EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114426306-55-01/F
Substance name: Reaction mass of 4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane and 4,4,14,14-tetraethoxy-3,15-dioxa-8,9,10-trithia-4,14-disilaheptadecane
List number: 915-748-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 16.04.2013
Registered tonnage band: 100-1000T

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 following testing proposal is accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS No 211519-85-6).**

Your following testing proposal is rejected:

2. **Two-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 416) in rat, oral route using the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS No 211519-85-6).**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **26 July 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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, Evaluation E3

[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 reaction mass of 4,4,13,13-tetraethoxy-3,14-dioxa-8,9-dithia-4,13-disilahexadecane and 4,4,14,14-tetraethoxy-3,15-dioxa-8,9,10-trithia-4,14-disilaheptadecane (EC no 915-748-1; hereafter referred to as "target" substance) and the submitted third party comments.

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

- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.),
- two-generation reproductive toxicity study (Annex IX, Section 8.7.3).

In your testing strategy you propose to test the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS No 211519-85-6) (hereafter referred to as "source substance 1"). The results from the 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.

ECHA has considered, first, the scientific validity of the proposed read-across and grouping approach (preliminary considerations; Section 0, below), before assessing the testing proposed (Sections 1 and 2 below).

0. Grouping of substances and read-across approach

a. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis

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 you 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 provides that information on intrinsic properties of substances may be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

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

b. Description of the proposed grouping and read-across approach

You have provided the following arguments to justify the read-across approach:

"*The basis of the read across is the structural similarity and similar toxicological profiles of the substances. In view of the inferred similar biotransformation routes of tri- and tetrasulfides and their disulphide homologues, in addition to the lack of acute toxicity for either substance and the similar toxicological profile seen in repeated-dose oral toxicity studies, read-across of reproductive and developmental toxicity data from a mixture of di-, tri, and tetrasulfidosilanes (CAS 211519-85-6) and disulfidosilane (CAS 56706-10-6) to the registration susbtance is considered to be valid and no disproportionate effects would be expected from treatment with the registration substance itself*".

c. Information submitted to support the grouping and read-across approach

You have provided several documents as separate attachments in IUCLID, Section 13, relevant to the testing proposed:

- [redacted] summarising the available physico-chemical and toxicological data on related alkoxysilanes.
- [redacted] (Jan 2013). The document is an overview of the grouping and read-across methods of Reconsile REACH submissions. The document describes the general principles applied but does not provide any substance-specific information. According to the report, "*each CSR needs to describe clearly whether Category, Analogue or QSAR methods have been applied, and which endpoints they are applied to, and the IUCLID entries must be consistent with this*"... Based on this document, ECHA understands that you intend to apply analogue approach as a basis for data gap filling which are further justified in each registration dossier and CSR.

In addition you have provided in the technical dossier of the target substance the following toxicological studies relevant to the testing proposed:

for the source substance 1:

- Acute oral toxicity (similar to OECD 401)
- Acute inhalation toxicity (OECD 403)
- Acute dermal toxicity (equivalent or similar to OECD 402)
- Skin irritation (according to FDA (1965). Part 191, Section 11.)
- Eye irritation (according to FDA 1965)
- Skin sensitisation (OECD 406)
- Repeated dose (28-day) oral toxicity (equivalent or similar to OECD 407), two studies
- Ames test (OECD 471)
- *In vitro* Mammalian Chromosome Aberration Test (OECD 473)
- *In vitro* Mammalian Cell Gene Mutation Test (OECD 476)

In addition, you have provided the following toxicological studies on disulfidosilane (CAS No 56706-10-6; a constituent of the registered (target) substance; hereafter referred to as source substance 2):

- Acute oral toxicity (OECD 401), two studies
- Acute dermal toxicity (OECD 402)
- Skin irritation (OECD 404), two studies
- Eye irritation (OECD 405), two studies
- Repeated dose (28-day) oral toxicity (according to OECD 407, and Japanese Ministry of Health and Welfare (MHW) Guidelines 1986), two studies
- Ames test (OECD 471)
- *In vitro* Mammalian Chromosome Aberration Test (equivalent or similar to OECD 473)
- Mammalian Erythrocyte Micronucleus Test (OECD 474)

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 the substance specific justification for read-across approach and supporting information provided by you, ECHA understands that no category hypothesis /justification has been included and the proposed prediction is based on the analogue approach using polysulfides, bis[3-(triethyoxysilyl)propyl (CAS No 211519-85-6) as a source substance.

According to ECHA's understanding the proposed read-across hypothesis is based on the structural similarity, similar biotransformation routes, and the similar toxicological profiles of the target and source substances.

In the following, ECHA examines whether the substances have indeed similar properties or that they would follow a regular pattern in their properties, before assessing the scientific validity of your hypothesis.

(i) Structural (dis)similarities and their impact on prediction

Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You have identified the structural similarities between target and source substances as both substances contain *"bis[3-(triethoxysilyl)propyl]- structures with the two (triethoxysilyl)propyl groups linked by di- or polysulfide groups"*. You have provided typical composition for the target substance: [redacted], and for the source substance: [redacted] You further claim that *"S2, S3 and S4 can be considered as toxicologically equivalent"*.

ECHA observes that you have not provided any mechanistical/chemical explanation on why the different components can be *"considered as toxicologically equivalent"*. However, ECHA notes that based on the toxicological data the toxicity profile of the substances seem to be similar as discussed in section (ii) under the heading "Toxicological data" below.

(ii) Similar properties or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that *"substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances"*. One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

Physico-chemical properties

You claim that due to similar structures, the target and source substances are predicted to have near identical physico-chemical properties. ECHA observes the physio-chemical properties of the target substance have been predicted from the data of the source substance 1. ECHA notes that based on the structural similarity of the substances physico-chemical properties can be expected to be in similar range.

Hydrolysis and metabolism

Due to low water solubility of the substances you have estimated the hydrolysis rate for each constituent to be 17 hours at pH 7, 20-25°C.

ECHA notes that the hydrolysis rate should be identical in the case of the target and source substances. The only difference is the presence of different proportions of the di-, tri- and tetra-sulphide components but all of these components should hydrolyse at more or less the same rate since the solubility will not change massively with the addition of another sulphur group and the hydrolysable ethoxy groups are identical in all constituents.

You argue that the metabolism of the target and source substances will be similar. ECHA notes that your claim seems plausible given that the weak point of the molecule will be the labile disulphide bonds. You further claim that thiol exchange reactions may result in the production of hydrogen sulphide from S3 structures which may render this constituent more toxicologically relevant. ECHA notes that irrespective of whether this occurs however, the concentration ranges of S3 in both source and target substances seem very similar so this may not have a major impact on toxicity profiles of the substances.

ECHA considers that based on the information provided hydrolysis and metabolism of the substances seem to be similar.

Toxicological data

You claim that the substances have similar toxicological profiles *and "In view of the inferred similar biotransformation routes of tri- and tetrasulphides and their disulphide homologues, in addition to the lack of acute toxicity for either substance and the similar toxicological profile seen in repeated-dose oral toxicity studies".*

ECHA observes that you have provided experimental studies conducted on S2 (main component of the target substance) and the source substance 1. The main components and typical concentrations of the target substance are [redacted] and the ones of the source substance 1: [redacted]

ECHA notes that the S2-component and the source substance have a similar toxicity profiles regarding lower tier endpoints: the substances have low oral and dermal acute toxicity, are not skin or eye irritant and not skin sensitisers and genotoxic. Based on the 28-day studies conducted with both substances, the repeated dose toxicity profiles seem to be also similar: NOAEL value of 200 mg/kg bw/day was obtained for S2-component (purity > 86%) and for the source substance 1 based on similar histopathological changes in the liver and kidney. In other 28-day studies only minor effects (increased liver weights) were observed and the following NOAEL values were obtained: 1221 for the S2-component (composition: [redacted]) and > 2309 mg/kg bw/day (the only dose tested) for the source substance 1.

ECHA notes that the different compositions and the number of polysulphide groups in the substances do not seem to impact the toxicity profile of S2-component and the source substance 1 as the target organs and NOAEL values are in similar range. In particular, same NOAEL values (200 mg/kg bw/day) and similar liver and kidney effects were observed in studies conducted with S2 (> 86%) and the source substance 1 (composition = S2+S3+S4) (detailed concentrations not reported).

ECHA considers that the data provided provides sufficient evidence to conclude that the different composition of the substances does not give rise to a different toxicological profile regarding pre-natal developmental toxicity, as the hydrolysis, metabolism and the toxicity profile regarding acute and repeated dose toxicity of the source substance 1 and 2 are similar.

Therefore ECHA concludes that based on the presented information there is an adequate basis for predicting the human health properties of the target substance from the data obtained with the source substance 1.

d. Conclusion on the read-across approach

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 endpoint 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 IX, Section 8.7.2.) in a first species**

a) Examination of the testing proposal

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

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.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS 211519-85-6).

ECHA has evaluated your proposal to perform the test with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS 211519-85-6). Based on the data submitted by you, ECHA concludes that you have provided adequate and reliable information to demonstrate that the read-across approach is plausible for the pre-natal developmental endpoint as explained in Section 0 "Read-across approach" of this decision, and your adaptation of the information requirement can be accepted.

ECHA considers that the proposed study performed with the analogue substance polysulphides, bis[3-(triethyoxysilyl)propyl (CAS 211519-85-6) is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. According to the test method EU B.31./OECD TG 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 rat or the rabbit as a first 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) R.7a, chapter 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.

b) Outcome

ECHA notes that in your comments on the draft decision you agreed with the draft decision.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the analogue substance polysulphides, bis[3-(triethyoxysilyl)propyl (CAS 211519-85-6): Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: EU B.31./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.

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

2. Reproductive toxicity study (Annex IX, Section 8.7.3.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

You have submitted a testing proposal for a two-generation reproductive toxicity study according to EU B.35./OECD TG 416 to be performed with the analogue substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS 211519-85-6).

As explained in more detail above (see Section "0."). ECHA considers that you provided adequate and reliable information to demonstrate that the read-across approach is plausible.

However, the requirement according to Annex IX, Section 8.7.3., i.e. nowadays the extended one-generation reproductive toxicity study,[2] is only an information requirement, if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD TG 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity.

ECHA observes in this regard that there are results of a short-term repeated dose toxicity studies (28 days) conducted with the source substance 1 and 2 available in the registration dossier that did not indicate adverse effects on reproductive organs or tissues or reveals other concerns in relation with reproductive toxicity.

ECHA further notes that you have not included any further justification why to perform a reproductive toxicity study at tonnage level 100 – 1000 tonnes per year.
Considering the above, ECHA concludes that a study is at this stage not necessary to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation, because no adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity have been observed in repeated dose toxicity studies.

b) Consideration of the information received during third party consultation

2 Please note that according to Annex IX, Section 8.7.3., as amended by Commission Regulation (EU) 2015/282 (entered into force on 13 March 2015), a two-generation reproductive toxicity study is longer an information requirement..

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.

Read-across information implies low acute oral toxicity and very limited systemic toxicity in a sub-acute study with centrilobular hypertrophy of the liver. Further data support a low toxicity profile. In analogy to structurally similar silanes the only slightly soluble substance is expected to be hydrolysed to liberate ethanol and silanetriols which are known to be reactive. They polymerise at concentrations > 500 ppm forming not bioavailable resins which further reduce the potential for systemic exposure. Consequently the registrant may consider fulfilling the information requirements in accordance with Annex XI of Regulation 1907/2006 by read-across to the hydrolysis product ethanol.

ECHA acknowledges that the third party has proposed a read across approach for you to consider. ECHA notes that the information provided by the third party regarding the use of ethanol as a source substance is insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. In any case, ECHA notes that you have provided adequate and reliable information to demonstrate that the read-across approach using the source substance polysulfides, bis[3-(triethyoxysilyl)propyl (CAS 211519-85-6) is plausible (see section "0.").

As already stated under section a) above, ECHA notes that according to Annex IX, Section 8.7.3., an extended one-generation reproductive toxicity study is an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity. For the substance subject to the present decision there is a 28-day study provided in the registration dossier that does not indicate adverse effects on reproductive organs or tissues or other concerns. ECHA has therefore rejected the testing proposal for a two-generation reproductive toxicity study.

c) Outcome

ECHA notes that in your comments on the draft decision you agreed with the draft decision.

ECHA concludes that at this stage there is no information gap for the information requirement of Annex IX, Section 8.7.3. Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed two-generation reproduction toxicity study (OECD TG 416) is rejected.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination pursuant to Article 40(1) on 16 April 2013.

ECHA held a third party consultation for the testing proposal(s) from 17 June 2014 until 1 August 2014. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **11 July 2016**, 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 took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, 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 test(s) 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 test(s) 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 test(s) 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 test(s) to be assessed.

4. In case the required test is 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 6 "How to report on read-across". This is required to demonstrate 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.