European Chemicals Agency

Decision number: TPE-D-0000001703-79-05/F Helsinki, 30/11/2011

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

**For 4,4'-methylenebis[N,N-bis(2,3-epoxypropyl)aniline], CAS 28768-32-3 (EC No 249-204-3), 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 **4,4'-methylenebis[N,N-bis(2,3-epoxypropyl)aniline]**, (CAS 28768-32-3, EC 249-204-3), submitted by [redacted] latest submission number [redacted] for 100-1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(d) 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:

- Sub-chronic toxicity study (90-day), dermal route
- Pre-natal developmental toxicity study, rat, oral route
- Two generation reproductive toxicity study, rat, oral route

The examination of the testing proposals was initiated on 6 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 26 January 2011 until 12 March 2011. ECHA received the following Third Party Information (TPI):

TPI 1. Result of a nonlinear classification ANN QSAR Model for prenatal developmental toxicity study accompanied by a sample QSAR Prediction Reporting Format (QPRF) labelled as "private".
TPI 2. Alternative testing strategy
TPI 3. Result of a nonlinear classification ANN QSAR Model for prenatal developmental toxicity study

ECHA examined the testing proposals and the information received from third parties and drafted a decision in accordance with Article 40 of REACH.

On 8 June 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments on the draft decision.

By 8 July 2011 the Registrant did not provide to ECHA comments on the draft decision. However, EXCHA amended the draft decision by clarifying further the statement of reasons.

On 29 July 2011 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. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision. Based on the proposed amendments, ECHA decided not to modify its draft decision.

On 31 August 2011 ECHA notified the Registrant of the 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. The Registrant did not provide any comments on the proposed amendments.

On 12 September 2011, the draft decision was referred to the Member State Committee.

After discussion in the Member State Committee meeting on 2-4 November 2011, the Member State Committee further amended the draft decision and a unanimous agreement of the Member State Committee on the further amended draft decision was reached on 4 November 2011.

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

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

- Sub-chronic toxicity study (90 day study) (Annex IX, 8.6.2, EU Method B.26) in rat by the oral route

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

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

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.

c) **Pursuant to Article 40(3)(d) of the REACH Regulation, the following test is currently rejected:**

- Two generation reproductive toxicity study in rat by oral route (Annex IX, 8.7.3)

If the results of the sub-chronic toxicity study (90-day) required by this decision indicate adverse effects on reproductive organs or tissues then the Registrant shall submit a testing proposal to cover the endpoint of Annex IX, 8.7.3. for reproductive toxicity unless the Registrant considers that the specific rules for adaptation from this information requirement mentioned in Column 2, Annex IX, 8.7. apply.

In any event the Registrant may on the basis of other considerations submit a testing proposal for this end-point at an earlier stage. Such reasons for testing should be indicated.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **02/12/2013** an update of the registration dossier containing the information required by this decision.

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**

A sub-chronic toxicity study (90-day), most appropriate route of administration, 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 dossier.

A third party has proposed a testing strategy for ECHA to consider. However, ECHA invited submission of "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal", as specified by Article 40(2), and the proposal for a strategy does not constitute "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". Consequently, ECHA concludes that this is not a sufficient basis for rejecting the testing proposed.

ECHA therefore agrees with the Registrant that a sub-chronic toxicity test is needed to address the information requirements of REACH. However, ECHA disagrees with the route of administration proposed by the Registrant. The Registrant proposed to conduct the test through the dermal route. However, the Registrant has provided no justification in his dossier why the dermal route was the most appropriate route for administration. As the oral route is in general considered to be the standard route to address systemic effects and as - according to the information given by the Registrant - dermal absorption was likely to be low, the oral route was considered to be the most appropriate route of exposure for the test.

Pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is therefore requested to carry out sub-chronic toxicity study (90 day study) (Annex IX, 8.6.2, EU Method B.26) in rat by the oral route.

**b) Prenatal developmental toxicity**

A pre-natal developmental toxicity study is a standard information requirement of Annex IX, section 8.7.2. of REACH at the present tonnage level. ECHA notes that this information is not available in the present dossier.

ECHA has examined the information submitted by third parties as follows:

TPI 1. A prediction using a QSAR Model for prenatal developmental toxicity study was provided. The compliance with Annex XI requirements of the model used could not be established as information concerning the validity, applicability domain, adequacy for classification & labelling, and documentation of the method used was not provided for both models. Therefore, the predicted result can not be used directly or extrapolated to meet the minimum information requirements according to Article 12 of the REACH Regulation.

TPI 2. A third party has proposed a testing strategy for ECHA to consider. However, ECHA invited submission of "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal", as specified by Article 40(2), and the proposal for a strategy does not constitute "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". Consequently, ECHA concludes that this is not a sufficient basis for rejecting the testing proposed.

TPI 3. A prediction using a QSAR Model for prenatal developmental toxicity study giving the result toxic was provided. The compliance with Annex XI requirements of the model used could not be established as information concerning the validity, applicability domain, adequacy for classification & labelling, and documentation of the method used was not provided. The predicted result can therefore not be directly used or extrapolated to fill a data gap according to the minimum information requirements according Article 12 of the REACH Regulation.

In conclusion as the registration dossier contains no sufficient information on developmental toxicity and no scientifically valid information has been provided to fill this data gap following the third party consultation ECHA considers that a prenatal developmental toxicity test in one species is needed to address the information requirements of REACH at this tonnage.

Pursuant to Article 40(3)(a) of the REACH Regulation the Registrant is therefore requested to carry out the Pre-natal developmental toxicity study (Annex IX, 8.7.2, EU Method B.31) in rat by the oral route.

**c) Two generation reproductive toxicity**

A two generation reproductive toxicity study is required at this tonnage level when the 28 day or 90 day study indicates adverse effects on reproductive organs or tissue (Annex IX, 8.7.3.).

Currently there is no information available in the dossier whether the conditions for requiring a two-generation reproductive toxicity study are fulfilled. ECHA therefore concludes that at this moment in time the legal requirements of Annex IX for the mandatory performance of the two-generation study are not met.

The Registrant provided no comments on the proposals for amendment and therefore did not indicate any reasons for performing the study immediately. On this basis the testing proposal is currently rejected. If the 90-day study shows adverse effects on reproductive organs or tissues, the Registrant shall submit a testing proposal to cover the endpoint of Annex IX, 8.7.3. as this would then constitute a standard information requirement for substances registered at 100 to 1000 tonnes per year.

In any event the Registrant may on the basis of other considerations submit a testing proposal for this end-point at an earlier stage. Such reasons for testing should be indicated.

**d) Deadline for submitting the required information**

In the draft decisions communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a 2-generation reproductive toxicity study. As the testing proposal for this study has currently been rejected, ECHA considers that a reasonable time period for providing the remaining required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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 reads:

> "*Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.*"

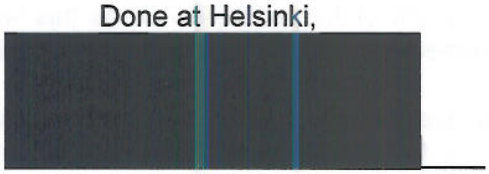
According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the 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 and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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.

Done at Helsinki,



Director of Regulatory Affairs