Decision number: TPE-D-0000002361-84-04/F Helsinki, 10 July 2012

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

For 3-hydroxy-2,2-dimethylpropyl 3-hydroxy-2,2-dimethylpropionate, CAS No 1115-20-4 (EC No 214-222-2), 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 testing proposals set out in the registration dossier for 3-hydroxy-2,2-dimethylpropyl 3-hydroxy-2,2-dimethylpropionate, CAS 1115-20-4, (EC No 214-222-2), submitted by [redacted] (Registrant), submission number [redacted]

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 Annexes IX and X:

- Genetic toxicity *in vivo* (OECD Guideline 474), intraperitoneal route
- Repeated dose 90-day oral toxicity (OECD Guideline 408), and additional examinations concerning reproductive toxicity
- Pre-natal developmental toxicity (OECD Guideline 414)

The examination of the testing proposals was initiated on 2 November 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 31 May 2011 until 15 July 2011 and received information from a third party (see Section III below).

On 2 December 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.

On 15 December ECHA received comments from the Registrant agreeing to ECHA's draft decision.

ECHA considered the Registrant's comments received and did not amend the draft decision.

On 2 March 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 4 April 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 has reviewed the proposals for amendment received and decided to amend the draft decision accordingly.

On 16 April 2012 ECHA referred the draft decision to the Member State Committee.

On 4 May 2012 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account and modified the draft decision.

After discussion in the Member State Committee meeting on 6-8 June 2012, a unanimous agreement of the Member State Committee on the amended draft decision was reached on 7 June 2012 and ECHA took the decision pursuant to Article 51(6) 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 present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant shall carry out the following proposed test (under modified conditions) using the indicated test method and the registered substance:

1. Mutagenicity - *In vivo* mammalian erythrocyte micronucleus test (Annex IX, 8.4., test method: EU B.12/OECD TG 474), via the oral route.

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following proposed tests using the indicated test methods and the registered substance:

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

   It is at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance. However, the Registrant is reminded that the proposed extension of this study to include additional examinations concerning reproductive toxicity does not fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex X, 8.7.3. unless Annex X, 8.7. column 2 adaptations apply.

3. Pre-natal developmental toxicity study in rats, oral route (Annexes IX, 8.7.2, test method: EU B.31/OECD TG 414).

The Registrant shall determine the appropriate order of the studies taking into account the possible outcomes and considering the possibilities for adaptations of the standard

information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **10 January 2014** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study in another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation subject to the Annex IX, 8.7.2. column 2 requirements. If the Registrant considers that testing is necessary to fulfil this information requirement taking into account the outcome of the first species pre-natal developmental toxicity study and all other relevant and available data, 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 proposals of the Registrant

1. Mutagenicity

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

The technical dossier includes the results of an *in vitro* chromosome aberration assay submitted in accordance with Annex VIII 8.4.2., showing positive results. Pursuant to Annex IX, 8.4. Column 2 of the REACH Regulation, if there is a positive result in any of the *in vitro* genetoxicity studies in Annex VII or VIII and no *in vivo* results are available, an appropriate *in vivo* somatic cell genetoxicity study shall be proposed by the registrant. The Registrant has followed this provision by proposing an *in vivo* Mammalian Erythrocyte Micronucleus Test and ECHA considers the proposed test relevant to fulfil the standard requirements of Annex IX, 8.4. of the REACH Regulation.

The Registrant did not specify the species to be tested. Therefore, the Registrant shall follow the recommendations in the test guideline when selecting the appropriate species for testing.

The Registrant proposed *in vivo* mammalian erythrocyte micronucleus test (test method: EU B.12/OECD TG 474) by the intraperitoneal route. A Member State Competent Authority submitted a proposal for amendment to change the intraperitoneal route to the oral route since the test compound was absorbed after oral administration as shown by systemic toxicity in male rats in the OECD Test Guideline 422 study. In its comments to the proposal for amendments, the Registrant agreed that it is more appropriate to perform the study via the oral route. In light of the above considerations ECHA decided to modify the route of administration to the oral route.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is required to carry out the proposed study: *In vivo* mammalian erythrocyte micronucleus test (test method: EU B.12/OECD TG 474), via the oral route.

2. 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.

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 the pre-natal developmental toxicity on one species 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.

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 by intubation. 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)(a) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414).

3. 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 day) 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 noticed that according to the corresponding chemical safety report, the substance is used [redacted] with the possibility of inhalational exposure. The eye irritating property of the substance together with the high dustiness of the powder-based [redacted] products and unknown particle size distribution after spraying of the [redacted] product containing the registered substance pose questions about the local toxicity of the registered substance to the respiratory tract. However, ECHA considers that for the registered substance no repeated dose toxicity study is available and that the relevant 28-day read-across study indicates systemic toxic effects. Therefore, ECHA considers that testing by the oral route is most appropriate using the registered substance.

According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the following study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408). It should be noted that the Registrant's proposed extension of this study to additional examinations concerning reproductive toxicity does not fulfil the standard information requirement in the registration dossier for reproductive toxicity set out

in Annex X, 8.7.3. unless Annex X, 8.7. column 2 adaptations apply. ECHA may therefore verify the compliance of this end-point (Annex X, 8.7.3.) in a compliance check at a later stage. It is however at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance.

b. Consideration of third party information

A third party has proposed that before a test on genetic toxicity in vivo (e.g. an in-vivo mammalian erythrocyte micronucleus test according to OECD Guideline 474/EU Method B.12), an Oral Sub-chronic Toxicity Study (OECD Guideline 408), and a Prenatal Developmental Toxicity Study (OECD Guideline 414) is conducted, consideration should be given to existing data or planned studies on metabolites and chemical analogues of metabolites for read-across.

ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the Registrant to use read-across. Furthermore, the registrant has to justify that the criteria set out in Annex XI, 1.5. of the REACH Regulation are met and that the information provides a sufficient basis to fulfil the data/information requirement(s).

IV. 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.

V. 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.

Geert Dancet
Executive Director