EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002878-59-03/F Helsinki, 22 April 2013

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

For trans-N1,N1,N4,N4-Tetrakis(2-hydroxyethyl)1,4-cyclohexanedicarboxamide, CAS No 1215841-86-3 (EC No 700-597-4), 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 the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for trans-N1,N1,N4,N4-Tetrakis(2-hydroxyethyl)1,4-cyclohexanedicarboxamide, CAS No 1215841-86-3 (EC No 700-597-4), by [redacted] (Registrant).

- OECD Guideline 414 (Prenatal Developmental Toxicity Study) with rats by using oral exposure
- OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day)

This decision is based on the registration dossier as submitted with submission number [redacted] for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates after 18 January 2013, 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 present dossier at a later stage.

The examination of the testing proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 16 April 2012.

ECHA held a third party consultation for the testing proposals from 18 June 2012 until 2 August 2012. ECHA did receive information from third parties (see section III below).

On 2 October 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 2 November 2012 the Registrant did not provide any comments on the draft decision to ECHA.

On 18 January 2013 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 did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

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).
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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, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408)

while the originally proposed test for a Sub-chronic toxicity study (90-day) for the inhalation route (OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day) 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 **22 April 2015** 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 proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

1. Pre-natal developmental toxicity study

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.

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 provide information for this endpoint.

The Registrant proposed to perform the test in rats by the oral route.
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) Consideration of the information received during third party consultation

ECHA did not receive third party information concerning this testing proposal during the third party consultation.

c) 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.

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X and XI.

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 of sub-chronic toxicity by the inhalation route. However, the Registrant did not provide any explanation on his choice of the route for testing. In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the inhalation route is not appropriate but testing should be performed via the oral route, as further argumented below.

In accordance with Column 1 of Annex IX, section 8.6.2 of the REACH Regulation the study should be performed via *"the most appropriate route of administration, having regard to the likely route of human exposure"*. Column 2 of Annex IX, section 8.6.2 defines that inhalation route is appropriate if *"exposure of humans via inhalation is likely taking into account (...) the possibility of exposure to aerosols, particles or droplets of an inhalable size"*. ECHA notes that all the uses with regard to industrial settings reported in section 3.5 of the IUCLID dossier appear to lead to inhahation exposure. However, the registered substance is a powder with only 0.04% particles of respirable size (< 32 µm) and consequently there is no indication of relevant exposure to particles of an inhalable size. Additionally, ECHA notes that for the registered substance there will be no deposition and retention in the respiratory tract due to its water solubility. Therefore, no local effects on the respiratory tract are to be expected, which would be a relevant element in the decision on whether to conduct a test via the inhalation route.

Therefore, ECHA concludes that, according to Column 2 of Annex IX, section 8.6.2, the inhalation route is not an appropriate route for testing. Consequently, the oral route, as the preferred route concerning repeated dose toxicity according to section R.7.5.4.3, Chapter R.7a, page 329 of *the Guidance on information requirements and chemical safety assessment* (May 2008) is the most appropriate route for testing.

ECHA also notes that a 14-day dose-range finding inhalation study is available in the dossier. The substance used for this study was ground in order to result in dust particles of 3.1 to 3.5 µm. Up to the highest technically feasible dust concentration of 1.03 mg/L, no toxic effect was observed in this study.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

The third party questions the relevance of the proposed inhalation route for the sub-chronic toxicity study based on the information provided by the Registrant in his dossier for this substance (physical-chemical properties, toxicological information and identified uses). The Third Party does not provide any new information that would affect the ECHA's conclusion and justification on the route. Nevertheless ECHA and the third party reached the same conclusion on the most appropriate route, as explained in point a) above, independently.

c) 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, oral route (test method: EU B.26/OECD 408) using the registered substance. Pursuant to Article 40(3)(d) of the REACH Regulation, the originally proposed test for Sub-chronic toxicity study (90-day), inhalation route (test method OECD 413) is rejected.

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 studies 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 studies must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grade registered to enable the relevance of the studies 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://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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Director of Regulatory Affairs