EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 19 January 2021

Addressees
Registrants of RECONSILE EC# 219-784-2 listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
24/01/2020

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: [3-(2,3-epoxypropoxy)propyl]trimethoxysilane
EC number: 219-784-2
CAS number: 2530-83-8

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 ***24 October 2022***.

The requested information must be generated using the Substance unless otherwise specified.

A. Information required from the Registrants subject to Annex IX of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays also requested, and specified, at B.1 below (triggered by Annex IX, Section 8.4., column 2);

B. Information required from the Registrants subject to Annex X of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays (triggered by Annex X, Section 8.4., column 2): test method: OECD TG 488 (updated on 26 June 2020[1]) in transgenic mice or rats, oral route on the following tissues: germ cells, liver, glandular stomach and duodenum with the Substance. The test material used should be freshly prepared.

Reasons for the request are explained in the following appendices:

- Appendixes A and B entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

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

[1] https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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.

Approved[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[2] 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 A: Reasons to request information required under Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted.

1. Transgenic rodent somatic and germ cell gene mutation assays

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X of the REACH Regulation. Paragraph 2 of column 2 of Annex IX, Section 8.4. provides that "*If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.*"

The dossier contains several *in vitro* studies (OECD TG 471 and OECD TG 476) with the Substance that show positive results, which indicate a concern for gene mutations. As an appropriate *in vivo* genotoxicity study to follow up the gene mutation concern was not available, you submitted a testing proposal for an *in vivo* alkaline comet assay (OECD TG 489) that was accepted by ECHA. The comet assay was carried out to clarify the potential for the substance to induce genotoxicity in somatic cells *in vivo*, and the result was clearly positive, i.e. a statistically significant increase in tail intensity was observed in all analysed tissues (glandular stomach, duodenum and liver) at all concentrations tested.

You have considered the potential for germ cell mutagenicity and you have now submitted a testing proposal for an *in vivo* transgenic rodent somatic and germ cell gene mutation assay (OECD TG 488) to be conducted with the Substance to evaluate mutagenicity in germ cells.

ECHA agrees that a study is necessary to address the germ cell mutagenicity concern.

For the assessment of the information provided to fulfil the information requirement and the study specifications, see Appendix B, Section 1.

Appendix B: Reasons to request information required under Annex X of REACH

This decision is based on the examination of the testing proposals you submitted

1. Transgenic rodent somatic and germ cell gene mutation assays

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X of the REACH Regulation. Paragraph 2 of column 2 of Annex X, Section 8.4. provides that "*If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.*"

As outlined at Appendix A., section 1, the dossier contains several *in vitro* studies (OECD TG 471 and OECD TG 476) with the Substance that show positive results, which indicate a concern for gene mutations. As an appropriate *in vivo* genotoxicity study to follow up the gene mutation concern was not available, you submitted a testing proposal for an *in vivo* alkaline comet assay (OECD TG 489) that was accepted by ECHA. The comet assay was carried out to clarify the potential for the substance to induce genotoxicity in somatic cells *in vivo*, and the result was clearly positive, i.e. a statistically significant increase in tail intensity was observed in all analysed tissues (glandular stomach, duodenum and liver) at all concentrations tested.

You have considered the potential for germ cell mutagenicity and you have now submitted a testing proposal for an *in vivo* transgenic rodent somatic and germ cell gene mutation assay (OECD TG 488) to be conducted with the Substance to evaluate mutagenicity in germ cells.

ECHA agrees that a study is necessary to address the germ cell mutagenicity concern.

You provided the following justification:

"Considering all available in vitro and in vivo genetic toxicity data and combining the available lines of evidence, a well-founded conclusion on germ cell mutagenicity can currently not be made. Consequently, a transgenic rodent somatic and germ cell gene mutation assay according to OECD TG 488 is proposed for directly examining potential effects of 3-(2,3-epoxypropoxy)propyltrimethoxysilane on gonadal cells in vivo after oral application. For establishing mutagenic potential at the first sites of contact with the body, the OECD TG 488 study is proposed to also include glandular stomach and duodenum tissues. The liver will be included as primary site of xenobiotic metabolism."

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity in vivo. ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA notes that the proposed test is an appropriate test to investigate gene mutations in germ cells *in vivo* as described in the ECHA Guidance, Chapter R.7a, section R.7.7.1. and figure R.7.7-1.

You proposed testing by the oral (gavage) route. According to the test method OECD TG 488, the test shall be performed in transgenic mice or rats and the Substance is usually administered orally.

Based on the positive results from an *in vivo* comet assay on liver, glandular stomach and duodenum tissues, you proposed to also include the abovementioned tissues in the testing proposal for the transgenic rodent assay. ECHA agrees with your proposal, as testing the same tissues that were found positive in the comet assay may allow the comparison of the outcome of the two tests. In particular, it may allow to determine whether the substance induces both DNA damage (as detected in the comet assay) and gene mutations (possibly detected in the transgenic rodent assay).

Please note that you should performed the assay as described in the updated OECD TG 488 that was adopted on 26 June 2020 (the relevant text can be found on the OECD website[3]). In particular, 1) the testing regimen should be 28 days of daily treatment followed by a collection of tissues 28 days after the end of the treatment and 2) the germ cells should be collected from the seminiferous tubules.

Under Article 40(3)(a) of REACH, you are requested to carry out the proposed test with the Substance.

[3] https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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[4].

B. 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[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix D: Procedure

ECHA received your testing proposal on 27 January 2020 and started the testing proposal evaluation in accordance with Article 40(1).

ECHA held a third party consultation for the testing proposal(s) from 17 June 2020 until 3 August 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 noted that your representative made an attempt to provide comments to the draft decision on behalf of you. However, no content was identified in the submitted comments. Given the circumstances, ECHA has contacted your representative seeking clarification of this intention on 15 September and 7 October 2020. As no comments from you nor any further response from your representative has been received by the commenting deadline, ECHA considered that it did not receive any comments within the notification 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 E: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[8]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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