EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000002289-68-04/F Helsinki, 6 June 2012

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

For 1,1,1,3,3,3-hexamethyldisilazane, CAS No 999-97-3 (EC No 213-668-5), 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 1,1,1,3,3,3-hexamethyldisilazane, CAS No 999-97-3 (EC No 213-668-5) submitted [redacted] (Registrant), latest submission number [redacted], for 1000 tonnes or more per year.

The compliance check was initiated on 26 October 2010.

On 22 August 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 21 September 2011 the Registrant provided to ECHA comments on the draft decision. On 21 October 2011 and 8 December 2011 update dossiers were received.

ECHA has taken into account the information received and decided to amend the draft decision.

On 20 January 2012 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 to amend the draft decision within 30 days. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision. ECHA reviewed the proposals for amendment received and decided to slightly modify the statement of reasons of the draft decision.

On 23 February 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification.

On 5 March ECHA referred the draft decision to the Member State Committee.

On 26 March 2012 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 24-27 April 2012, the Member State Committee modified the draft decision and a unanimous agreement of the Member State Committee on the draft decision was reached on 26 April 2012.

II. Information required

Pursuant to Articles 41(1)(a), 41(3) and Annexes IX-X of the REACH Regulation the Registrant shall submit the information using the test method as indicated below:

a) A sub-chronic repeated dose toxicity study (90-day) with the registered substance, via the inhalation route in the rat (Annex IX, 8.6.2; OECD TG 413; EU Test Method B.29);

b) A pre-natal developmental toxicity study with trimethylsilanol, the relevant hydrolysis product of the registered substance, via the oral route in the rat (Annex IX, 8.7.2; OECD TG 414; EU Test Method B.31)

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 **6 June 2014.**

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.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage. Particularly, ECHA may need to re-assess the need to request a two generation reproductive toxicity study and/or a developmental study on a second species, in light of the findings of the sub-chronic and pre-natal developmental toxicity studies. The Registrant may anyway come to the conclusion that further studies on reproductive toxicity are necessary and submit testing proposals accordingly.

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 in accordance with Article 6 of the REACH Regulation, does not comply with the requirements of Articles 10 and 12 and with Annexes I, IX, X and XI 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.

Missing information related to endpoints

Pursuant to Articles 10(a)(vi) and 12(1)(e) 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 -X of the REACH Regulation.

a) Sub-chronic repeated dose toxicity (Annex IX, 8.6.2)

At this tonnage level a 90-day repeated dose toxicity study is required. Instead, the Registrant submitted the results of a combined 28-day study with screening for reproduction toxicity via the inhalation route. The Registrant waived the 90-day sub-chronic repeated dose toxicity study, stating that "*In accordance with Section 3 of REACH Annex XI,*

a 90-day repeated dose toxicity test (required in Section 8.6.2) does not need to be conducted on the grounds of exposure-based considerations. A full exposure assessment and risk characterisation have been carried out in accordance with REACH guidance, as documented in the Chemical Safety Report and supporting documents. The substance is extremely reactive and is handled under highly controlled conditions at industrial locations. It is fully consumed during use and there is no potential for exposure to the general public either from direct use or from residual unreacted substance in end products. Using a conservative approach to exposure estimation and Derived No Effect Levels (based on data available for the hydrolysis products of HMDZ), all risk characterisation ratios are below 1." Indeed, in the assessment the Registrant used a DNEL-value derived from the 28-day study for the sub-chronic endpoint.

In order for substance-tailored exposure-driven testing to apply (Annex XI, section 3), all of the conditions set in Annex XI, 3.2(a) need to be fulfilled. Condition (i) requires that the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses. This condition has not been fulfilled, as there is a mention of low levels of exposure on a repeated basis as the typical pattern of worker exposure in the Chemical Safety Report (page 49), whilst all intended uses are industrial. Condition (ii) is not fulfilled, as the footnote to Annex XI, 3.2(a) states "*For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.*"

On these grounds, the adaptation of the standard information requirement cannot be accepted.

ECHA notes that in the comments submitted during the 30-days commenting period, the Registrant has agreed on the need for further information for sub-chronic repeated dose toxicity.

ECHA considers it of importance to obtain information for the toxicity of the registered substance for the inhalation route. Only with such route-specific information it will be possible to derive appropriate data on which to base worker protection measures. The Registrant's proposal to use hexamethyldisiloxane or trimethylsilanol to cover the information requirement was therefore analysed starting from this need.

ECHA considers trimethylsilanol (one hydrolysis product of the registered substance) as proposed test substance instead of the registered substance as not acceptable for the purpose of determining the inhalation-route specific toxicity and the local effects in the respiratory tract.

The Registrant included in the updated dossier an OECD 422 combined screening test by inhalation for the hydrolysis product trimethylsilanol. In this test with trimethylsilanol, no relevant signs of toxicity concerning systemic toxicity and reproduction have been observed up to the highest concentration tested (NOAEC = 2.2 mg/l = 600 ppm). However, the dossier also contains another OECD 422 combined screening test by inhalation with the registered substance hexamethyldisilazane (as the Registrant himself prefers to name it). In that test, signs of systemic toxicity to liver, kidney, as well as effects on blood count, epididymes weight and neurotoxicity were present at 400 ppm (2,66 mg/l). Although female animals in particular did show signs of toxicity, these findings have been observed in the so called "toxicity group" and can not be attributed to increased sensitivity of female animals

during pregnancy. Therefore, the results of the screening study with the registered substance raise concern with regard to systemic toxicity via the inhalation route which should be further investigated by a study with longer duration.

The dossier contains information on the speed of hydrolysis of hexamethyldisilazane in water while no information on the speed of hydrolysis in air is provided. It can be assumed that in air not all the parent compound will be hydrolysed immediately to trimethylsilanol and ammonia but rather a mixture of the three substances (registered substance and the two hydrolysis products) in air is to be expected to reach the respiratory system. Hence, testing the trimethylsilanol would not provide information on the possible interaction between the three substances and would not fully allow the investigation of all possible toxic effects of the registered substance via the inhalation route.

The Registrant has not demonstrated that the inhalation effects would be adequately addressed by just applying the OEL of one of the hydrolysis products (ammonia) instead of testing the registered substance, deriving the DNEL accordingly and thus covering also the potential interaction of the three substances (registered substance and the two hydrolysis products) on the absorption and toxicity in the respiratory system. Hence, trimethylsilanol cannot be accepted as test substance instead of the registered substance for the purpose of this test.

ECHA considers hexamethyldisiloxane as not acceptable to cover the information requirement for the registered substance, since hexamethyldisiloxane and hexamethyldisilazane (registered substance) hydrolyse at different speed and produce different hydrolysis products. Hexamethyldisilazane disintegrates much faster, particularly several orders of magnitude (hexamethyldisilazane $t_{1/2}$ less than 30 s, hexamethyldisiloxane $t_{1/2}$ 120 h compared to hexamethyldisiloxane at the same pH 7). Hence, the kinetics of trimethylsilanol formation will be very different after exposure to hexamethyldisilazane and hexamethyldisiloxane. Additionally, hexamethyldisilazane (registered substance) gives rise to ammonia whereas hexamethyldisiloxane does not. Therefore, the systemic effects as well as the local effects of hexamethyldisiloxane on the respiratory tract are expected to differ from the effects caused by hexamethyldisilazane.

The Registrant is accordingly requested to submit information on sub-chronic repeated dose toxicity (90 days) performed with the registered substance hexamethyldisilazane, in the rat, via the inhalation route by the EU test method B.29 according to Commission Regulation (EC) No 440/2008 or by OECD 413. It should, finally, be noted that due to the reactivity of the substance, determination and measurement of the actual substance or mixture of substances in the tubes leading to the animal breathing zones or in the chamber atmosphere is recommended.

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

At this tonnage level at least a pre-natal developmental toxicity study in one species is required. Instead, the Registrant performed a combined 28-day repeated dose toxicity study with screening for reproduction toxicity via the inhalation route. The Registrant waived the prenatal developmental toxicity study, stating that "*In accordance with Section 3 of REACH Annex XI, a developmental toxicity test (required in Section 8.7.2) does not need to be conducted on the grounds of exposure-based considerations. A full exposure assessment and risk characterisation have been carried out in accordance with REACH guidance, as documented in the Chemical Safety Report and supporting reports. The substance is extremely reactive and is handled under highly controlled conditions at industrial locations.*

It is fully consumed during use and there is no potential for exposure to the general public either from direct use or from residual unreacted substance in end products. Using a conservative approach to exposure estimation and Derived No Effect Levels (based on screening data), all risk characterisation ratios are below 1". Indeed, in the assessment the Registrant used a DNEL-value derived from the screening study for the developmental endpoint.

In order for substance-tailored exposure-driven testing to apply (Annex XI, section 3), all of the conditions set in Annex XI, 3.2(a) need to be fulfilled. Condition (i) is not fulfilled, as there is a mention of low levels of exposure on a repeated basis as the typical pattern of worker exposure in the Chemical Safety Report (page 49), whilst all intended uses are industrial. Condition (ii) is not fulfilled, as the footnote to Annex XI, 3.2(a) states "*For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study.*"

On these grounds, the adaptation of the standard information requirement cannot be accepted.

ECHA notes that in the comments submitted during the 30-days commenting period, the Registrant has agreed on the need for further information for pre-natal developmental toxicity. The Registrant has therefore proposed to perform a pre-natal developmental toxicity study with the hydrolysis product trimethylsilanol and/or to cover the information requirement by using available data on hexamethyldisiloxane.

ECHA considers hexamethyldisiloxane as not acceptable to cover the information requirement for the registered substance, for the reasons given above under point 1.a).

ECHA considers trimethylsilanol (one hydrolysis product of the registered substance) as proposed test substance instead of the registered substance as acceptable for the purpose of determining as, in this case, administration is oral to maximise systemic exposure. The registered substance hydrolyses with a half-life of minutes to trimethylsilanol and ammonia. Therefore the degradation products of the hydrolysis reaction are the most relevant substances for assessing the reproductive toxicity in a pre-natal developmental toxicity test. In fact, the Registrant has already provided data in the update registration dossier for the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test carried out on the hydrolysis product, trimethylsilanol. However, ECHA notes that if an oral developmental study is going to be performed with trimethylsilanol, the pre-natal developmental toxicity effects of ammonia need also to be covered. There is an OECD SIDS report for ammonium concluding that no developmental effects were observed up to 1,500 mg/kg bw/day. ECHA considers that this information may allow to conclude that testing with trimethylsilanol will provide sufficient information to cover the information requirement of pre-natal developmental toxicity for the registered substance.

The Registrant is, thus, requested to perform the pre-natal developmental toxicity study with trimethylsilanol via the oral route in the rat (Annex X, 8.7.2; OECD TG 414; EU Test Method B.31).

IV. Adequate identification of the composition of the tested material

ECHA notes that this dossier is the lead dossier of a joint submission. The evaluation process set out in Article 41 of the REACH Regulation aims to ensure that the generation of information is tailored to real information needs in order to prevent unnecessary testing. In relation to the tests imposed, the sample of substance to be used for these tests 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. The outcome of the studies should be shared by the joint registrants concerned.

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

ECHA always 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). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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