ECHA
EUROPEAN CHEMICALS AGENCY

For final decision: TPE-D-0000002082-86-05/F Helsinki, 25 July 2012

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

For diethylmethylbenzenediamine, CAS No. 68479-98-1 (EC No. 270-877-4), 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 a testing proposal set out in the registration dossier for diethylmethylbenzenediamine, CAS No. 68479-98-1 (EC No. 270-877-4), 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 proposal as part of the registration dossier to fulfil the information requirements set out in Annexes IX and X:

Pre-natal developmental toxicity study (test method: OECD 414), Annexes IX and X, 8.7.2.

The examination of the testing proposal was initiated on 1 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 29 July 2011 until 12 September 2011. ECHA received information from third parties (see section III below).

On 1 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 20 December 2011 ECHA received comments from the Registrant agreeing to ECHA's draft decision but asking for an extension of the deadline to submit an update of the registration dossier containing the information required by this decision.

ECHA considered the Registrant's comments received and amended 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, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 4 April 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 has reviewed the proposal for amendment received and decided to amend the draft decision.

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

On 4 May 2012 the Registrant provided comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 21 May 2012 in a written procedure launched on 10 May 2012.

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 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 following test using the indicated test method and the registered substance:

Pre-natal developmental toxicity study in rats, oral route (Annex IX, 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 **25 July 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 submitted by the Registrant for the registered substance and scientific information submitted by third parties.

a) Examination of the testing proposal

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.

In addition to a testing proposal, the registrant has invoked two adaptations to testing.

First, the Registrant proposes to waive the study since "the information from the general toxicity studies indicates that effects on the pancreas can be considered the primary and most important mode of DETDA toxicity in rodents. In several repeated dose toxicity studies, the substance showed pancreatic toxicity at low dose levels, which require classification as STOT-RE (Cat.2). Specific developmental toxicity is not a predominant feature to characterize the toxicity profile of aromatic amines in general. In view of the very specific pancreas effects at relatively low dose levels that already trigger risk management measures and the need to consider animal welfare, a developmental toxicity study in this case is not considered to have highest priority."

However, the registrant's justification in the presented adaptation according to Annex XI is not acceptable since classification for specific target organ toxicity (STOT) is not an argument in the legal text or in the guidance for waiving a pre-natal developmental toxicity study.

Second, the Registrant has proposed an adaptation to testing for the pre-natal developmental toxicity endpoint by using a QSAR model (T.E.S.T. 3.3).

Based on this model it can only be assumed that the chemical may have a developmental toxicity effect, but this information alone cannot be used to conclude that the substance is a developmental toxicant. Therefore, the use of the proposed QSAR model, as an adaptation according to Annex XI, 1.3, is not accepted, since the results of the QSAR model are not adequate for the purpose of classification and labelling and/or risk assessment. Hence the adaptation cannot be used to replace the pre-natal developmental toxicity study.

Furthermore, even if the QSAR model were to be considered adequate in the present case, the information on the modelling is very limited. On the other hand, the Registrant interprets that the result of the QSAR model is positive i.e. indicating that the substance is a developmental toxicant. However, the Registrant does not classify the substance on this basis nor does the EU harmonised classification contain data on the developmental toxicity endpoint. Moreover, regarding the validity and applicability of the QSAR model, ECHA is of the opinion that the Registrant has not interpreted the QSAR model prediction correctly. The T.E.S.T. model gives only a probability for a chemical to be a developmental toxicant (in the range 0 to 1) whilst the Registrant interpreted these 0 to 1 scores as effect levels in mg/kg/day. Based on the predicted values it can only be assumed that the chemical may have a developmental toxicity effect, but this information alone cannot be used to conclude that the substance is a developmental toxicant.

Therefore, none of the Annexes IX and X, column 2 or Annex XI, Section 1.3 adaptations apply, hence the data gap has not been fulfilled and the proposed study must be carried out.

In the presented testing proposal for the pre-natal developmental toxicity endpoint, the Registrant propose to perform the study according to OECD Guideline 414, however 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 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 proposed study: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414) using the registered substance.

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 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 is not sufficient to fulfil this information requirement.

The following third party comments were received:

"Before the proposed test in vertebrate animals is conducted, in addition to the T.E.S.T. QSAR model prediction in the dossier, existing experimental in vivo data for diaminotoluenes should be evaluated (read-across, weight-of-evidence). (References: WHO (1987) International Programme on Chemical Safety (IPCS), Environmental Health Criteria 74, Diaminotoluenes)."

First in relation to the existing in vivo data concerning diaminotoluenes, ECHA notes that it is the responsibility of the Registrant to conduct an assessment with appropriate and scientifically justified methods. In the present case, the Registrant has supplied information generated with the registered substance and only in the case of prenatal developmental toxicity the Registrant refers to a QSAR method. It is not obvious that the information in the EHC 74 publication can be used as a read-across to the registered substance and such justification is lacking in the dossier at issue.

Second, as was discussed in section III a), based on the information from the QSAR model it can only be assumed that the chemical may have a developmental toxicity effect, but this information alone cannot be used to conclude that the substance is a developmental toxicant. 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, since the results of the QSAR model are not adequate for the purpose of classification and labelling and/or risk assessment. Hence the adaptation cannot be used to replace the pre-natal developmental toxicity study.

ECHA concludes that in this occasion the third party has rather proposed a strategy to collect information than submitted real data relevant for the registered substance and thus this is not a sufficient basis for rejecting the Testing Proposal.

During the commenting period the Registrant expressed consent to submit the proposed test but proposed to extend the timeline to provide the requested information from 12 to 24 months starting from the date of the final decision. The request of the Registrant was based on workload and availability of test laboratories to conduct such tests and the fact that another regulatory body has also requested the Registrant similar study. Within this regulatory process an approval is required for the protocol details prior to starting the test. ECHA agrees with the Registrant's request to conduct a developmental toxicity study on a 1st species that will be acceptable for both regulatory bodies and therefore, consent to extend the deadline to provide the requested information from 12 to 24 months starting from the date of the final decision.

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 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 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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