EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002003-92-05/F Helsinki, 4 July 2012

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

For Trimethylolpropane Diallyl Ether/ 2,2-bis(allyloxymethyl)butan-1-ol / 2,2-bis[(allyloxy)methyl]butan-1-ol, CAS No. 682-09-7 (EC No. 211-661-1), 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 testing proposals set out in the registration dossier for Trimethylolpropane Diallyl Ether/ 2,2-bis(allyloxymethyl)butan-1-ol / 2,2-bis[(allyloxy)methyl]butan-1-ol, CAS No. 682-09-7 (EC No. 211-661-1), submitted by [redacted] (Registrant), latest submission number [redacted], for 1000 tonnes or more per year.

In accordance with Articles 10(a)(ix) and 12(1)(e) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex X:

- Annex IX, 8.6.2: Sub-chronic toxicity study (90-day) in rat by the oral route;
- Annex X, 8.7.2: Pre-natal developmental toxicity study in rat by the oral route.

The examination of the testing proposal was initiated on 19.07.2010.

ECHA opened a third party consultation for testing proposals including testing on vertebrate animals that was held from 26.01.2011 until 14.03.2011. ECHA received information from third parties (see section III below).

On 31 October 2011 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

By 1 December 2011 the Registrant did not provide any comments on the draft decision to ECHA.

On 20 January 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. ECHA has reviewed the proposals for amendment received and decided not to modify the draft decision.

On 23 February 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 within 30 days of the receipt of the notification.

On 5 March 2012 ECHA referred the draft decision to the Member State Committee.

The Member State Committee amended the draft decision.

The Registrant did not provide any comments on the proposals for amendment.

A unanimous agreement of the Member State Committee on the amended draft decision was reached on 12 April 2012 in a written procedure launched on 2 April 2012.

This decision does not imply that the information provided by the Registrant in the 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 present dossier at a later stage.

II. Testing required

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

a) Sub-chronic toxicity study (90-day), in rat, oral route, Annex IX, 8.6.2., test method: EU B.26/ OECD 408; and

b) Prenatal developmental toxicity study, in rat, oral route, Annex X, 8.7.2., test method: EU B. 31/ OECD 414.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA **by 7 January 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 proposals of the Registrant for the registered substance and scientific information submitted by third parties.

Sub-chronic toxicity study (90-day)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test. A sub-chronic toxicity study (90 days) is a standard information requirement as laid down in Annex IX, section 8.6.2. 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.

ECHA considers the proposed default parameters of testing in rat by the oral route as appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the registered substance Trimethylolpropane Diallyl Ether / 2,2-bis(allyloxymethyl)butan-1-ol / 2,2-bis[(allyloxy)methyl]butan-1-ol.

Pre-natal developmental toxicity study

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test. A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, 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.

ECHA considers the proposed default parameters of testing in rat by the oral route as appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414) using the registered substance Trimethylolpropane Diallyl Ether / 2,2-bis(allyloxymethyl)butan-1-ol / 2,2-bis[(allyloxy)methyl]butan-1-ol.

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.

Comments from third parties

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 is not sufficient to fulfil this information requirement.

1. Third party comment 1: *"Evaluate the need to conduct a sub-chronic toxicity study (OECD Guideline 408 or 411) based on results of existing data."*

   The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. In particular, it has been proposed that the findings of the available 28-day study can be extrapolated to longer exposure duration, and suggests the use of assessment factors. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". A DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study. As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

2. Third party comment 2: *"Evaluate the need to conduct a Prenatal Developmental Toxicity Study, (OECD Guideline 414) in light of the results of the existing 28-day or 90-day study (OECD Guideline 407 [EU Method B.7] or 408 [EU Method B.26]) and other toxicological data."*

   The third party has indicated that Annex IX and X specify that reproductive toxicity studies should not be conducted "if the substance is of low toxicological activity (no evidence of toxicity has been seen in any of the tests available), it can be proven from toxicokinetics data that no systemic absorption occurs via relevant routes of exposure, and there is no or no significant human exposure. ECHA notes that the Registrant has provided qualitative indications about potential exposure and a theoretical toxicokinetic assessment stating that oral absorption is rapid and extensive renal and/or hepatic excretion of parent and its metabolites is likely. In addition, evidence of adverse effects has been seen in the 28-day repeated dose toxicity study.

   Therefore, ECHA concludes that the proposed arguments cannot constitute an acceptable adaptation to standard information requirements for developmental toxicity.

3. Third party comment 3: *"Perform in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use results to waive developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414)* [EU Method B.31]*."*

   A 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 as information or studies, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposals.

   Additionally, ECHA notes the following. For *in vitro* tests (embryonic stem cell test, the limb bud micromass culture and the whole embryo culture), the Guidance on information requirements and chemical safety assessment R.7, chapter R.7.6, states that these tests have limited value in a regulatory context. Considering the possibility of establishing a weight of evidence approach on the basis of such tests and existing *in vivo* data, which could fulfil the information

requirements of REACH, it is the registrant's responsibility and cannot be requested by ECHA.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of *in vitro* methods set out in Annex XI, Section 1.4. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

4. Third party comment 4: *"Exposure considerations: use the TTC for repeated dose and reproduction toxicity endpoints."*

The third party states that since testing can be exempted based on the negligible exposure, exposure should be thoroughly analysed before conducting the test. In addition, they suggest that the Threshold of Toxicological Concern (TTC) concept should be used.

According to Annex XI, Section 3 of the REACH Regulation, the testing can be omitted if it can be demonstrated that there is no or no significant exposure. The Registrant did not use substance-tailored exposure-driven testing according to Annex XI, Section 3 but indicated that some exposure will occur.

Therefore, ECHA concludes that the testing cannot be omitted based on negligible exposure.

5. Third party comment 5: *"Use of a non-linear classification ANN QSAR Model for the prenatal developmental toxicity endpoint."*

A third party presented a nonlinear ANN QSAR Model for developmental toxicity. 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 indicates that the registered substance might be outside the applicability domain of the model. The 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.

IV. Adequate identification of the composition of the tested material

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in the registration dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. It is noted, 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 tests, the sample of substance used for the new studies 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 the joint registrants of the same substance to agree with the tests proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint registrant. Finally, the studies must be shared by the joint registrants concerned.

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

ECHA always 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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Geert Dancet
Executive Director