~~Confidential~~

Helsinki, 21 June 2022

Addressees
Registrants of RECONSILE EC#915-748-1 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
23/11/2020

Registered substance subject to this decision ("the Substance")
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
EC number: 915-748-1

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***27 March 2024*.**

Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats, with the analogue substance *Polysulfides, bis[3-(triethoxysilyl)propyl]*, EC No. 915-673-4. The study must include the following to investigate the kidney function after administration of the test substance:
    - urinalysis (for specifications see OECD TG 408, para. 37); and
    - histopathological examination of the kidneys of all male animals in all dose groups with an additional immunohistochemical staining for alpha-2µ globulin.

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under

REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

Contents

Reasons for the decision(s) related to the information under Annex IX of REACH

1. Sub-chronic toxicity study (90-days)

1 A sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH (Section 8.6.2.).

1.1. Information provided to fulfil the information requirement

2 You have submitted a testing proposal for a Sub-chronic toxicity study (90 day) according to OECD TG 408 to be performed with the analogue substance Polysulfides, bis[3-(triethoxysilyl)propyl] (EC No. 915-673-4).

3 ECHA requested your considerations for alternative methods to fulfil the information requirement for repeated dose toxicity. 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.

4 ECHA agrees that a 90-day study is necessary.

1.2. Evaluation of read-across approach

5 ECHA understands that you intend to fulfil the information required for a sub-chronic toxicity study (90 day) by way of adaptation under Annex XI, Section 1.5 ('Read-across and grouping of substances').

6 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

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

7 You have provided a read-across justification document in IUCLID Section 13.2.

8 You propose that the properties of the Substance may be predicted from data to be generated with the source substance Polysulfides, bis[3-(triethoxysilyl)propyl] (EC No. 915-673-4).

9 Your read-across hypothesis is based on structural similarity of the substances (the Substance is a constituent of the source substance) and hydrolysis to common and non-common products (non-common hydrolysis products are structurally very similar) which lead to similar toxicological properties.

1.2.2. Structural (dis)similarities and their impact on prediction

10 You have identified the structural similarities between the Substance and the source substance as you explain that the constituents of the substances are all bis[3-(triethoxysilyl)propyl]-structures where the two (triethoxysilyl)propyl groups are linked by di-, tri- or tetrasulfide groups (S2, S3 and S4, respectively).

11 The Substance (S2/S3) is part of the source substance (S2/S3/S4) composition. The difference in the structures is the number of bridging sulfurs between the two (triethoxysilyl)propyl groups. Typical composition of the Substance is S2 ([redacted]) and S3

([redacted]); S4 is present as an impurity ([redacted]). Typical composition for the source substance is S2 ([redacted]), S3 ([redacted]) and S4 ([redacted]). Impurities present only in the source substance are S(n>4) ([redacted])

1.2.3. Similar properties as a result of structural similarity

12 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.

1.2.3.1. Hydrolysis and metabolism

13 You explain that all constituents hydrolyse to give bis[3-(trihydroxysilyl)propyl]-di, tri or tetrasulfides. The other hydrolysis product in all cases is ethanol.

14 You predict the hydrolysis rate ($t_{1/2}$) at pH 2 and 37.5°C, the conditions relevant for oral exposure, to be 11-18 seconds for the Substance, and 11-20 seconds for the source substance. Hydrolysis predictions for the S2, S3 and S4 constituents are all in the range of 11-20 seconds. Systemic exposure following oral administration will be predominantly to the breakdown products.

15 You claim that there are no apparent differences in metabolic pathways. ECHA notes that your claim seems plausible given that the weak point of the molecule will be the labile disulphide bonds.

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

1.2.3.2. Toxicological data

17 You claim that the substances have very similar toxicological profiles.

18 To support this, you have provided in your dossier four studies which are relevant to the testing proposal:

(i) Repeated-dose toxicity study (28-day; 2000a) with constituent S2

(ii) Repeated-dose toxicity study (28-day; 2000b) with the source substance Polysulfides, bis[3-(triethoxysilyl)propyl] (EC No. 915-673-4).

(iii) Repeated-dose toxicity study (28-day; 2002) with 'low purity S2' which contains S2 and S3

(iv) Repeated-dose toxicity study (28-day; 1983) with the source substance Polysulfides, bis[3-(triethoxysilyl)propyl] (EC No. 915-673-4).

19 Based on the studies, ECHA considers that the repeated dose toxicity profiles seem to be similar based on similar effects observed in liver and kidney. The different compositions and the number of polysulphide groups in the substances do not seem to impact the toxicity profile.

1.2.4. Conclusion

20 ECHA agrees that based on the read-across justification provided and the other information available in the dossier at this point in time, there is a basis for considering the read across plausible. Therefore, you have plausibly demonstrated that relevant properties of the Substance may be predicted from data on the source substance.

21 However, ECHA emphasises that any final determination on the validity of your read-across adaptation will only be possible when the information on the requested study will be available in the dossier.

1.3. Specification of the study design

22 You proposed testing in the rat. ECHA agrees with your proposal because the rat is the preferred species according to the OECD TG 408. Therefore, the study must be conducted in the rat.

23 You proposed testing by the oral route. ECHA agrees with your proposal because this route of administration is appropriate to investigate systemic toxicity; Guidance on IRs and CSA, Section R.7.5.4.3.2.

24 In addition, studies (i), (ii) and (iii) show adverse effects in the kidneys of male rats: increased kidney weights, basophilic renal tubules and an increase in acidophilic bodies and hyaline droplets. This indicates that the kidney is a target organ.

25 Alpha-2µ-globulin-mediated nephropathy may occur in male rats. Since this mode of action is not considered relevant to humans, the involvement of alpha-2µ-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for human risk assessment.

26 Therefore, the study must include the following to investigate the kidney function after administration of the Substance:

- urinalysis (for specifications see OECD TG 408, para. 37); and
- histopathological examination of the kidneys of all male animals in all dose groups with an additional immunohistochemical staining for alpha-2µ globulin.

1.4. Outcome

27 Under Article 40(3)(b) your testing proposal is accepted under modified conditions, and you are requested to conduct the test with analogue substance Polysulfides, bis[3-(triethoxysilyl)propyl] (EC No. 915-673-4), as specified above.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 6 April 2020.

ECHA held a third party consultation for the testing proposal(s) from 25 May 2020 until 9 July 2020. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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

ECHA did not receive any comments within the commenting period.

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: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals