EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000003049-75-05/F Helsinki, 14 October 2013

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For Cyclohexyldimethoxymethylsilane, CAS No 17865-32-6 (EC No 402-140-1), 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 40(1) of the REACH Regulation, ECHA has examined the following testing proposal submitted as part of the jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12 (1)(d) thereof for Cyclohexyldimethoxymethylsilane, CAS No 17865-32-6 (EC No 402-140-1), by [redacted] (Registrant):

- Prenatal Developmental Toxicity study (OECD 414) in rats, oral route (gavage) using the analogue substance dicyclopentyldimethoxysilane (CAS 126990-35-0).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This registration dossier initially contained testing proposals for a sub-chronic toxicity study and a prenatal developmental toxicity study using the registered substance (the intial testing proposals).

This decision does not take into account any updates after 8 March 2013, 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 decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

The examination of the initial testing proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 15 November 2011.

ECHA held a third party consultation for these testing proposals from 16/01/2012 until 01/03/2012. ECHA received information from third parties, only with respect to the initially proposed sub-chronic toxicity study.

On 23 April 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 22 May 2012 ECHA received comments from the Registrant.

On 25 June and 10 September 2012 the Registrant updated his registration dossier withdrawing the testing proposal for a sub-chronic toxicity study and amending the proposal for a pre-natal developmental toxicity study to a proposal for a study to be performed on

the analogue substance dicyclopentyldimethoxysilane (CAS 126990-35-0) instead of the registered substance.

ECHA considered the Registrant's comments received as well as the registration updates received before 8 March 2013 and amended the draft decision.

On 8 March 2013 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 of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 11 April 2013 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 on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and did not amend the draft decision.

On 22 April 2013 ECHA referred the draft decision to the Member State Committee.

The Registrant did not provide any comments on the proposed amendments.

After discussion in the Member State Committee meeting on 11-14 June 2013, a unanimous agreement of the Member State Committee on the draft decision as modified in the meeting was reached on 13 June 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following additional test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

- Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

While the proposed test for prenatal developmental toxicity study (OECD 414) proposed to be carried out using the analogue substance dicyclopentyldimethoxysilane (CAS 126990-35-0) is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **14 October 2014** an update of the registration dossier containing the information required by this decision.

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

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

Prenatal developmental toxicity

a) Examination of the testing proposal

Pursuant to Article 40(3)(c) of the REACH Regulation ECHA may take decisions rejecting a testing proposal in accordance with Article 40(3)(d) but requiring 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.

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.

(1) Proposal to test on a read-across substance

Read across is a possible adaptation for the Registrant when the relevant criteria set out in Annex XI, 1.5 are fulfilled. In particular the first paragraph of Annex XI, 1.5 provides that (1) the group/read across concept can be applied to "substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity" and (2) the application of the group concept requires that "physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach)".

The similarities may be based on:
(1) a common functional group;
(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or
(3) a constant pattern in the changing of the potency of the properties across the category.
However, this needs in particular to be justified and supported by adequate documentation.

Annex XI, 1.5 further provides that in all cases read-across requires results that should:
— be adequate for the purpose of classification and labelling and/or risk assessment,
— have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),
— cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and
— adequate and reliable documentation of the applied method shall be provided.

In assessing whether a substance meets the conditions for read-across to another substance ECHA first has to examine this latter condition, i.e. whether the Registrant has provided adequate and reliable documentation supporting the read-across approach. Only thereafter ECHA can fully examine whether the criteria of structural predictability of the effects from the reference substance have been fulfilled. Indeed, in cases where the documentation supporting a read-across approach is not adequate or reliable ECHA will not

be in a position to evaluate the overall read-across approach and consequently will be unable to verify that there is compliance with the rules of Annex XI, 1.5.

In relation to the testing proposal subject to the present decision, the Registrant has proposed to use a read-across approach, in accordance with Annex XI, 1.5, and to perform the test on an analogue substance, dicyclopentyldimethoxysilane (CAS 126990-35-0).
The Registrant claims that the results of a not yet performed prenatal developmental toxicity study with dicyclopentyldimethoxysilane (DCPDS) can be used to meet the data requirements under REACH for cyclohexyldimethoxymethylsilane (CHDMS) pertaining to the toxicological endpoint covered by this test. Thus, the Registrant proposes to read-across from the source substance DCPDS to the target substance CHDMS, which is the registered substance. In his justification of this read-across the Registrant also refers to a third substance, dicyclopentylsilanediol (DCPS), which is postulated by the Registrant to be one of the two hydrolysis products of DCPDS, the other one being methanol. Information on the toxicological properties of DCPS is presented by the Registrant to support the justification of the read-across.
The explanation by the Registrant why the read-across is possible (read-across hypothesis or read-across justification) consists of three basic elements:

1. After oral exposure both, the source substance (DCPDS) and the target substance (CHDMS) are postulated to be hydrolysed so rapidly and completely that any systemic exposure to the target and source, i.e., the parent compounds can be deemed negligible and that, therefore, any systemic effects are solely caused by the hydrolysis products.
2. The hydrolysis is postulated to result also in methanol for both, DCPDS and CHDMS. As both molecules will under this assumption yield two molecules of methanol, the postulated complete hydrolysis before or immediately after absorption may be expected to result in an equal systemic exposure to methanol for DCPDS and CHDMS.
3. DCPDS and CHDMS differ as regards the other hydrolysis product postulated; for DCPDS this is dicyclopentylsilanediol (DCPS) and for CHDMS this is cyclohexylmethylsilanediol (CHMS). The Registrant assumes that the formation of these different hydrolysis products does not affect the possibilities to read-across.

Thus ECHA understands that the Registrant is predominantely referring in his read-across justification to point (2) of Annex XI, 1.5.

The Registrant undertook to substantiate this explanation why read-across is possible (read-across hypothesis or read-across justification) through the following arguments and observations.

- The Registrant refers to a hydrolysis study in water with DCPDS, which points to the half-live at pH 4 and 25°C of 0.17 hours. It is stated that at the prevailing pH in the stomach and the higher temperature in that organ, half life will be shorter. Hydrolysis studies are available on CHDMS but the Registrant prefers an approach where the results of the hydrolysis study with DCPDS are read-across to CHDMS.

  ECHA finds the results of the study insufficient to conclude that oral exposure to DCPDS does only result in negligible systemic exposure to this substance. For CHDMS limited and thus insufficient hydrolysis data are available and the read-across applied, if altogether valid, implies that also for this substance systemic exposure cannot be declared negligible a priori. Thus the postulated impact of the hydrolysis on the toxicological profile of the registered substance is based on assumptions of a semi-quantitative nature that are not validated by toxicokinetic data in the living organism. As a result it cannot be excluded that after exposure to the registered substance,

toxicologically relevant amounts of it are still present in the organism for a sufficient long period of time to cause developmental effects.

- It is stated by the Registrant "There are no structural features in either substance [i.e. dicyclopentyldimethoxysilane and cyclohexyldimethoxymethylsilane] that are indicative of a concern for reproductive or developmental toxicity."

  ECHA notes that this statement is not substantiated at all by the Registrant. Without substantiation it does not support the read-across possibility. It should be convincingly explained and supported by data, that functional groups or structural features that are not common to DCPDS and CHDMS are actually not expected to affect the anticipated toxicity, and, thereby the possibility to read across.
  ECHA further notes that an absence of data on the effects of a specific structural feature does not equate to evidence that it has no adverse effect or that it does not affect the possibility to read across.

- The Registrant claims that the outcome of a comparison of the physicochemical characteristics of DCPDS, CHDMS and DCPS supports the proposed read-across.

  ECHA notes that the Registrant fails to explain how the outcome of the comparison could support the possibility to read-across for developmental toxicity. This would require a mechanistic explanation how the compared physicochemical characteristics relate to the toxicological endpoint under consideration. Such an explanation is absent. In addition, ECHA notes that substances that are comparable as regards the investigated physicochemical characteristics can still have different toxicological effects.

- As a further argument in support of the read-across, the Registrant points to the absence of severe effects in repeated dose studies with DCPDS, CHDMS and DCPS.

  ECHA notes that the Registrant fails to explain in what way the obtained results are relevant for developmental toxicity. Repeated-dose toxicity studies do not sufficiently cover the endpoint for which the read-across is applied. This is why studies are normally required for this endpoint. Absence of effects in repeated-dose toxicity studies can, therefore, in general not be accepted as convincing evidence that prenatal developmental effects cannot be caused by the substance.

- As regards the toxicity of the hydrolysis products that are different, i.e., CHMS and DCPS, the Registrant only refers to results of one 90-day repeated dose toxicity study with DCPS.

  ECHA notes that any comparative consideration or data on the toxicity of the two hydrolysis products that support the proposed read-across, are missing. Exposure to the two parent substances results in systemic exposure in clearly different hydrolysis products. Thus the possibility to read-across for the endpoint under consideration requires convincing evidence that these hydrolysis products do not affect the endpoint under consideration or do so in a qualitatively and quantitatively similar way. Such evidence is not provided in the registration dossier. The results obtained in a repeated-dose toxicity study with one of the hydrolysis products do not represent such evidence.

In summary, the Registrant does not justify the claim that read-across is possible for the endpoint under consideration. This means that the proposed adaptation according to Annex XI, 1.5 to satisfy the information requirement by means of read-across, can not be accepted by ECHA on the basis of the reasoning and data provided by the Registrant.
The shortcomings of the Registrant's read-across proposal pertain to Annex XI, 1.5, where it is stipulated that adequate and reliable documentation of the applied method shall be

provided. Therefore, the similarity of the proposed read-across substance to the registered substance in the context of the proposed test has not been demonstrated.

Consequently the testing proposal for a test on a read-across substance is not appropriate to fulfil the information requirements of the substance subject to the present decision.

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA rejects the proposal to carry out the test on dicyclopentyldimethoxysilane rather than the registered substance.

(2) Species and route of testing

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.

b) Consideration of the information received during third party consultation

ECHA received no third party information concerning the testing proposal during the third party consultation.

c) Outcome

Therefore, pursuant to Article 40(3) (c) of the REACH Regulation, ECHA has rejected the testing proposal with the read-across substance in accordance with Article 40(3)(d), and the Registrant is required instead to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new study meets real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for evaluation of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same 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 proposed test, the sample of substance used for the new study 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 of the same substance to agree to the test proposed (as applicable to their tonnage level) 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 study 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 study must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade registered to enable the relevance of the study 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 appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the 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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