EUROPEAN CHEMICALS AGENCY

Helsinki, 10 September 2018

Addressee: [redacted]

Decision number: TPE-D-2114440323-61-01/F
Substance name: Decamethylcyclopentasiloxane
EC number: 208-764-9
CAS number: 541-02-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23 October 2017
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.

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

1. **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), inhalation route using the registered substance.**

You are additionally requested to perform:

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), inhalation 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 to the REACH Regulation. 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 have to submit the requested information in an updated registration dossier by ***17 March 2020***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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.

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.

1. **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), inhalation route using the registered substance.**

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 inhalation route (vapour) with the registered substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding 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 proposed testing by the inhalation (vapour) route.

ECHA considers that the oral route is usually 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. ECHA notes that the substance is not a gas. However, in the Guidance it is also stated that "*case-specific deviations from the default approach must be justified, such as in the case of available information on route-specific toxicity or toxicokinetics indicating that the use of oral administration of substance would not be relevant for assessing the human health hazards via inhalation, which would be the main route of exposure".*

ECHA notes that you did not provide any endpoint-specific justification for the selected inhalation route of administration. However, in the toxicokinetic section of the chemical

safety report (CSR), you state that "*The distribution and kinetics of D5 after oral dosing differed significantly from the predictions of the PBTK model that adequately described the inhalation and dermal exposure routes (Reddy et al., 2007, 2008). The differences in toxicokinetics after oral administration as compared to inhalation or skin contact suggest that D5 is transferred from the gastrointestinal tract to the blood by different mechanisms as compared to those that operate after inhalation or dermal administration. The oral route may deliver microemulsions of D5 that do not readily dissolve in plasma and blood and are distributed as such. Uptake may be more associated with lipid transport, such as chylomicron formation and thus D5 may not be completely available for tissue interactions. The microemulsions may be removed from the circulation by the reticuloendothelial system in liver and spleen.*" You conclude that "*... only inhalation and dermal toxicity studies will provide useful information on their hazard properties potentially relevant to humans*" and "*after inhalation, D5 is absorbed through the lungs and inhalation therefore is the only reasonable route of exposure resulting with a potentially important contribution to systemic availability*".

ECHA acknowledges the information regarding the toxicokinetic behaviour of the substance after inhalation administration. In addition, it is in line with Scientific Committee on Consumer Safety (SCCS) opinion (SCCS/1241/10;https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_029.pdf) on cyclomethicone D4/D5, which concludes that "*the pharmacokinetics of D5 is heavily influenced by an unusual set of properties, high lipid partitioning coupled with very high blood clearance due to exhalation and metabolism. The more unusual characteristic with this compound is the qualitative differences for inhalation/dermal routes versus oral route. The former appear to involve absorption of molecular forms of D5 and the latter appears to involve absorption of micro-emulsions or chylomicrons*" and that "*these dose route differences argue that the oral dose route may have little relevance for assessing risks of D5 and results from oral studies using oral gavage in corn oil have to be used with caution for drawing broad conclusions about safety or risks arising from more common routes of exposure or from oral dosing studies with much lower doses associated or mixed with feed*"

Taking into account the information based on PBTK model about the different toxicokinetic behaviour of the registered substance after inhalation/dermal and oral administration, ECHA considers that the inhalation route is the appropriate one.

ECHA further notes that you have used inhalation (vapour) as a route of administration in the following studies, carried out with the registered substance:

- One key two-generation reproductive toxicity study (EPA Guideline, GLP, Klimish score 1) in rats ([redacted], 1999). NOAEC for parental toxicity, reproductive toxicity, and for neonatal toxicity was ≥160 ppm (equivalent to [redacted], the HDT).
- One supporting one-generation toxicity study (GLP, no guideline, Klimish score 2) in rats ([redacted] 1995). NOAEC was ≥ 132 ppm (equivalent to [redacted] No adverse effects on fertility or pups were observed.
- One key two-year combined chronic toxicity and carcinogenicity study (OECD 453, GLP, Klimish score 1) in rats ([redacted], 2005). The NOAEC for systemic toxicity was ≥160 ppm (equivalent to [redacted] the HDT).

ECHA notes that in the above-mentioned studies, no systemic adverse effects were observed at 160 ppm (equivalent to [redacted], the highest concentration tested). ECHA further notes that there are data showing that D4 (octamethylcyclotetrasiloxane), a structural analogue of D5, has a NOAEC for reproduction of 300 ppm (equivalent to [redacted], based on reduced fertility indices and reduced mean live litter sizes at 500 ppm (equivalent to [redacted]) and above, derived from a two-generation reproductive toxicity study (OECD TG 416; CSR). ECHA therefore considers that some toxic effects, including reproductive toxicity of D5, once administered at higher concentrations, cannot be ruled out.

Further, according to the OECD TG 414 for pre-natal developmental toxicity study "*the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*".

In regard to these, ECHA considers that in order to achieve "*some developmental and/or maternal toxicity*", the study should be performed by the inhalation route including concentrations higher that 160 ppm ([redacted]).

In the comments to the draft decision you pointed out the technical issues associated with study concentrations of D5 exeeding 160 ppm ([redacted]). You stated that based on your experience and "*on earlier inhalation studies conducted with D5, at a concentration of 224 ppm approximately [redacted]% of the D5 would be in the form of liquid aerosol rather than the vapour*". You further state that "*the saturated vapor concentration of D5 was experimentally evaluated to be in the range of 140-180 ppm, and these liquid droplets of D5 would be deposited in the alveoli*". Thus, you claim that 160 ppm is the "*highest vapor concentration that could be reliably and effectively generated without appreciable aerosol or condensation*" and it is "*in good correlation between actual and nominal concentrations (difference in concentration <[redacted]%) and could be consistently generated for repeated exposures*".

ECHA understands that the pre-natal developmental toxicity test via inhalation (vapour) at concentrations of D5 higher than 160 ppm is technically not feasible due to aerosol formation. ECHA notes that this argument need to be supported by a confirmatory statement from the test laboratory performing the study. Appropriate investigations have to be conducted to determine the highest test concentration feasible. The results of these investigations need to be reported in the robust study summary submitted in the updated dossier.

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), inhalation route (test method: EU B.31./OECD TG 414).

2. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), inhalation route using the registered substance.

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

As outlined above under 1, ECHA has approved your testing proposal for a pre-natal developmental toxicity study in a first species according to EU B.31./OECD TG 414.

You have sought to adapt the information requirement for a pre-natal developmental toxicity study in a second species. In the CSR you have provided the following justification: *"In accordance with Annex X column 2 of REACH, the decision to conduct the prenatal developmental toxicity study in a second species should be based on the outcome of the test in the first species. A decision on whether to conduct a prenatal developmental toxicity study on a second species will be made when the results of the proposed test in rats is available"*

ECHA notes that your justification for data waiving given above refers to specific adaptation rules in Annex IX, Section 8.7.2. column 2 of the REACH Regulation. However, ECHA notes that you registered your substance for 1000 tonnes or more per year and a study in a second species is a standard information requirement (Annex X, Section 8.7.2.). In this respect, ECHA points out that the information requirements in column 1 at Annex X is cumulative to Annex IX, requiring one prenatal developmental toxicity study more in addition to that required in Annex IX. Thus, at Annex X level information on two species is required and that information requirement cannot be adapted as proposed.

A pre-natal developmental toxicity study in a second species is required according to Annex X, Section 8.7.2 unless the specific rules for adaptation in Annex X, Section 8.7., column 2 or the general rules for adaptation in Annex XI are met.

You have not provided a general adaptation proposal according to Annex XI. Because of your adaptation proposal, referring specific adaptation rules, ECHA has evaluated if any of the specific adaptation rules in Annex X, Section 8.7, column 2 applies to your substance. According to Column 2 of Annex X, 8.7, reproductive toxicity studies do not need to be conducted if:

- the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or

- the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or

- the substance is of a low toxicological activity (no evidence of toxicity seen in any of the test available), it can be proven from toxicokinetics data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

ECHA notes that the two first options are not met, as based on data available in the registration dossier, the substance is not known to be either a genotoxic carcinogen or germ cell mutagen.

Regarding the third option for data waiving, based on low toxicological activity, you have provided experimental toxicokinetic studies via oral and inhalation route of administration, carried out with the registered substance, in which you showed that nearly 20% of the substance is absorbed after oral administration and 3% - after inhalation. Further, you showed that short (14-day and 28-day) and long-term (90-day) oral administration as well as long-term (2-year) inhalation administration of D5 results in statistically increased liver weight. Even though, in section 5.6.3. in the CSR you state that "[..] *increased liver weight without related histopathological findings [...] were considered to be adaptive changes and are therefore not of toxicological relevance",* ECHA concludes that systemic absorption occurs via oral and inhalation exposure. Further, ECHA notes that based on the information provided in the CSR it cannot be concluded that there is no or no significant human exposure. In particular, the use of the registered substance in household care products (PROC 7), e.g. washing and cleaning products, solid and sprayed type polishes and in personal care products – antipersperants, deodorants, hair sprays. Hence, it cannot be considered there is no or no significant human exposure.

Therefore, based on the information provided in the registration dossier, none of the situations for waiving the standard information requirement mentioned in Section 8.7, Column 2 of Annex X is obviously given, and you did not provide any adequate and reliable justification to adapt the information requirement under the general rules for adaptation according to Annex XI. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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 in a second species (rabbit or rats), depending on the species tested in the first pre-natal developmental toxicity study.

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,* Chapter R.7a, Section R.7.6.2.3.2 (version 6.0, July 2017). However, due to the different toxicokinetic behaviour of the registered substance after inhalation/dermal and oral administration, discussed under Section 1. above, ECHA considers that the inhalation route is the appropriate one.

In the comments to the draft decision you state: "*Regarding the pre-natal development test in a 2^{d} species, according to the note for our consideration in ECHA's draft decision, a decision on whether to conduct a prenatal developmental toxicity study on a second species will be made when the results of the proposed test in a 1st species is available and all other relevant existing data were taken into account".*

ECHA reiterates that a pre-natal developmental toxicity study in the second species is a standard information requirement for substances registered at 1000 tonnes or more.
Any 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. As ECHA has already explained in the decision, the specific adaptation possibilities according to column 2 of Annex X, section 8.7.2. are not met.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out an additional study with the registered substance subject to the present decision: Pre-

natal developmental toxicity study in a second species (rabbit or rat), inhalation route (test method: EU B.31./OECD TG 414).

Notes for your consideration for sections 1. and 2. above

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

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 in accordance with Article 40(1) on 31 July 2017.

ECHA held a third party consultation for the testing proposals from 25 October 2017 until 11 December 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **23 April 2018**, 30 calendar days after the end of the commenting period.

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).

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.