EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000004624-74-06/F Helsinki, 22 August 2014

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For Dodecamethylcyclohexasiloxane, CAS No 540-97-6 (EC No 208-762-8), registration number [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for Dodecamethylcyclohexasiloxane, CAS No 540-97-6 (EC No 208-762-8) submitted by [redacted] (Registrant).

This decision is based on the registration dossier as submitted with submission number [redacted] for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 3 January 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the registration at a later stage.

The compliance check was initiated on 2 November 2012.

On 31 January 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted]

On 1 March 2013 ECHA received comments from the Registrant.

On 6 September 2013 the Registrant updated his registration dossier (submission number [redacted]

The ECHA Secretariat considered the Registrant's comments and update. On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 3 January 2014 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposals for amendment to the draft decision were submitted.

On 7 February 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

On 17 February 2014 ECHA referred the draft decision to the Member State Committee.

By 10 March 2014 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision relating to the *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3), and developmental toxicity study in rats or rabbits by oral route was reached on 24 March 2014 in a written procedure launched on 13 March 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

The present decision relates solely to a compliance check examination for *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3), and Developmental toxicity study in rats or rabbits by oral route (Annex X, 8.7.2). The other compliance check requirement of the two-generation reproductive toxicity study is addressed in a separate decision although all endpoints were initially addressed together in the same draft decision.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vi), 12(1)(a), 13 and Annex VII of the REACH Regulation the Registrant shall submit the following information using the test method as indicated on:

a) *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.; EU method B.17 (OECD test guideline 476 study)); and
b) Developmental toxicity study in rats or rabbits by oral route (Annex X, 8.7.2.; EU Method B.31 (OECD test guideline 414)).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **31 August 2015**.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance for the purpose of registration within the applicable tonnage band of 1000 tonnes or more per year in accordance with Article 6 and 11(2) of the REACH Regulation, does not comply with the requirements of Articles 10, 12 and 13 and with Annexes VIII, IX, X thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vi), 12(1)(a) and (b) of the REACH Regulation, a registration for a substance produced in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

(a) The following information is missing in relation to the mutagenicity end-point:

- *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.);

At this tonnage level an *in vitro* gene mutation study in mammalian cells is required if negative results are obtained in Annex VII, Section 8.4.1. (*in vitro* gene mutation study in bacteria) and Annex VIII, Section 8.4.2. (*in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study). Since both the *in vitro* gene mutation study in bacteria and the *in vitro* micronucleus study available in the registration dossier were negative, an *in vitro* gene mutation study in mammalian cells is required. The technical dossier does not contain any adaptation relating to the relevant study.

The Registrant, in his comments submitted according to Article 51(1) of the REACH Regulation, expressed no objections to carry out the test. He reconfirmed this in his comments to the proposals for amendments.

The Registrant is accordingly requested to submit the information for this endpoint performed with the registered substance.

(b) The technical dossier contains an adaptation to the standard information requirements for the endpoint on:

- Pre-natal developmental toxicity study (Annex IX, 8.7.2.);

At this tonnage level a pre-natal developmental toxicity study in two species is required. Instead, the Registrant submitted the results of the combined repeat dose oral toxicity study and reproductive/developmental toxicity screening study (OECD 422). In that study, no pre-natal developmental toxicity effects were observed. The Registrant presented an adaptation to the information requirement for the endpoint pre-natal developmental toxicity study (PNDT), stating that "*In accordance with Section 1 of REACH Annex XI, the developmental toxicity test does not need to be conducted due to the following reasons. A combined repeat dose oral toxicity study and reproductive/developmental toxicity screening study was carried out for D6 according to OECD 422 and in compliance with GLP (DCC 2005). There were no statistically significant adverse effects on reproductive and developmental endpoints at the highest dose tested, 1000 mg/kg/d. Another element to consider is that a 90-day subchronic inhalation toxicity study is proposed in this CSR which will provide further information relevant to any potential reproductive toxicity (some*

information with regard to sex organ toxicity will be obtained). Based on the existing and planned studies, in addition to the spirit of REACH to minimise use of animals, it is proposed that the developmental toxicity test can be waived."

In the view of ECHA, the arguments presented by the Registrant are not sufficient to cover Annex XI, Section 1. In this section it is stated that "*There may be sufficient weight of evidence from several sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion*". For the registered substance, the only source available for the pre-natal developmental toxicity endpoint is the combined repeat dose oral toxicity study and reproductive/developmental toxicity screening study (OECD 422). Therefore, the requirement of evidence from several independent sources is not fulfilled. In addition, in a screening study (OECD 422), foetuses are not examined, only pups. If the newly born pups are seriously malformed, the dam usually eats them before examination can be carried out. Therefore, a screening study in which no adverse effects are observed in pups does not constitute evidence that a substance has no adverse pre-natal developmental effects.

Furthermore, it is stated in the technical dossier: "*The prenatal developmental toxicity study (OECD 414) requires groups of 20 females, whereas this combined test calls for 10 females. The very limited examination of foetuses is consistent with the guidelines for this screening study.*" Although consistent with the OECD 422 testing guideline the examination of pre-natal effects in the combined OECD 422 and reproductive/developmental toxicity screening study is very limited – compared to the pre-natal developmental toxicity study (OECD 414).

In addition, the 90-day study, as required on the registered substance in decision TPE-D-0000001989-55-03/F, cannot provide sufficient information for this endpoint, since in such studies, pre-natal developmental toxicity is not investigated. Therefore, it cannot be used as a weight of evidence for absence of adverse pre-natal developmental effects.

In conclusion, the adaptation cannot be accepted, and the information for this endpoint with the test performed needs to be generated.

According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

The Registrant, in his comments submitted according to Article 51(1) of the REACH Regulation, expressed no objections to carry out the pre-natal developmental toxicity study, but challenged the choice of the route of administration (oral) and proposed to carry out the test by the inhalation route for the following reasons: "*1) ECHA has accepted our testing proposal for a 90-day inhalation test. The test is on-going.2) Exposure to vapor occurs for all relevant human exposure scenarios and this was the primary reason to select the inhalation route for the 90-day study. 3) The learning from the 90-day study will be much better used if the 2-generation study is run via the inhalation route rather than via the oral route. 4) High doses typical of oral dose administration testing are not representative of real-life situations based on known uses and applications of D6* [i.e. the registered substance]."

ECHA considers that the test should be done by the oral route for the following reasons:

1) REACH requires testing for reproductive toxicity at Annex IX and X, Section 8.7. by the "most appropriate route of administration, having regard to the likely route of human exposure".

2) ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7a: Endpoint specific guidance, indicates in Section R.7.6.1 that "it is important that the potential hazardous properties with respect to reproduction are established for chemicals with relevant human exposure that may be present in the environment, at the workplace and in consumer products." To establish reproductive hazard properties of the substance, systemic availability of the substance should be ensured. Systemic exposure is ensured by using the oral route as a route of exposure in testing.
3) ECHA Guidance on information requirements and chemical safety assessment, Therefore, ECHA considers the oral route as most appropriate for reproductive toxicity studies to identify the hazard of a substance.

With regard to the reproductive hazard of the registered substance, ECHA recognises the following:

1) In the 90-day study by whole-body inhalation, there were local effects in the nasal mucosa at 10 ppm (182 mg/m^3) and in the lung at 30 ppm (546 mg/m^3). Liver effects (periportal hepatocellular vacuolation) were observed at 10 and 30 ppm. The NOAEC was set at 1 ppm.
2) The available screening study with oral administration of the substance indicated liver effects even at the lowest dose of 100 mg/kg bw/d and a possible effect on female fertility (increased number of non-gravid sperm-positive females) at 1000 mg/kg bw/d, which was statistically not significant. The Registrant set the NOAEL at 1000 mg/kg bw/d.
3) To perform the reproductive toxicity studies via inhalation as proposed by the Registrant, exposure would be limited due to the irritating properties of the substance so that the concern for impairment of fertility might not be investigated.

ECHA considers that the Registrant's arguments for choosing the inhalation route are not appropriate since:
1) Accepting the 90-day study by inhalation does not mean that PNDT study should also be done by the inhalation route.
2) Exposure to vapour is probably rather low, since the vapour pressure at 25 centigrades is only 4.7 Pa.
3) Planning of the PNDT study can be done based on the oral OECD 422 that already exists in the dossier.
4) The doses of the PNDT study should be selected based on systemic toxicity observed and not based on exposure in real-life situations.

In his comments to the proposal for amendments, the Registrant had no objection to performing the test.

The Registrant is accordingly requested to submit the information for this endpoint performed with the registered substance.

(c) Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study (Annex X, 8.7.3.). As this endpoint is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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