EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114424726-47-01/F
Substance name: 1,1,1,3,5,5,5-heptamethyltrisiloxane
EC number: 217-496-1
CAS number: 1873-88-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30.06.2017
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 and decided as follows.

Your testing proposal is accepted and you are requested to perform:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using the analogue substance octamethyltrisiloxane, CAS No 107-51-7 (EC No 203-497-4).**

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 **26 July 2019**. 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 submitted by you for the registered substance 1,1,1,3,5,5,5-heptamethyltrisiloxane (H-L3), CAS 1873-88-7 (EC No 217-496-1)(hereafter referred to as "target substance") taking into account the updated dossier.

ECHA notes that in the dossier with submission number [redacted] based on which the initial daft decision was prepared, you proposed to conduct a pre-natal developmental toxicity studywith two analogue substances octamethyltrisiloxane (CAS No 107-51-7; EC No 203-497-4) and 1,1,3,3-tetramethyldisiloxane (CAS 3277-26-7, EC No 221-906-4).

ECHA considered the proposed analogue approach with octamethyltrisiloxane as plausible and requested testing for the pre-natal developmental toxicity study on this first analogue substance while rejecting such testing proposed with the second analogue substance, 1,1,3,3-tetramethyldisiloxane.

In your comments to the draft decision you did not provide considerations to any specific endpoints.

After receiving the draft decision you updated your registration dossier with the submission number [redacted] and changed your strategy with respect to the pre-natal developmental toxicity study (Annex IX, Section 8.7.2). In particular, you have removed testing proposal for pre-natal developmental toxicity study with the following justification: "*A study is being conducted on analogue substance octamethyltrisiloxane (CAS 107-51-7) based on the decision TPE-D-2114300032-77-01/F. See read-across justification. Once the results are available, the dossier will be updated with the read-across approach.*"

ECHA notes that although you have unticked the IUCLID tick box 'experimental study planned' you still have an intention of testing an analogue substance octamethyltrisiloxane in order to fulfil the standard information requirement for a pre-natal developmental toxicity study of the registered substance. ECHA has to examine 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. As your intention of testing an analogue substance octamethyltrisiloxane (hereafter referred to as L3) (CAS No 107-51-7, EC No 203-497-4) is clearly demonstrated in your recent update, the decision-making process of the testing proposal will continue.

ECHA has considered first the scientific validity of the proposed read-across and grouping approach (Section 0, below), before assessing the testing proposed (Section 1, below).

0. Grouping of substances and read-across approach

a. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis.

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*".

The first Recital and the first Article of the REACH Regulation establish the "promotion of alternative methods for assessment of hazards of substances" as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to the present decision by using the results of the proposed tests is plausible based on the information currently available.

b. Description of the proposed grouping and read-across approach

You provided the following statement to justify the read-across approach:

"The registration substance belongs to the structural class of siloxanes (alkyl, vinyl, aryl or hydrogen substituted), assigned structural class I-3 in PFA, 2013a. H-L3 and L3 are closely related substances, consisting of three Si atoms linked by oxygen, with methyl groups and hydrogen attached. L3 is fully methylated (i.e. contains 8 methyl groups), whereas in H-L3 one of the methyl groups is replaced by hydrogen.

In section 1.4.2 of the chemical safety report (CSR) you have provided the following arguments to justify the read-across approach:

"All of the substances are susceptible to hydrolysis although at pH 7 the rates of hydrolysis vary considerably. However, at pH 2 (relevant for oral exposure), hydrolysis is very rapid in all cases. As well as hydrolysis of the Si-O groups, the Si-H bond in H-L3 and H2-L2 can also undergo reaction to form a silanol group. L3 and H-L3 share a common hydrolysis product, trimethylsilanol. The parent substances all have high lipophilicity and low water solubility".

In section 5.6.3 of the CSR you state the following:

"In the case of repeated dose toxicity and reproductive toxicity, relevant properties are structural similarity as well as physical-chemical and basic toxicological parameters in the same range.

The read-across of data from L3 to H-L3 is initially justified by the similarities in structure and physicochemical properties of the two substances. However, there is some uncertainty in the read-across since it is not known with confidence whether the reactivity of the Si-H group may contribute towards adverse toxicological effects following exposure to H-L3.

"It is therefore proposed that read-across of the existing sub-chronic data for L3 should be used for the registration substance H-L3.".

"*Pre-natal developmental toxicity studies via the oral route are proposed for the L3 according to OECD test guideline 414. It is therefore proposed that the need for an additional OECD 414 test with H-L3 should be reviewed once the results of the above studies are available, otherwise the developmental toxicity endpoint for H-L3 will be filled by read-across or a weight of evidence approach based on data for the related substances.*"

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

You have provided the following information to support the grouping and read-across approach:

[redacted]

The provided data matrix report ("[redacted]") summarises the available physico-chemical, and toxicological data on the registered and source substances and on related siloxanes.

The Reconsile Category/Analogue/QSAR strategy report (16 May 2013) is an overview of the grouping and read-across methods of Reconsile REACH submissions. The document is an overview of the grouping and read-across methods of Reconsile REACH submissions. The document describes the general principles applied but does not provide any substance-specific information. According to the report, "*each CSR needs to describe clearly whether Category, Analogue or QSAR methods have been applied, and which endpoints they are applied to, and the IUCLID entries must be consistent with this*".
Based on this document, ECHA understands that you intend to apply analogue approach as a basis for data gap filling which are further justified in each registration dossier and CSR.

Apart from the above general information you have provided the substance specific read-across hypothesis and justification, in the technical dossier, under the endpoint study summary for repeated dose toxicity, in Section 7.5 and in the Chemical Safety Report (CSR) in section 5.

This information includes the read-across hypothesis and justification, supported by the identification of the source and target substances; comparison of the structural features, physico-chemical properties, predicted toxicokinetics properties and acute dose toxicity of the source and target substances. In the same place you also discuss the repeated systemic toxicity and reproductive and developmental toxicity of the target and source substances and conclude on your read-across approach.

In addition, you have provided the following toxicological studies in the technical dossier of the target substance, relevant to the testing proposed:
For the target substance:

- Acute oral toxicity (OECD 425, [redacted] 2008)
- Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD Guideline 422, [redacted] 2010a).

For the source substance octamethyltrisiloxane (L3):

- Acute inhalation toxicity study (OECD 403, [redacted], 2004b)
- Sub-chronic Inhalation Toxicity: 90-Day (OECD 413, [redacted] (2011a).

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

ECHA notes that the registrants of siloxanes (alkyl, vinyl, aryl or hydrogen substituted) have grouped the substances in 'Analogue group', including the substance subject to the current decision, but the category approach is not proposed. Based on the substance specific justification for read-across approach and supporting information provided by you, ECHA understands that no category hypothesis /justification has been included and the proposed prediction is based on the analogue approach using octamethyltrisiloxane (L3), CAS No 107-51-7 (EC No 203-497-4)

ECHA notes that in your updated dossier (submission number [redacted]) you propose only octamethyltrisiloxane (L3), CAS No 107-51-7 (EC No 203-497-4) as a source substance.

According to ECHA's understanding you suggest that based on their structural similarities target and the source substance have similar properties:

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

ECHA also understands that your read-across approach is also based on predicted rapid and complete hydrolysis of the parent substances at pH 2 and 37.5°C, leading to the formation of the proposed structurally similar silanol hydrolysis products (trimethylsilanol and methylsilanetriol from the target substance and dimethylsilanediol and trimethylsilanol from the source substance.

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

Structural similarity is a prerequisite for applying the grouping and read-across approach, but 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.

You have described the structural similarities between target and source substances as follows:
"H-L3 and L3 are closely related substances, consisting of three Si atoms linked by oxygen, with methyl groups and hydrogen attached. L3 is fully methylated (i.e. contains 8 methyl groups), whereas in H-L3 one of the methyl groups is replaced by hydrogen.

You have clearly identified the structural basis for the prediction, i.e. you postulate that both the source substance and the target substance hydrolyse, forming structurally similar silanol hydrolysis products, methylsilanetriol, dimethylsilanediol and trimethylsilanol , respectively. ECHA observes that due to the described structural differences of target and source substances the silanol hydrolysis products formed from the parent substances are different.

ECHA notes that the methylsilanetriol - formed from the target substance - and dimethylsilanediol–formed from the source substance - differ in the number of the hydroxyl groups and in the presence of a methyl group bound to the silicon atom.

You acknowledged a structural difference between the parent substances. However your claim that "*there is some uncertainty in the read-across since it is not known with confidence whether the reactivity of the Si-H group may contribute towards adverse toxicological effects following exposure to H-L3.*" does not explain what is the consequence of such structural difference on the possibility to predict.

ECHA notes that you have not provided any information on how the structural differences in the parent substances and consequently in the silanol hydrolysis products may impact the toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substance.

The provided explanation is therefore not sufficient to establish a scientifically credible link between the structural similarity and the prediction.

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

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 prerequisite for a prediction based on read-across therefore is that the substances involved are structural 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.

In your read-across justification you state that physico-chemical parameters/properties of target and source substances are "*in the same range*" and thus support the similar toxicokinetic behaviour of the substances. ECHA observes that the physico-chemical properties of target and source substances are in the same range.

With respect to your claim in the similarity with toxicokinetic behaviour of the target and source substances, ECHA notes that in the absence of toxicokinetics studies for the target and source substances, you have provided toxicokinetics predictions/assessments which are based on the physico-chemical properties of the substances itself and/or its hydrolysis products.

You further propose that "*in case of repeated dose toxicity and reproductive toxicity, relevant properties (..) basic toxicological parameters in the same range*".
Based on the data provided, ECHA notes that the target and source substance have similar acute oral toxicity profiles. The substances are not classified as skin or eye irritants and skin sensitisers and not genotoxic.

ECHA observes that you have provided a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)for the target substance (oral OECD 422 study) and sub-chronic repeated dose toxicity study (90-day) for the source substance L3 (inhalation, OECD 413).

With respect to the source substance L3 you state: "*similar effects are seen for both H-L3 and L3, and for both the oral and inhalation routes*" and that "*Neither of the available*

screening studies for H-L3 and L3 show any evidence of adverse effects on reproductive parameters up to the highest dose tested (800 mg/kg bw and 30 436 mg/m3, respectively). Specifically, you refer to the oral OECD 422 study (doses 50, 200 or 800 mg/kg bw/day) conducted with the target substance H-L3, where dose-related adverse effects on liver and kidney weights, hepatic brown pigment accumulation and male-specific rat effects (assumed to be alpha-2u-globulin) were observed. You conclude on that NOAEL of the target substance is 200 mg/kg bw/day. ECHA, however, notes that in the section 5.6.3. of the CSR, page 54 you state that the NOAEL value is 50 mg/kg bw/day.

You also state that "*Developmental screening tests are available for both H-L3 and L3. In the test with L3 ([redacted], 2008), conducted by the inhalation route, no effects were observed on developmental parameters up to the highest dose level tested of 30 436 mg/m3.*"

You have provided also a sub-chronic inhalation toxicity study OECD 413 conducted with the source substance L3 (doses 95, 400 and 3200 ppm, respectively). Similar adverse effects on liver and kidney and absence of local effects were reported. For this study you considered NOAEC of 400 ppm (3870 mg/m^3).

In the chemical safety report and in the data matrix, you further refer to the similar findings noted in the oral sub-acute toxicity study OECD 407 conducted on the source substance L3 and NOAEL was considered to be 25 mg/kg/day in males and 250 mg/kg day in females. ECHA notes that the effects are similar and, based on the provided details, the effects of L3 seem to be more severe (hepatic brown pigment accumulation accompanied with periportal chronic inflammation and bile duct proliferation) than the ones caused by the target substance.

You conclude that the critical adverse effects are liver effects (hepatic brown pigment accumulation) and male-rat specific kidney effects (assumed to be alpha-2u-globulin).

ECHA considers that you provided sufficient evidence to demonstrate that the systemic toxicity profiles of the target and source substance L3 are similar, and therefore there is an adequate basis for predicting the properties of the target substance from the data obtained with the source substance L3.

(iii) Hydrolysis

ECHA understands that the hypothesis relies on the assumption that both target and source substances undergo rapid and complete hydrolysis at pH 2 and 37.5 °C (within seconds) and they form structurally similar silanol hydrolysis products: methylsilanetriol and trimethylsilanol from H-L3, dimethylsilanediol and trimethylsilanol from L3. You state that *"L3 and H-L3 share a common hydrolysis product, trimethylsilanol".*

Firstly, ECHA observes that hydrolysis half-life rate at pH 2 are based on assumptions which are not substantiated by data. You postulate that "*at pH 2 (relevant for oral exposure), hydrolysis is very rapid in all cases".* ECHA notes that there is no hydrolysis data available in the registration dossier for pH 2 (neither for the target nor for the source substances) but that you have postulated that the rate of the hydrolysis reaction is dependent on either the hydronium ion or hydroxide concentration and that there will be a 100 fold increase in hydrolysis rate on going from pH 4 to pH 2. ECHA accepts that the hydrolysis is catalysed by either the hydronium ion or hydroxide concentration, however there is no evidence provided to suggest such a dependence on the hydronium ion concentration and consequently ECHA

considers the assumption of a 100 fold increase in hydrolysis rate on going from pH 4 to pH 2 as not supported by scientific evidence.

Secondly, ECHA notes that the formation of the proposed silanol hydrolysis products which supports the hypothesis is not supported by data. Specifically, ECHA notes that the formation of the proposed silanol hydrolysis product from the target substance would involve three hydrolysis steps. The formation of the proposed silanol hydrolysis product from the source substance would involve two or three hydrolysis steps. In the hydrolysis studies/read-across data provided in the registration dossier there is no evidence of the formation of the proposed silanol hydrolysis products so it is not possible to verify that ultimate hydrolysis of both target and source substances has indeed occurred within the timeframe of the test.

Furthermore, there is no discussion or analysis of the possible intermediate hydrolysis products of the target substance.

ECHA therefore considers that you have not provided reliable data to support the rapid hydrolysis at pH 2 and 37.5°C, and formation of the claimed hydrolysis products. Consequently, the impact of the parent substances and other possible hydrolysis products on toxicity in oral studies cannot be excluded.

However, ECHA considers that in this particular case the hydrolysis does not seem to impact the toxicity of the target substance and source substance L3, as the adverse systemic effects observed in the repeated dose toxicity study available on the source substance and screening study conducted with the target substance were similar, as discussed in section (ii) above.

e. Conclusion on the read-across approach

Based on the above considerations ECHA concludes that you have provided adequate and reliable information on source substance octamethyltrisiloxane (L3, CAS No 107-51-7, EC No 203-497-4) to demonstrate that the proposed read-across approach is plausible for the endpoint in consideration.

ECHA therefore concludes that the criteria of Annex XI, Section 1.5, are met, and consequently the testing proposed on the read-across substance L3 is appropriate to fulfil the information requirement(s)of the substance subject to the present decision.

1. 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.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route with the analogue substanceoctamethyltrisiloxane (L3), CAS No 107-51-7 (EC No 203-497-4).

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 you could adapt the information requirements by applying read-across approach. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance L3. As explained in the Section 0 '*Read-across approach*' of this decision, your adaptation of the information requirement with the source substance L3 is acceptable.

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 proposed testing by the oral route. ECHA agrees 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.

Therefore, pursuant to Article 40(3) (a) of the REACH Regulation, you are requested to carry out the proposed study with the analogue substance octamethyltrisiloxane (L3), CAS No 107-51-7 (EC No 203-497-4): 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 proposals for examination pursuant to Article 40(1) on 9 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 26 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 11 July 2016.

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 30 June 2017. ECHA took the information in the updated registration into account, and removed the requests for sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.), 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 has addressed your changed strategy for the pre-natal developmental toxicity study (Annex IX, Section 8.7.2) in sections 0. and 1. of this decision.

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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

2. 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.

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 the Member States.

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.