EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002087-76-06/F Helsinki, 22 March 2013

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For 2-Oxepanone, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, CAS No 37625-56-2 (EC No 500-099-5), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 2-Oxepanone, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, CAS No 37625-56-2 (EC No 500-099-5), by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study: TMP testing proposal (OECD 414).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 6 September 2012, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the present dossier at a later stage.

On 1 October 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposal set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposal from 15 July 2011 until 29 August 2011. ECHA did not receive information from third parties.

On 29 May 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 26 June 2012 ECHA received comments from the Registrant. ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III) whereas no amendments to the Testing Required (Section II) were made.

On 6 September 2012 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 10 October 2012 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on that proposal for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposal for amendment received and amended the draft decision accordingly.

On 12 and 26 October 2012, in the context of providing comments on the proposals for amendment, the Registrant provided comments and justification for an extension of the deadline for providing the information required by this decision. On this basis, ECHA modified the deadline in Section II. The Statement of Reasons (Section III) was changed accordingly.

On 22 October 2012 ECHA referred the draft decision to the Member State Committee.

A unanimous agreement of the Member State Committee on the draft decision was reached on 26 November 2012 in a written procedure launched on 14 November 2012. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following additional test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

- Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414)

while the originally proposed test for a Pre-natal developmental toxicity study (OECD 414) proposed to be carried out using the analogue substance TMP is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit the information in the form of an updated registration to ECHA by **22 September 2014.**

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2 of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7 column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance.

Pre-natal developmental toxicity

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, 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 generate the data for this endpoint.

The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

ECHA further observes that in his testing proposal the Registrant has proposed to use trimethylolpropane (TMP, CAS No 77-99-6) as test material instead of the registered substance 2-Oxepanone, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, CAS No 37625-56-2 (EC No 500-099-5). If the Registrant proposes to carry out the tests required by Annex IX with a substance other than the registered substance, Article 13(1) and Annexes IX and X, third introductory paragraph, require the Registrant to clearly state reasons for adapting the standard information according to the rules laid down in Annex XI of the REACH Regulation. In particular Section 1.5 of this Annex applies in such cases. This section covers the "Grouping of substances and read-across approach". It stipulates that substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the group approach requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) by interpolation to other substances in the group (read-across approach).

It is inter alia required by Annex XI, Section 1.5 that "adequate and reliable documentation of the applied method shall be provided." As explained below, ECHA deems the read-across proposal by the Registrant to be inadequate as regards this requirement.

ECHA notes that the Registrant fails to justify the read-across in terms of a lack of information or experimental data that substantiate the following claims:

1. *"Systemic absorption of the intact substance is not predicted, based on its molecular size and hydrolysis; systemic exposure to the intact substance is therefore not predicted."*

   ECHA notes that no details about the prediction of the absorption of the intact substance are provided. The Registrant claims that hydrolysis takes place and that systemic

exposure is limited to the two hydrolysis products. However, no information or experimental data are available that support this claim.

2. *"The hydrolysis products of the substance are predicted to be trimethylolpropane (TMP) and 6-hydroxyhexanoic acid."*

   ECHA notes that this prediction is not substantiated or supported by experimental data or other information.

3. *"... toxicity data for e-caprolactone and adipic acid are provided to address the potential toxicity of this hydrolysis product." ... "The metabolic pathway of 6-hydroxyhexanoic acid can be predicted; the first step in the metabolism of this substance would be the formation through alcohol oxidation to the corresponding acid, adipic acid. The OECD QSAR Toolbox predicts further metabolism of adipic acid to the endogenous compounds succinic acid and acetic acid."*

   ECHA notes that the read-across from the source adipic acid to the target 6-hydroxyhexanoic acid is not adequately substantiated. The Registrant should explain in a scientifically credible manner as to why he thinks that the read-across is possible, if necessary based on, or supported by experimental data. The substantiation of the described metabolic pathway by means of additional information, preferably experimental data, is important. This should include the possible half-life of 6-hydroxyhexanoic acid. The question whether or not 6-hydroxyhexanoic acid can have its own effects before it is converted to adipic acid should be addressed.

ECHA notes that "adequate and reliable documentation of the applied method" in the form of a scientific credible explanation as to how the prediction can be made is lacking in the dossier. Therefore ECHA concludes that as adequate justification for the proposed read-across is not provided by the Registrant according to the requirements of Annex XI, Section 1.5 of the REACH Regulation, the read-across proposal cannot be accepted.

In its comments the Registrant acknowledged ECHA's reasoning regarding the read-across and accepted to perform the study on the registered substance.

b) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance 2-Oxepanone, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, CAS No 37625-56-2 (EC No 500-099-5) while pursuant to Article 40(3)(d) of the REACH Regulation the originally proposed Pre-natal developmental toxicity study (test method: EU B.31/OECD 414) using the read-across substance TMP is rejected.

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

b) Deadline
Regarding the timeline to submit an updated IUCLID dossier, in its comments the Registrant first requested an extension of the submission deadline from 12 months to 24 months of the date of the decision. Subsequently, the Registrant specified that 18 months would be needed for performance of the experimental study. This was motivated and documented by reference to test lab availabilities. ECHA considers that the request made by the Registrant, as substantiated by the letter of the test laboratory, is adequately justified. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

It is important to ensure that the particular sample of substance tested in the new study 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. If the registration of the substance covers different grades, the sample used for the new study must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade registered to enable the relevance of the study to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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