EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114425317-53-01/F
Substance name: (chloromethyl)triethoxysilane
EC number: 239-311-3
CAS number: 15267-95-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30.04.2015
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

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

In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2; test method: EU B.12./OECD TG 474) in mice or rats, oral route using the registered substance if the test substance or its metabolite(s) will reach the target tissue

or

In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum using the registered substance.

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 proposal(s) submitted by you.

***In vivo* mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2)**
or
***In vivo* mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)**

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

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro* study *"In vitro Mammalian Chromosome Aberration Test in Chinese Hamster V79 cells with (Chloromethyl)triethoxysilane" (2012)* performed according to OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) with the registered substance that show positive results without metabolic activation. The positive result indicate that the substance is inducing chromosomal aberrations under the conditions of the test.

An appropriate *in vivo* genotoxicity study to follow up the concern on chromosomal aberrations is not available for the registered substance but shall be proposed by the Registrant. Consequently, there is an information gap and you proposed to generate information for this endpoint.

Hence, you have submitted a testing proposal for a OECD Guideline 474 (mammalian erythrocyte micronucleus test) in rat by oral administration.

ECHA notes that the proposed test is an appropriate test to investigate effects on chromosomal aberrations *in vivo* as described in the ECHA *Guidance document on information requirements and chemical safety assessment* R.7a, chapter R.7.7.1. and figure R.7.7-1 (version 6.0, July 2017) if the test substance or its metabolite(s) will reach the target tissue as specified in the respective test method (OECD TG 474). According to this test method, the mammalian erythrocyte micronucleus test shall be performed in mice or rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

ECHA highlights that according to paragraph 10 of OECD TG 474 (September 2014) "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*". Additionally, according to paragraph 48 (d) of the OECD TG 474, a test chemical is considered clearly negative if "*Bone marrow exposure to the test substance(s) occurred*". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

Therefore, in case it is unlikely or it is foreseeable that it cannot be demonstrated that the substance or its metabolites will reach the bone marrow, ECHA recommends you to perform instead the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489). According to ECHA *Guidance document on information requirements and chemical safety assessment* R.7a, (version 6.0, July 2017), Chapter R.7a, section R.7.7.6.3, this test is suitable to follow up positive *in vitro* result for gene mutation and chromosomal aberrations. Furthermore, this test is suitable to detect genotoxic effects at the site of contact. According to the test method OECD TG 489, the comet assay shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate. According to the test method OECD TG 489, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism and glandular stomach and duodenum as sites of contact. In view of several expected or possible variables (different tissue structure and function of the glandular stomach and the duodenum; different pH conditions; variable physico-chemical properties and fate of the substance; and probable different absorption rates of the substance and its possible breakdown product(s) between these two tissues), ECHA considers that it is necessary to increase the reliability of the analysis of genotoxicity at the site of contact by sampling both tissues.

Hence, ECHA provides you the alternative to perform the comet assay in case the micronucleus test might not be appropriate.

In your comments to the draft decision you did not provide considerations to this specific endpoint.

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 subject to the present decision: *In vivo* mammalian erythrocyte micronucleus test (test method: EU B.12/OECD TG 474) in mice or rats, oral route if the test substance or its metabolite(s) will reach the target tissue *or In vivo* mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum.

Notes for your consideration

You are reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are 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".

In case of a positive result in the mammalian erythrocyte micronucleus test, you may consider making a testing proposal to conduct the mammalian spermatogonial chromosome aberration test (OECD TG 483).

In case you decided to perform the comet assay, you may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence

may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 7 May 2013.

ECHA held a third party consultation for the testing proposal(s) from 16 October 2014 until 1 December 2014. ECHA did not receive information from third parties.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments and did not amend the request(s).

You were notified that the draft decision does not take into account any updates after 6 July 2016, 30 calendar days after the end of the commenting period.

However, following your request and justification provided (including interlinked read-across testing strategy on several supposedly related registered substances) ECHA has exceptionally granted you additional time until 30 June 2017 for the update of the IUCLID dossier.

You did not update the dossier by 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 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 carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, 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.