ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 4 November 2019

Addressee: [redacted]

Decision number: TPE-D-2114489552-39-01/F
Substance name: 4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane
EC number: 260-350-7
CAS number: 56706-10-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04/01/2018
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 proposals are accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), oral route using the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6).**
2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6) specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by ***11 May 2022***. You shall also update the chemical safety report, where relevant. The deadline 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, Hazard Assessment

[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 for the registered substance 4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane (EC 260-350-7; 56706-10-6; hereafter referred to as "target" substance).

Your testing proposals contain for multiple endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of the proposed read-across and grouping approach in general, before assessing the testing proposed (Sections 1 and 2).

Grouping of substances and read-across approach

You propose a testing strategy intending to fulfil the standard information requirements for

- a pre-natal developmental toxicity study in a second species (Annex IX, Section 8.7.2.), and
- an extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.).

In your testing strategy you propose to test the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6) (hereafter referred to as "source substance"). The results from this structural analogue will then be used to adapt the standard information requirements by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation.

You provide several documents as separate attachments in IUCLID, Section 13 (such as [redacted]), relevant to the testing proposed and a read-across justification in the endpoint summary of IUCLID section 7.8.
These documents contain your read-across hypothesis, justification and data matrices for the target and source substances.

ECHA notes that the registrants of silanes have grouped the substances in 'Analogue group', including the substance subject to the current decision, but the category approach is not proposed.

Based on your substance-specific justification for readacross and supporting information, ECHA understands that the proposed read-across is based on an analogue approach using polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6) as a source substance.

According to ECHA's understanding the proposed read-across hypothesis is based on the structural similarity, similar physicochemcal properties, similar biotransformation routes, and the similar toxicological profiles of the target and source substances:
"Read-across hypothesis
The read-across hypothesis is that the source (polysulfides; 211519-85-6) and target (S2; [redacted] substances have similar toxicological properties because:

- *The target substance is a constituent of the source substance;*
- *Other constituents of the source substance are structurally very similar and their physicochemical properties are very similar;*

- *All of these constituents are expected to follow a common metabolic pathway;*
- *The constituents hydrolyse to a common product and to non-common products;*
- *The non-common hydrolysis products are structurally very similar;*
- *Physicochemical properties of the non-common hydrolysis products are very similar;*
- *The non-common hydrolysis products follow a common metabolic pathway.*

This prediction is supported by data on the toxicological properties of the substances, known rapid hydrolysis, and the presence in the molecules of sulfur bridges, which are subject to known metabolism."

ECHA notes that your read across approach addresses the aspects that are considered crucial to establish that relevant properties of the registered substance can be predicted from data on the source substance [2].

First, ECHA notes that you have provided in your IUCLID dossier the typical composition for the target substance:

- **S2:** [redacted]
- **S3:** [redacted]
- **S4:** [redacted]

And for the source substance:

- **S2:** [redacted]
- **S3:** [redacted]
- **S4:** [redacted]
- **S5:** [redacted]
- **S6:** [redacted]
- **S8:** [redacted]

and you claim that the target substance is a constituent of the source substance.

ECHA notes that, although at different typical concentrations, the main constituent of the target substance S2 and the impurities S3, S4 and ([redacted] are present in the source substance.

Second, you have established structural similarities between target and source substances as "*The constituents and major impurities of the source and target substances have two functional groups in common:*

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

- *The triethoxysilane, Si(OEt)3, group (there are two of these per molecule, therefore each molecule has six reactive ethoxy groups).*
- *The (poly)sulfide, CH2SnCH2(n = 1-4), group.*
- *Clearly the only difference between the constituents/major impurities is the number of sulfur atoms in the sulfide bridge."*

Third, you have shown that due the very similar chemical structures, the substances and constituents are predicted to have near identical physicochemical properties.
In addition, you provided toxicokinetic information including consideration on the labile S-S bond, resulting in a variety of metabolic routes for detoxification, and on the metabolic pathways of tri- or polysulfides.

ECHA looked further into the metabolic pathways of tri- or polysulfides and found that the available information (e.g. Pan et al; 2013) supports your hypothesis that S_3 bonds undergo cleavage with release of hydrogen sulfide which might be considered as toxicologically relevant for target and source substances.

Furthermore, ECHA observes that you took into account a possible mixture effects between the different sulfidosilane constituents.

Finally, there are indications that the toxicological properties of the source substance are similar to those of the target substance (S2) – e.g. kidney and liver toxicity.

Based on the above considerations ECHA concludes that you have provided adequate and reliable information to demonstrate that the proposed read-across approach is plausible for the endpoints in consideration.

ECHA therefore concludes that the criteria of Annex XI, Section 1.5, are met, and consequently the testing proposed on the read-across substance is appropriate to fulfil the information requirement of the substance subject to the present decision.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

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).

The dossier contains a pre-natal developmental toxicity study in rats as first species ([redacted] 2016). However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbits) according to OECD TG 414 by the oral route with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6).

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 and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6) and as explained in section "Grouping and read-across approach" your adaptation of the information requirement is deemed to be plausible.

ECHA considers that the proposed study performed with the analogue substance is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rabbit as a second species. The test in the first species was carried out with rats. According to the test method OECD 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 rabbit as a second species.

You proposed testing by the oral route. ECHA agrees 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* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are thus requested to carry out the propose study with the analogue substance: Pre-natal developmental toxicity study in a second species (rabbit), oral route (test method: OECD TG 414).

Notes for your consideration

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.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement as laid down in column 1 of Section 8.7.3., Annex X of the REACH Regulation, whereas column 2 defines when the study design needs to be expanded.

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 an EOGRTS according to OECD TG 443 by the oral (gavage) route in rats with "at least 2 weeks" premating exposure duration to be performed with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (EC 915-673-4; CAS 211519-85-6) as a source substance.

You have provided the following justification, according to the criteria described in column 2 of Section 8.7.3 of Annex X[3]: "*-Premating exposure duration for parental (P0) animals: At least 2 weeks. No adverse findings were observed in relation to the reproductive organs in repeated dose tests.*
- Basis for dose level selection: The doses will be based on a weight of evidence from available toxicity tests conducted via the oral route, and if necessary, a dose range-finding study will be performed.
- Inclusion/exclusion of extension of Cohort 1B: The study design will not include extension of Cohort 1B. The substance does not display genotoxic effects in somatic cell mutagenicity tests in vivo *which could lead to classifying it as Mutagen Category 2, and there are no indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, and there are no indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches.*
- Inclusion/exclusion of developmental neurotoxicity Cohorts 2A and 2B: The study design will not include Cohorts 2A and 2B. The available data for the substance do not indicate a particular concern to justify inclusion of the developmental neurotoxicity cohorts [...].
- Inclusion/exclusion of developmental immunotoxicity Cohort 3: The study design will not include Cohorts 3. The available data for the substance do not indicate a particular concern to justify inclusion of the developmental immunotoxicity cohorts [...]."

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance and as explained in section "Grouping and read-across approach" your adaptation of the information requirement is deemed to be plausible.

ECHA concludes that an EOGRTS according to column 1 of Section 8.7.3., Annex X is required with your proposed study design with further specifications. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed that premating exposure duration for parental (P0) animals should be "*at least 2 weeks. No adverse findings were observed in relation to the reproductive organs in repeated dose tests.*"

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance[3]. Ten weeks exposure duration is supported also by the lipophilicity of the

[3] ECHA Guidance *on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

substance ($logK_{ow}$ = 5.2 at xx°C) to ensure that the steady state in parental animals has been reached before mating.

You proposed that "*the doses will be based on a weight of evidence from available toxicity tests conducted via the oral route, and if necessary, a dose range-finding study will be performed.*" ECHA emphasises that the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels. If there is no relevant data to be used for dose-level setting, it is recommended that a range-finding study (or range finding studies) is performed and that its results are reported with the main study. This will support the justifications of the dose-level selections and interpretation of the results.

Species and route selection

You proposed testing by oral (gavage) route in rats. ECHA agrees with your proposal concludes that gavage-dosing seems appropriate based on previous oral studies.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance, as specified above.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA Guidance[3]. You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Appendix 2: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 04 January 2018.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 07 June 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **11 March 2019**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA did not receive any comments within the given deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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 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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.