EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002054-85-05/F Helsinki, 5 November 2012

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

For 2,2,2`,2`-Tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol, CAS No 126-58-9 (EC No 204-794-1), 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 jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol, CAS No 126-58-9 (EC No 204-794-1), submitted by [redacted] (Registrant).

> Developmental toxicity study (OECD Guideline 414) using propylidynetrimethanol as substance to be tested instead of the registered substance.

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 14 June 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 requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the registration at a later stage.

The examination of the testing proposal was initiated on 7 September 2010.

ECHA opened a third party consultation for the testing proposal including testing on vertebrate animals that was held from 15 March 2011 until 29 April 2011 and received information from third parties (see Section III below).

On 21 November 2011 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days from the receipt of the draft decision.

On 20 December 2011 ECHA received comments from the Registrant.

ECHA considered the comments received from the Registrant, as well as a request for extension of a deadline for submission of the dossier update received from a registrant of an analogue substance of the group under evaluation, and amended the draft decision.

On 14 June 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, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 18 July 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and decided to amend the draft decision.

On 30 July 2012 ECHA referred the draft decision to the Member State Committee.

On 17 August 2012, the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 19-21 September 2012, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 21 September 2012. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

Pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant shall carry out the following test using the indicated test method:

> Pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2, test method: EU B.31/OECD 414) using the registered substance 2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol

while the originally proposed test for a pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2., test method: EU B.31/OECD 414) proposed to be carried out using propylidynetrimethanol is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **5 February 2014** an update of the registration dossier containing the information required by this decision.

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 fulfil 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.

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.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal of the Registrant for the registered substance and scientific information submitted by third parties.

a) Examination of the testing proposal

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out additional tests in case 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 provide information for this endpoint.

The Registrant has suggested meeting this standard information requirement by proposing a pre-natal developmental toxicity study with the substance propylidynetrimethanol. The Registrant used a category approach including the substances 2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol (Di-Penta; EC No. 204-794-1), 2,2'-[oxybis(methylene)]bis[2-ethylpropane-1,3-diol] (Di-TMP; EC No. 245-509-0), 2,2-bis(hydroxymethyl)-1,3-propanediol (pentaerythritol) (Penta; EC No. 204-104-9) and propylidynetrimethanol (TMP; EC No. 201-074-9). The Registrant concluded that the four substances are considered to be environmentally and toxicologically comparable based on structural considerations, theoretical considerations and the existing toxicological dataset. According to the Registrant the existing database demonstrates comparably low toxicity for all four substances. Therefore read-across is argued to be appropriate in order to meet the REACH data requirements for which studies are not yet available.

ECHA evaluated the Registrant's read-across justification and concluded that the Annex XI, 1.5 criteria of the REACH Regulation are not met: grouping of the substances is not sufficiently justified within the group. Furthermore, application of the group concept does not apply since the substances do not show similar toxicity but indicate different toxicokinetics and/or modes of action. Based on the outcome of the available data on repeated-dose toxicity, 2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol is of low toxicity with no effects at 1000 mg/kg bw/d. In contrast, propylidynetrimethanol induced hematological effects at doses of 200 mg/kg bw/d and more, leads to "distinct ill effects" at doses of 667 mg/kg bw/d, and to pathological changes in liver and kidney at the dose of 800 mg/kg bw/d. Therefore, ECHA concludes that the read-across approach proposed by the Registrant is not sufficiently justified and testing shall be performed with the registered substance.

The Registrant provided comments on the draft decision. These comments included information which according to the registrant "*describes justification for grouping TMP, Di-TMP, Penta and Di-Penta and gives further information on why testing on TMP also fulfil the data requirements on Di-TMP, Penta and Di-Penta for pre-natal developmental toxicity.*" Furthermore, the Registrant provided in response to the proposals for

amendment submitted by the Competent Authorities of the Member States a "Response to the Draft Decision on testing proposals for trimethylolpropane (TMP), di-TMP, pentaerythritol (Penta) and di-pentaerythritol (di-Penta)". ECHA took the Registrants comments into account and concluded that based on the information provided by the Registrant, the criteria set out in Annex XI, 1.5 are still not met and the category/read-across approach can not be applied.

More specifically, the Registrant provided further explanation to account for the differences in toxicity of propylidynetrimethanol seen in the two repeated dose toxicity studies with different oral administration (by gavage versus dietary administration). However, the Registrant did not provide sufficient information to support the explanation that toxicokinetic differences resulting from the mode of administration contribute to the observed difference. In addition, the Registrant provided information of possible metabolites of the substances which are included in the category based soley on one prediction model. However, the Registrant did not provide information on the likelihood of common breakdown products as indicated in REACH Annex XI, 1.5. In addition, no information on the validity of the prediction model that was used for these compounds was provided.

While it is recognised that further documentation and elaboration of arguments presented by the Registrant in support of the proposed adaptation may be possible, the shortcomings addressed above with regard to the fulfilment of adaptation criteria under Annex XI, 1.5 of the REACH Regulation presently remain. As a result, the Registrant failed to sufficiently document their approach for grouping and read-across. For the reasons stated above, this approach has to be rejected on the basis of the currently available information in accordance with Article 40(3)(d) of the REACH Regulation and testing for developmental toxicity shall be performed with the substance subject to this decision 2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol.

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 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 as a first species to be used.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following test: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414) with the registered substance 2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol. The proposed pre-natal developmental toxicity study with the analogue substance propylidynetrimethanol to cover the information requirement of Annex X, 8.7.2 for the substance subject to the present decision (2,2,2`,2`-tetrakis(hydroxymethyl)-3,3`-oxydipropan-1-ol) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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.

b) Consideration of the third party information

ECHA received third party information concerning the testing proposal during the public consultation. For the reasons explained further below the information provided by third parties was not sufficient to fulfil this information requirement.

Third party information 1:

A third party proposed that before a Prenatal Developmental Toxicity Study (OECD Guideline 414) is conducted consideration should be given to alternative testing strategies.

The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposals.

Third party information 2:

A third party provided results of a nonlinear classification ANN QSAR Model for prenatal developmental toxicity study.

The result from the QSAR classification model (i.e. "toxic" or "non-toxic") is not suitable for the purposes of classification and labelling and/or risk assessment for the endpoint for which testing has been proposed to meet the information requirement (Annex IX or X, 8.7). Compliance with the Annex XI section 1.3 requirements could not be established as the required information concerning the validity, adequacy for classification and labelling and documentation of the model was not provided. In addition, the submitted information suggests that the registered substance might be outside the applicability domain of the model. The (Q)SAR Model Reporting Format (QMRF) does not provide sufficient information to deduce whether the training set was constructed from studies that cover the information requirements of the OECD 414 guideline, or important study aspects, such as the species, dose selection and number of animals used.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of QSAR models set out in Annex XI, Section 1.3. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

c) Deadline for submitting the required information

The Registrant of the substance which was proposed for read-across (propylidynetrimethanol) requested extension of the deadline for submitting the required information from 12 to 15 months. ECHA evaluated the justification provided and decided to change the deadline as requested. Accordingly, ECHA decided to change the deadline for providing the required information for the registered substance from 12 to 15 months. ECHA has amended the decision accordingly.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new study meets real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to

the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed test, the sample of substance used for the new study must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the test proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new study 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 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).

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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