EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002541-82-05/F Helsinki, 16 April 2013

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

For 8,9,10-trinorborn-2-ene, CAS No 498-66-8 (EC No. 207-866-0), 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 the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 8,9,10-trinorborn-2-ene, CAS No. 498-66-8 (EC No. 207-866-0), by [redacted] (Registrant).

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 6 September 2012, 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.

- Prenatal Developmental Toxicity Study (OECD 414).
- Repeated Dose 90-day Oral Toxicity Study in Rodents (OECD 408).

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 present dossier at a later stage.

On 9 December 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 16 June until 1 August 2011. ECHA did not receive information from third parties.

On 6 July 2012 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 6 August 2012 the Registrant did not provide any comments on the draft decision to ECHA.

On 6 September 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 10 October 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 reviewed the proposals for amendment received and decided to amend the draft decision in accordance with one of these proposals.

On 22 October 2012 ECHA referred the draft decision to the Member State Committee.

The Registrant did not provide any comments on the proposed amendments.

After discussion in the Member State Committee meeting on 10-14 December 2012, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 12 December 2012. 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

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(a) 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 rats or rabbits, oral route (Annex IX, 8.7.2., test method: EU B.31/OECD 414).

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

2. Sub-chronic toxicity study (90-day) in rats, inhalation route (Annex IX, 8.6.2., test method: OECD 413) modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

while the originally proposed test for a sub-chronic toxicity study (90-day) oral route (Annex IX, 8.6.2., test method: EU B.26/OECD 408) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome 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 **16 April 2015** 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 fulfill 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.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance.

1. Pre-natal developmental toxicity

a) Examination of the testing proposal

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 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 provide information for this endpoint.

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 or the rabbit as a first species to be used.

b) Outcome

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 or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance 8,9,10-trinorborn-2-ene.

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.

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.

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

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 provide information for this endpoint.

The Registrant proposed testing by the oral route. ECHA evaluated the route to be tested. Based on Annex IX, 8.6.2, column 2 of the REACH Regulation, testing by the inhalation route is appropriate if "exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of inhalable size". ECHA notes that the substance is a paste with a high vapour pressure indicating a potential for inhalation exposure. Moreover, worker exposure was calculated up to 4.5 ppm with a risk characterization ratio (RCR) for inhalation of 0.9. The RCRs are based on the NOAEL of a repeated dose toxicity study with oral administration and are therefore suitable to cover systemic toxicity and the results may be used for route-to-route extrapolation for systemic effects. Such results will not cover route-specific toxicity associated with inhalation. The substance is classified as eye irritant and therefore, respiratory tract irritation might be expected to occur. To account for local effects in the respiratory tract, oral-to-inhalation extrapolation is not appropriate since the respiratory tract has a higher sensitivity for irritating effects than the gastrointestinal tract. Therefore, the calculated RCRs based on systemic toxicity are not appropriate for local effects in the respiratory tract. Risk characterisation ratios for local effects in the respiratory tract need to be based on a long-term DNEL, inhalation, local. Such a DNEL can only be derived from an inhalation study. No such inhalation study is available. Therefore, ECHA considers testing via the inhalation route as the most appropriate. In addition to respiratory tract irritation, this study will also evaluate whether other route specific toxicity occurs when the substance is inhaled.

The Registrant did not specify the species to be tested. According to the test method OECD 413 the rat is the preferred rodent species. In the dossier, the Registrant stated that "hyaline droplet formation in the renal proximal epithelium is related to alpha2-microglobulin agglomeration". This effect was seen only in the male rat. This statement raises the question whether the mouse should be used instead of the rat. ECHA however noted that (1) there is no clear evidence that hyaline droplets observed in the kidney are due to alpha-2u globulin binding, and (2) the toxic effect observed in the range finding study that limited the maximal dose tested is probably not related to the alpha-2u globulin binding. ECHA proposes to perform the 90-day study on the rat. Moreover, due to the possible alpha-2u globulin nephropathy effect, ECHA requests the Registrant's to include additional parameters to the test. The additional parameters are urinalysis to investigate kidney function and a full histopathological examination, which is to include immunohistochemical investigation of renal pathology to determine if the renal lesions are indeed mediated by alpha-2u globulin nephropathy.

b) Outcome

Therefore, pursuant to Article 40(3) (c) of the REACH Regulation, the Registrant is required to carry out the following study: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD 413) using the registered substance 8,9,10-trinorborn-2-ene .
The following additional parameters to the test are requested: urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

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.

IV. 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.

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.

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