EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000004393-75-04/F Helsinki, 30 May 2014

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

For 4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane, CAS No 56706-10-6 (EC No 260-350-7), 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 proposals submitted as part of the jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane, CAS No 56706-10-6 (EC No 260-350-7), by [redacted] (Registrant).

- Prenatal Developmental Toxicity Study (OECD 414, rat, oral route, on Polysulfides, bis[3-(triethyoxysilyl)propyl];
- Two-Generation Reproduction Toxicity Study (OECD 416), rat, oral route, on Polysulfides, bis[3-(triethyoxysilyl)propyl].

The present decision relates solely to the examination of the testing proposal for a pre-natal developmental toxicity study. The other testing proposal is addressed in a separate decision, although both testing proposals were initially addressed together in the same draft decision.

This decision is based on the updated 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 31 October 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 from initiating a compliance check on the registration at a later stage.

On 25 August 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 15 March 2011 until 29 April 2011. ECHA did receive information from third parties (see section III below).

On 31 July 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. That draft decision was based on submission number [redacted].

On 6 November 2012 the Registrant updated his registration dossier (submission number [redacted]). The Registrant had originally proposed an OECD 421 test to cover the information requirements, and in this update, the test methods were changed to OECD 414 and 416. The Registrant also provided an updated justification for read-across.

ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III, section 0 in particular) whereas no amendments to the Testing Required (Section II) were made.

On 31 October 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 5 December 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.

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

On 16 December 2013 ECHA referred the draft decision to the Member State Committee.

By 7 January 2014, in accordance to Article 51(5), the Registrant provided comments on the proposal(s) for amendment. The Member State Committee took the comments of the Registrant on the proposal(s) for amendment into account.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposals a prenatal developmental toxicity study.

After discussion in the Member State Committee meeting on 3-7 February 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 5 February 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

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

1. 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 originally proposed test for a Prenatal Developmental Toxicity Study (test method: OECD 414), proposed to be carried out using the analogue substance Polysulfides, bis[3-(triethyoxysilyl)propyl] is rejected pursuant to 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 **8 June 2015** an update of the registration dossier containing the information required by this decision.

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

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.

In relation to the testing proposals subject to the present decision, the Registrant has proposed to use a read-across and grouping approach, in accordance with Annex XI, Section 1.5, and to perform the proposed tests on an analogue substance. 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). The analysis of the grouping and read-across approach set out below is an analysis of the registrant's read-across justification as set out in the updated registration dossier as submitted with submission number [redacted].

0.1. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis brought forward by the Registrant

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 Registrants 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 requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), "provided that the conditions set out in Annex XI are met".

According to Annex XI, Section 1.5 there needs to be structural similarity among the substances within a group such that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation.
The Registrant has submitted testing proposals, based on a grouping and read-across approach, intended to fulfil information requirements for pre-natal developmental toxicity (Annexes IX and X, 8.7.2.), and toxicity to reproduction (Annex X, 8.7.3).

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 this decision by using the results of the proposed tests is sufficiently plausible based on the information currently available.

0.2. Grouping of substances and read-across hypothesis as proposed by the Registrant

According to the Registrant, the substance subject to this decision can be grouped with Polysulfides, bis[3-(triethyoxysilyl)propyl] for the purpose of read-across. The grouping is based on the fact that the two substances are structurally related. In ECHA's understanding, the Registrant's read-across hypothesis is that the two substances consequently have similar physicochemical characteristics, that they have similar acute and repeated dose systemic toxicity, that based on the similar physicochemical properties they have similar toxicokinetics, and a conclusion based on all relevant information that read-across of reproductive and developmental toxicity data from a mixture of di-, tri, and tetrasulfidosilanes (CAS 211519-85-6) to the disulfidosilane (CAS 56706-10-6) is considered to be valid and no disproportionate effects would be expected from treatment with the disulfidosilane alone. ECHA understands that this read-across hypothesis is the basis whereby the Registrant aims to satisfy the requirement of Annex XI, Section 1.5, that human health effects "... may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group ..."(read-across approach).

0.3. Information submitted by the Registrant to support the grouping of substances and read-across hypothesis

In the original dossier, as stated in the draft decision of 31 July 2012 sent to the Registrant for his comments, the Registrant's proposed read-across was not supported by adequate and reliable documentation. In its updated dossier, the Registrant has provided a justification for the read-across in the endpoint summary of section 8.7 of IUCLID. This justification sets out the basis for the approach summarised in section 0.2 above.

The Registrant has provided argumentation that there is similarity of the registered and read-across substance, from comparison of 28-day studies on the two substances, and some summary information is provided, under the headings (a) Structural similarity (b) Similar physicochemical characteristics (c) Similar acute and repeated dose systemic toxicity (d) Similar toxicokinetics and (e) Conclusions. While a robust study summary of the tests on the registered substance is provided in the registration dossier of the registered substance, a similar level of detail is not provided for the studies on the read-across substance in the registration dossier of the registered substance.

0.4. ECHA analysis of the grouping approach and the read-across hypothesis of the Registrant in light of the requirements of Annex XI, Section 1.5

Firstly, ECHA considers that the structural similarity identified and the similarity of physicochemical characteristics, are an inadequate basis for being able to predict the human health properties of the registered substance from the read-across substance, Polysulfides, bis[3-(triethyoxysilyl)propyl].

Similar acute and repeated dose systemic toxicity: ECHA considers that information on acute dose toxicity is not an adequate basis for being able to predict the human health properties of the registered substance from the read-across substance, Polysulfides, bis[3-(triethyoxysilyl)propyl]. For repeated-dose toxicity, ECHA notes that the 28-day studies on the registered substance provided by the Registrant in his updated dossier are not compliant with OECD guideline 407, since they do not contain adequate histopathological evaluation of all organs and tissues that are required in this test method to be evaluated. Especially, histopathological examination is missing for all reproductive organs and tissues. ECHA therefore considers that there is not an adequate basis for establishing toxicological similarity between the two substances with these studies. Further, ECHA would be unable to conclude adequately on similarity of repeated dose toxicity (including toxicity on reproductive organs) for these two substances in the absence of information fulfilling the information requirement of Annex IX, 8.6.2. Moreover, the Registrant has not provided adequate information on reproductive and developmental parameters, which demonstrate that it is possible to predict the reproductive and developmental toxicity of the registered substance from the read-across substance. ECHA therefore concludes that the Registrant's arguments on similar acute and repeated-dose toxicity are an inadequate basis for being able to predict the human health properties of the registered substance from the read-across substance, Polysulfides, bis[3-(triethyoxysilyl)propyl].

Similar toxicokinetics: The Registrant argues in its updated dossier similar toxicokinetics, citing both similar absorption, distribution, metabolism and excretion in general, and metabolism to common products. Although the Registrant makes reference to general literature on distantly related compounds, there is insufficient factual information on the registered or read-across substance, and the inferences that are drawn about the registered and read-across substances remain speculative. ECHA therefore considers that the Registrant's arguments on similar toxicokinetics are an inadequate basis for being able to predict the human health properties of the registered substance from the read-across substance, Polysulfides, bis[3-(triethyoxysilyl)propyl].

The Registrant concludes based on the arguments set out above, and other considerations, "that read-across of reproductive and developmental toxicity data from a mixture of di-, tri, and tetrasulfidosilanes (CAS 211519-85-6) to the disulfidosilane (CAS 56706-10-6) is considered to be valid". ECHA considers, taking into account all the arguments and information proposed by the Registrant in the updated dossier, that the Registrant has failed to demonstrate that human health effects may be predicted for the registered substance from data within the group by interpolation to other substances in the group. Moreover, the Registrant has failed to address the requirement of Annex XI, Section 1.5, that the prediction of human health effects be performed using interpolation, and on this basis also, the proposed read-across fails to meet the requirements of Annex XI, Section 1.5.

Additionally, ECHA considers that the Registrant has not considered the differing composition of the registered and read-across substances nor the possibility of 'mixture effects', or qualitatively different components, which might affect the ability to predict results from the read-across substance to the registered substance.

ECHA emphasises that it is the Registrant's responsibility to substantiate the read-across justification according to Annex XI, 1.5 and to use all relevant available data.

The Registrant commented on the Proposals for Amendment from the Member State Competent Authorities. The Registrant raised three issues (i) that he agreed with the Proposal for Amendment from a Member State Competent Authority that the read-across from the Polysulfide is plausible (ii) in support of this agreement, he raises arguments that were included in the read-across justification in the dossier and (iii) proposes to update his dossier with new information. In respect of (ii), ECHA has addressed the arguments raised by the Registrant in his dossier in Section III 0.1-0.4 above, and in respect of (iii), notes that dossier updates submitted after referral to Member State Competent Authorities cannot be taken into account in the decision making due to the timelines set out in Article 51(5) and (6) of the REACH Regulation and the fact that new information cannot be assessed by ECHA and Member State Competent Authorities with due care at this stage of the decision making. In respect of (i), a Member State Competent Authority argued that the read-across is supported by structural similarity, similar physicochemical and toxicological profile, that toxicokinetic information is not key to the case, and that the quality of the 28-day study on the registered substance needs to be reassessed. These arguments are addressed in section III 0.1-0.4 above.

ECHA considers that the Registrant has failed to demonstrate that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). The proposed adaptation to use information generated on Polysulfides, bis[3-(triethyoxysilyl)propyl] thus fails to meet the requirements of Annex XI, 1.5, the adaptation cannot be accepted, and testing must be performed on the Registered substance.

1. Pre-natal developmental toxicity study

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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.

The Registrant has proposed a test on a read-across substance, Polysulfides, bis[3-(triethyoxysilyl)propyl]. As set out in Section III.0, ECHA considers that the read-across does not meet the requirements of Annex XI, 1.5, and so the test must be performed on the registered substance.

The Registrant proposed testing in rats. He proposed testing by the oral route. 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 third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party submitted the following proposal:

1. Evaluate the need to conduct a Prenatal Developmental Toxicity Study (OECD Guideline 414) and a Two-Generation Reproduction Toxicity Study (OECD Guideline 416) in light of the results of the existing 28-day repeated dose toxicity studies and other toxicological data.
2. Perform in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use results to waive developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414).
3. Conduct an EOGRTS instead of a 2-generation reproduction toxicity study (OECD Guideline 416) and use the results from the EOGRTS to waive/evaluate the need of the developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414).
4. Exposure considerations: use the TTC for reproduction toxicity end points.

ECHA examined the comments and concluded the following:

The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded as information or studies, ECHA concludes that this is not a sufficient basis to fulfil the information requirement.

With reference to the first point, ECHA notes that the third party has proposed adaptations which do not constitute a valid basis for adapting the testing requirement according to Annex IX, 8.7.2, column 1 or 2, or according to Annex XI. Where the third party proposes adaptation based on low toxicological activity, according to column 2 of Annex IX, 8.7., the column 2 provisions additionally require the demonstration of no systemic absorption and no, or no significant, human exposure. These have not been demonstrated, and so there is not a valid adaptation according to column 2 of Annex IX, 8.7.

With reference to the third point, the third party has proposed to conduct an extended one generation reproductive toxicity study (EOGRTS) instead of a two-generation reproduction toxicity study. ECHA acknowledges that the OECD test guideline for an extended one generation reproductive toxicity study may be used as a valid option by the Registrant, if appropriate specifications to the study design are provided. In EOGRTS the developmental toxicity parameters such as skeletal and visceral malformations are not examined and, thus, EOGRTS do not provide adequate information on developmental toxicity to waive the prenatal developmental toxicity study.

With reference to the fourth point, and the proposed use of the TTC concept (Threshold of Toxicological Concern) in order to evaluate if exposure is negligible, the Registrant has not proposed to adapt the information requirement on the basis of Annex XI, Section 3 of the REACH Regulation. Furthermore, based on the exposure assessment carried out by the Registrant the conditions in Annex XI, Section 3.2 (a) (i) "absence or no significant exposure" are not met.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required 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 [4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane].

Note for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

2. Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested another study (reproductive toxicity study, Annex X, 8.7.3.). As the testing proposal for this study 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

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination 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 tests, 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 tests 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 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 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.

[redacted]
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