EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000004808-64-09/F Helsinki, 25 September 2014

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

For dichloromethylbenzene, CAS No 29797-40-8 (EC No 249-854-8), 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 following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for dichloromethylbenzene, CAS No 29797-40-8 (EC No 249-854-8, submitted by [redacted] (Registrant).

- Prenatal developmental toxicity study according OECD Guideline 414 in a second species, mice proposed as species

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 24 July 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) 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 REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

The examination of the testing proposal was initiated upon the date when receipt of the complete registration dossier was confirmed on 05 November 2013.

ECHA held a third party consultation for the testing proposal from 31 January 2014 until 17 March 2014. ECHA did not receive information from third parties.

On 28 April 2014 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 4 June 2014 the Registrant did not provide any comments on the draft decision to ECHA.

On 24 July 2014 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 for amendmends of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following modified test pursuant to Article 40(3)(b) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study in rabbits, oral route (Annex X, Section 8.7.2.; test method: EU B.31/OECD 414).

Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **2 October 2015** an update of the registration dossier containing the information required by this decision.

Note for consideration by the Registrant

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a sound scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request in this decision, or to fulfil otherwise the information requirement with a valid and documented adaptation, will result in a notification to the Authorities of the Member States for enforcement.

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.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.)

a) Examination of the testing proposal

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

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The dossier contains a pre-natal developmental toxicity study in rats as first species. However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in a second species according to EU B.31/OECD 414 and has proposed mice as species to be tested.

The results of the pre-natal developmental toxicity study in the rat as first species with the registered substance and according to OECD 414 (2013) and GLP were reported in the updated dossier subsequent to an ECHA decision on a first testing proposal (TPE-D-0000002138-77-05/F). For this study the Registrant reported: maternal toxicity at 250 mg/kg bw/day and developmental toxicity except fetuses at 750 mg/kg bw/day. For fetal weight and degree of ossification a NOAEL could not be identified (< 250 mg/kg bw/day). In particular, a treatment related effect on skeletal deviations (retardations, variations, including cartilaginous tissue findings) is assumed for retarded ossification of many localizations (digits, metacarpals, toes, metatarsals, sternebrae, cervical vertebral bodies, caudal vertebral bodies) at the 750 mg/kg level, and it cannot be excluded for retarded ossification of several localizations at the 500 mg/kg and 250 mg/kg levels due to also decreased fetal weights at all dose levels. Furthermore, a treatment related effect cannot be excluded for increased incidences of 14th ribs at the 750 mg/kg and 500 mg/kg levels.

Based on these results ECHA concludes that for pre-natal developmental toxicity there is a concern and the testing proposal for a pre-natal developmental toxicity study in a second species is appropriate. ECHA considers that the proposed study method OECD 414 is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in mice. Although no specific justification for the choice of the mouse as test species has been presented for the pre-natal developmental toxicity test, ECHA assumes that the Registrant's choice is related to the rat kidney toxicity observed in male rats. This was demonstrated to be based on male rat specific hyaline droplet formation due to alpha 2-microglobulin accumulation. Therefore the Registrant concludes that rat is not a suitable animal model and proposed the mouse for all further animal tests, such as for the 90-day repeated dose toxicity test as well as for the 2-generation reproduction toxicity test. The mouse does not not have the rat specific kidney toxicity mechanism based on alpha 2-microglobulin accumulation. However, rabbits also do not have the rat specific kidney toxicity mechanism based on alpha 2-microglobulin accumulation. Therefore the reasoning is not valid to prefer the mouse over the rabbit. ECHA stresses that for a comprehensive assessment of developmental toxicity according to Annexes IX and X information from two species, one rodent (usually the rat) and one non-rodent (usually the rabbit) should be considered (see Chapter R.7.6.6.5 (p. 333) in ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 2.4, February 2014)). Also according to the test method EU B.31/OECD 414, the rat is the preferred rodent species and the rabbit is the preferred non-rodent species. The test in the first species was carried out by testing a rodent species (rat) and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. Hence, testing shall be performed in rabbits.

The Registrant did not specify the route for testing. The oral route is the default route in EU B.31/OECD 414 and ECHA considers this appropriate also in the current case and testing should be performed by the oral route.

b) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present

decision: Pre-natal developmental toxicity study in rabbits, oral route (test method: EU B.31/OECD 414).

IV. Adequate identification of the composition of the tested material

It is important to ensure that the particular sample of substance tested in the new study is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured. If the registration of the substance covers different grades, the sample used for the new study must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the study to be assessed.

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

ECHA 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).

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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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