:

a. *The effects were observed in the screening study on the target substance but not in the 2 generation study on the source substance.*
ECHA considers that the effects observed in the OECD 422 study cannot be disregarded even if such effects were not seen in the 2-generation reproductive toxicity study which has a higher statistical power (e.g. more animals used, longer duration, more parameters and endpoints analysed). In the OECD 422 study on the target substance the litter losses (leading to decreased postnatal survival) were observed in two females, i.e. 20% of the group. ECHA therefore considers that the severity of this potential developmental effect should be confirmed with the pre-natal developmental toxicity study with the target substance.

b. *The effects were observed in the high dose group only.*
ECHA considers that the highest dose used in the OECD 422 study (600 mg/kg bw/day) is still below the limit dose as outlined in the test guidelines (1000 mg/kg bw/day), and further, the effects were observed without major maternal toxicity.

c. *Consistent toxicological findings for the target and source substance in other repeated dose toxicity studies and there are no route-specific findings.*
ECHA does not agree with you on either of the accounts. First, as explained above and in Section 1, there are dissimilar toxicological findings in the repeated dose toxicity studies that together with structural differences between the target and the source substance do not support the claim of consistent toxicological profile of the substances. Second, full comparison between the oral (OECD 422) and inhalation route (28-day) for the target substance cannot be made as the concentrations used in the inhalation study were too low compared to test concentrations used in the studies with the source substance.

Based on the above considerations ECHA concludes that due to the structural differences of the parent compounds and metabolites, and in the light of dissimilar toxicological profiles of the target and source substances there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

ECHA therefore concludes that the criteria of Annex XI, Section 1.5, are not met, and consequently, using the data to be generated on the source substance is not appropriate to fulfil the information requirement(s) of the substance subject to the present decision.

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

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: 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).

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 notes that the tonnage band for several members of the joint submission is 100 to 1000 tonnes per year.

ECHA held a third party consultation for the testing proposals from 25 June 2015 until 10 August 2015. ECHA did not receive information from third parties.

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 6 July 2016, 30 calendar days after the end of the commenting period.

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

You updated your registration dossier on 05 April 2017, 26 April 2017 and again on 19 June 2017. ECHA took the information in the update of registration of 19 June 2017 into account for this decision, and removed the requests for long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4.1. Column 2), long-term toxicity testing on plants (Annex IX, Section 9.4.3., Column 2) and effects on soil micro-organisms (Annex IX, Section 9.4.2.).

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

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

Appendix 3: Further information, observations and technical guidance

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

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

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