EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002012-93-05/F Helsinki, 2 July 2012

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

For 3,5,5-trimethylhexanoic acid, CAS No 3302-10-1 (EC No 221-975-0), 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 3,5,5-trimethylhexanoic acid, CAS No 3302-10-1 (EC No 249-707-8) 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 IX:

- Annex IX, 8.6.2: Sub-chronic toxicity (90 days) by oral route in rodents;
- Annex IX, 8.7.2.: Pre-natal developmental toxicity study by gavage in rats.

The examination of the testing proposals was initiated on 8 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. ECHA received a comment from a third party proposing a quantitative structure-activity relationship model (QSAR) to waive the sub-chronic toxicity study. More information is provided in the statement of reasons in section III below.

On 24 October 2011 ECHA sent a draft decision to the Registrant for comments.

On 18 November 2011 ECHA received comments from the Registrant agreeing to ECHA's draft decision.

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 of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to 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 for amendment within 30 days of the receipt of the notification.

ECHA has reviewed the proposals for amendment received and decided not to amend the draft decision.

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

By 26 March 2012 the Registrant did not provide comments on the proposals for amendment.

The Member State Committee modified the decision.

The Member State Committee reached unanimous agreement on the draft decision relating to the testing proposal for a pre-natal developmental toxicity study and sub-chronic toxicity (90 days) by oral route in rodents in a written procedure launched on 2 April and closed on 12 April 2012.

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 tests:

a. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2, EU Method B.26) in rat by the oral route, modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin nephropathy.

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

b. Pre-natal developmental toxicity study (Annex IX, 8.7.2, EU Method B.31) in rat by the oral route.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **2 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 proposal of the Registrant for the registered substance and scientific information submitted by third parties.

a. Sub-chronic toxicity study (90-day)

A sub-chronic toxicity study (90-day) is a standard information requirement of Annex IX, 8.6.2 at the present tonnage level. ECHA notes that this standard information is not available in the present registration dossier. For the reasons set out below ECHA has decided to accept the testing proposal of the Registrant subject to conditions.

1) Analysis of third party comments

ECHA has examined the information submitted by a third party. A third party presented a quantitative structure-activity relationship model (QSAR) for repeated dose 90-day oral toxicity study in rodents. The third party has indicated that their information is confidential and this information is therefore not provided to the Registrant.

The compliance with the Annex XI section 1.3 requirements could not be established as the required information concerning the validity, adequacy for classification & labelling and documentation of the model was found insufficient. The submitted documents provide evidence that the descriptors of the predicted substance fall within the ranges of the individual descriptors, used for development of the model. However, the possibility that the substance does not fall in the applicability domain of the model for another reason could not be ruled out. 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 408 guideline, or important study aspects, such as the uniform selection of species, dose selection and number of animals used. In addition, the submitted QPRF does not contain any indication on the adequacy with an interpretation of the model result in relation to the defined regulatory purpose of the testing proposal.

Due to the failure to meet the requirements of Annex XI, 1.3, there is not a sufficient basis in the third-party comment to reject the testing proposal.

2) Analysis of information in the registration dossier

The dossier contains a 28-day rat study by oral route. The test for sub-chronic (90-day) toxicity as proposed by the Registrant is necessary to fulfil the information requirement of section 8.6.2 of Annex IX to the REACH Regulation.

The 28-day oral study in rats gives a NOAEL of 50 mg/kg bw/d and a LOAEL of 200 mg/kg bw/d for decreased motor activity, liver effects, alterations in clinical chemistry and urinalysis parameters. The leading effect is male specific kidney toxicity at all doses including 10 mg/kg/day. Due to the alpha-2u globulin nephropathy effect ECHA decided to modify the Registrant's testing proposal by including additional parameters to the test. The additional parameters are urinalysis (which is optional in paragraph 30 of OECD 408, and the relevant part of section 1.5.2.2. of EU Method B.26) to investigate kidney function, and a full histopathological examination (paragraph 36 of OECD 408, section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the renal lesions are indeed mediated by alpha-2u globulin nephropathy.

3) Conclusion

Pursuant to Article 40(3)(b) ECHA may take a decision requiring the Registrant to carry out the proposed test, but modifying the conditions under which the test is to be carried out.

Accordingly, pursuant to that Article the Registrant is requested to provide information on the Annex IX, 8.6.2 endpoint by carrying out a sub-chronic toxicity study (90-day) in rat by the oral route by using EU Method B.26, modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin nephropathy.

b. Pre-natal developmental toxicity study

1) Analysis of information in the registration dossier

ECHA agrees with the Registrant that a pre-natal developmental toxicity study for a first species is a standard information requirement under Annex IX, 8.7.2 of the REACH Regulation. ECHA notes that this standard information is not available in the present registration dossier, but a testing proposal concerning a pre-natal developmental toxicity study has been made.

The Registrant has based his testing proposal on the fact that the available screening study for reproduction and development does not allow a final conclusion with regard to developmental toxicity/teratogenicity.

2) Conclusion

Pursuant to Article 40(3)(a) ECHA may take a decision requiring the Registrant to carry out the proposed test.

Therefore, pursuant to Article 40(3) (a) 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 B.31. of Regulation (EC) No 440/2008).

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.

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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