Decision number: TPE-D-2114308219-53-01/F Helsinki, 11 September 2015

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

For 1,6-Bis(2,3-epoxypropoxy)hexane, EC No 618-939-5 (CAS No 933999-84-9), 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 1,6-Bis(2,3-epoxypropoxy)hexane, EC No 618-939-5 (CAS No 933999-84-9), submitted by [redacted] (Registrant).

- Viscosity (OECD 114)
- Subchronic Dermal Toxicity 90-day study (OECD 411) in rat
- Developmental toxicity / teratogenicity (OECD 414)

This decision is based on the registration 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 25 June 2015, i.e. 30 calendar days after the end of the commenting period.

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.

ECHA received the updated registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 20 October 2014.

ECHA held a third party consultation for the testing proposals from 18 November 2014 until 2 January 2015. ECHA received information from third parties (see section III below).

On 17 April 2015 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 25 May 2015 the Registrant did not provide any comments on the draft decision to ECHA.

On 23 July 2015 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 amendment 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

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Viscosity (Annex IX, Section 7.17.; test method OECD 114);

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral/inhalation route.

The Registrant shall carry out the following additional test pursuant to Article 40(3)(c) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats;

while the originally proposed test for a Subchronic Dermal Toxicity 90-day study (OECD 411) proposed to be carried out using the registered substance is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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 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(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. 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 **18 September 2017** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

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.

A. Tests required pursuant to Article 40(3)

1. Viscosity (Annex IX, Section 7.17.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.
"Viscosity" is a standard information requirement as laid down in Annex IX, Section 7.17. of the REACH Regulation. The information on this endpoint is not available for the registered substance subject to the present decision 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 has submitted a testing proposal for a viscosity test.

ECHA considers the proposed test appropriate and testing should be performed with the registered substance [1,6-Bis(2,3-epoxypropoxy)hexane].

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed test using the registered substance substance [1,6-Bis(2,3-epoxypropoxy)hexane]: Viscosity of liquids (test method: OECD 114).

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 has submitted a testing proposal for a pre-natal developmental toxicity study in rat and rabbits according to EU B.31/OECD 414 with the following justification: *"O.E.C.D. Test Guideline 414 Developmental studies in the rat and rabbit by an appropriate route are proposed by the consortium members as per RIP 3.3. Chapter R.7A, Section R.7.6.6.4. Elements of ITS, subject to approval of the Test Plan by E.C.H.A. Conduct of the second study will be dependent upon the outcome of the first study".*

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in rat and rabbits. He did not specify the route 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) Consideration of the information received during third party consultation

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

The third party has referred to the local irritating/corrosive and sensitising property of the substance and the dermal route not being appropriate from both scientific and an animal welfare point of view.

ECHA acknowledges that – as specified in the general part of Annexes VII-X – "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided". The test methods for repeated dose toxicity and reproductive toxicity specify that the highest dose level should induce "toxicity but not death or severe suffering". Therefore, it is the Registrant's responsibility to ensure that appropriate dose/exposure levels are used in the requested studies.

A third party has proposed "A testing proposal of a pre-natal developmental toxicity study to be conducted with the related substance 1,4-bis(2,3-epoxypropoxy)butane may rise the possibility of a read-across approach to fulfil the information requirements of the registered UVCB substance which is also referred to as 1,6-bis(2,3-epoxypropoxy)hexane".

ECHA acknowledges that – as specified in the general part of Annexes VII-X – "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided". The test methods for repeated dose toxicity and reproductive toxicity specify that the highest dose level should induce "toxicity but not death or severe suffering". Therefore, it is the Registrant's responsibility to ensure that appropriate dose/exposure levels are used in the requested studies. Therefore, the Registrant may assess whether he can justify an adaptation using a read-across approach in accordance with Annex XI, 1.5. of the REACH Regulation as suggested by the third party. If the information requirement can be met by way of adaptation, he may include the adaptation argument with all necessary documentation according to Annex XI, Section 1.5 in the registration dossier.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision [1,6-Bis(2,3-epoxypropoxy)hexane]: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

d) Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

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, Section 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. If the Registrant considers that the conditions for adaptations are not fulfilled, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for proposing to adapt the standard information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

3. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

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 or 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 has submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats with the dermal route (EU B.28/OECD 411) with the following justification *"As per REACH Annex IX, Section 8.6.2. a 90-day, rat subchronic O.E.C.D. Testing Guideline study by the appropriate route of administration is proposed by the consortium members, subject to approval of the Test Plan by E.C.H.A. according to the guideline OECD 411"*.

ECHA considers that the proposed study via the dermal route is not appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation because the proposed route is not the most appropriate route of administration having regard to the likely route of human exposure due to the following reasons.

According to the REACH Regulation testing by the dermal route is appropriate if:
(1) skin contact in production and/or use is likely; and
(2) the physicochemical properties suggest a significant rate of absorption through the skin; and
(3) one of the following conditions is met:
- toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test, or
- systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies, or
- in vitro tests indicate significant dermal absorption, or
- significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

ECHA notes that the substance is classified as Skin Irrit. 2 (causes skin irritation), Eye Irrit. 2 (causes serious eye irritation), Skin Sens. 1 (may cause an allergic skin reaction). Due to the sensitising property of the substance, minimisation of skin contact is required and skin contact should not be likely in production and/or use. Hence, the criteria of the appropriateness of the dermal route for testing following REACH Annex IX, Section 8.6.2., column 2 are not met. Therefore, the proposal to test by the dermal route is rejected.

The substance is a liquid of very low vapour pressure. Based on PROC 11 (non-industrial spray application), aerosol generation of potential inhalable size is possible. Hence, testing by the inhalation route would be appropriate following REACH Annex X, Section 8.6.2., column 2. However, a 28-day inhalation study is available with the registered substance on which the DNEL for long-term inhalation, local effects is based. Therefore, ECHA considers that the inhalation route has been addressed by the Registrant in the chemical safety report.

The ECHA Guidance on information requirements and chemical safety assessment R.7a chapter R.7.5.4.3 (August 2014) concerning repeated dose toxicity testing states that the oral route is the preferred one. Furthermore, a short-term repeated dose toxicity study by the oral route according to OECD 422 is provided in the registration that indicates adverse effects at the dose of 500 mg/kg bw/d. Taking into consideration the result of this study, the physico-chemical properties of this substance (liquid of very low vapour pressure) and its toxicity profile (skin sensitising), ECHA concludes that the oral route is the most appropriate route of administration and testing should be requested by the oral route.

b) Consideration of the information received during third party consultation

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

The third party has referred to the local irritating/corrosive and sensitising property of the substance and the dermal route not being appropriate from both a scientific and an animal welfare point of view.

ECHA acknowledges that – as specified in the general part of Annexes VII-X – "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided". The test methods for repeated dose toxicity and reproductive toxicity specify that the highest dose level should induce "toxicity but not death or severe suffering". Therefore, it is the Registrant's responsibility to ensure that appropriate dose/exposure levels are used in the requested studies.

ECHA acknowledges that the third party has proposed a read across approach for the Registrant to consider. The third party stated "a testing proposal of a (dermal) 90-day sub-chronic toxicity study to be conducted with the related substance 1,4-bis(2,3-epoxypropoxy)butane may rise the possibility of a read-across approach to fulfil the information requirement for the repeated dose toxicity endpoint".

ECHA notes that it is the Registrant's responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5. Therefore, the Registrant may assess whether he can justify a read-across as suggested by the third party. If the information requirement can be met by way of adaptation, he may include the adaptation argument with all necessary documentation according to Annex XI, Section 1.5. in the registration dossier.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision [1,6-Bis(2,3-epoxypropoxy)hexane]: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408). The proposed dermal sub-chronic toxicity study (90-day) (EU B.28/OECD 411) is rejected as non-compliant pursuant to Article 40(3)(d) of the REACH Regulation.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal

In relation to the proposed tests, the sample of substance used for the new studies 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 joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

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

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

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.