Decision number: TPE-D-2114343019-54-01/F Helsinki, 6 September 2016

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

For 4,4'-Isopropylidenedicyclohexanol, oligomeric reaction products with 1-chloro-2,3-epoxypropane, EC No 500-070-7 (CAS No 30583-72-3), 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 the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for 4,4'-Isopropylidenedicyclohexanol, oligomeric reaction products with 1-chloro-2,3-epoxypropane, EC No 500-070-7 (CAS No 30583-72-3), submitted by [redacted] (Registrant).

- Repeated dose 90-day oral toxicity study in rats according to OECD 408;
- Mammalian bone marrow chromosome aberration Test in rats according to OECD 475;
- Prenatal developmental toxicity study on a first species (rat) according to OECD 414;
- Prenatal developmental toxicity study on a second species (rabbit) according to OECD 414, pending the outcome of the first rat developmental toxicity study; and
- Two-generation reproduction toxicity study in rats according to OECD 416, pending the outcome of the OECD 408 repeated-dose 90-day study.

This decision is based on the registration 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 4 November 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 10 May 2013.

ECHA held a third party consultation for the testing proposals from 2 June 2014 until 17 July 2014. ECHA received information from third parties (see section III below).

On 27 August 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. That draft decision was based on submission number [redacted].

On 1 October 2015 ECHA received comments from the Registrant on the draft decision.

On 1 October 2015 the Registrant updated his registration with submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update.
On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 3 March 2016 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.

Subsequently, proposal(s) for amendment to the draft decision were submitted.

On 8 April 2016 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal for amendment received and amended the draft decision.

On 18 April 2016 ECHA referred the draft decision to the Member State Committee.

By 10 May 2016 the Registrant did not provide comments on the proposal for amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 23 May 2016 in a written procedure launched on 13 May 2016.

ECHA took the decision pursuant to Article 51(6) 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. *In vivo* mammalian bone marrow chromosomal aberration test (Annex IX, Section 8.4, column 2; test method: OECD 475) in rats, oral route;
2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route;
3. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD 408) in rats;

while the originally proposed tests for

1. Prenatal developmental toxicity study on a second species (Annex IX, Section 8.7.2., column 2; test method: EU B.31/OECD 414) in rabbits; and

2. Two-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.35/OECD 416)

are 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 requests in this decision, or to fulfil otherwise the information requirements 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 **13 September 2018** 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. *In vivo* mammalian bone marrow chromosomal aberration test (Annex IX, Section 8.4., column 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.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro mammalian chromosome aberration test performed according to OECD Guideline 473* with the registered substance that show positive results. The positive results indicate that the substance is inducing chromosomal aberrations under the conditions of the test.

An appropriate *in vivo* genotoxicity study to follow up the concern on chromosomal aberrations is not available for the registered substance but shall be proposed by the

Registrant. Consequently, there is an information gap and the Registrant proposed to generate information for this endpoint.
Hence, the Registrant has submitted a testing proposal for an *in vivo* mammalian bone marrow chromosomal aberration test.

The Registrant proposed testing in rats. According to the test method OECD 475 "*Rats, mice and Chinese hamsters are commonly used, although any appropriate mammalian species may be used.*" Therefore, ECHA concludes that testing in rats is appropriate.

b) 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: *In vivo* mammalian bone marrow chromosomal aberration test (test method: OECD 475) in rats, oral route.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) on a first species

a) Examination of the testing proposal

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 rats according to EU B.31/OECD 414.

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

The Registrant proposed testing in rats. He proposed testing 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) 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: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

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

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 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 via the oral route (EU B.26/OECD 408).

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

ECHA considers that the proposed oral route is the most appropriate route of administration having regard to the likely route of human exposure due to the following reasons:
The Registrant states in his comments to the draft decision that no adverse effects with respect to respiratory irritation have been observed and that "*in the originally submitted dossier (and subsequently exported CSR) the drop down menu selection 'adverse effect observed' regarding respiratory irritation was selected in error.*" The CSR and the endpoint summary of section 7.3. of the IUCLID dossier have been corrected accordingly in the submitted update of 1 October 2015 (submission number [redacted]). The updated IUCLID dossier and CSR disclose that the substance is used in spraying applications by workers (PROC 7, industrial spraying and PROC 11, non-industrial spraying) at concentrations below [redacted]%, and the registered substance is not classified as eye or skin irritant. Furthermore, the registered substance is a viscous liquid with a low vapour pressure of 0.00187 Pa at 20°C. In the light of this information, ECHA considers that testing by the oral route is most appropriate.

The Registrant proposed testing in rats. According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

b) 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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD 408).

4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2) on a second species

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

The Registrant has submitted a conditional testing proposal for a pre-natal developmental toxicity study in rabbits as the second species according to OECD 414 (see section 7.8.2. of the IUCLID dossier: "*A second O.E.C.D. 414 study in the rabbit may be conducted pending the outcome of the first rat developmental toxicity study as per REACH Annex IX, Column 2, Section 8.7.2.*").

According to Annex IX, Section 8.7.2., column 2, the decision on the need to perform a pre-natal developmental toxicity study on a second species at this tonnage level "*should be based on the outcome of the first test and all other relevant available data.*" ECHA notes, however, that there is no pre-natal developmental toxicity study on a first species available in the registration dossier.

ECHA therefore considers that the proposed study on a second species cannot be accepted at this stage to fulfil the information requirement of Annex IX, Section 8.7.2., column 2 of the REACH Regulation because no pre-natal developmental toxicity study on a first species

is currently available to evaluate whether performance of a pre-natal developmental toxicity study on a second-species is required at that tonnage level.
b) Outcome

On this basis ECHA concludes that there is at this stage no information gap for the standard information requirement of Annex IX, Section 8.7.2., column 2. Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed test for a pre-natal developmental toxicity study in a second species (OECD 414) is rejected.

5. Two-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

The Registrant has submitted a testing proposal for OECD reproductive toxicity study in rats with the following justification: "*An O.E.C.D. rat reproductive toxicity study is proposed, pending the outcome of the O.E.C.D. 408 repeated-dose 90-day study as per REACH Annex IX, Column 1, Section 8.7.3.*"

According to Annex IX, Section 8.7.3., as amended by Commission Regulation (EU) 2015/282 (entered into force on 13 March 2015), a two-generation reproductive toxicity study is no longer a standard information requirement as it has been replaced by an extended one-generation reproductive toxicity study (B.56/OECD 443).

ECHA notes that the new information requirement under Annex IX, Section 8.7.3. (for the tonnage band of 100-1000 tonnes per year), i.e. the extended one-generation reproductive toxicity study, is only an information requirement, if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity.

However, there is no repeated dose toxicity study available in the registration dossier. ECHA therefore concludes that at this stage there is no information gap for the information requirement of Annex IX, Section 8.7.3.

b) Consideration of the information received during third party consultation

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

A third party has indicated "*that the proposed study is not a standard information requirement pursuant to Annex IX of Regulation (EC) 1907/2006. In terms of animal welfare we therefore highlight the option of a sequential testing strategy which gives priority to the proposed 90-day repeated dose toxicity and in vivo genotoxicity studies. The results will inform the decision on the need of a Two-Generation, or preferably the Extended One-Generation Reproductive Toxicity Study (EOGRTS) according to OECD Test Guideline 443.*"

As already stated above, ECHA notes that according to Annex IX, Section 8.7.3., an extended one-generation reproductive toxicity study is an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity. For the substance subject to the present decision there are no repeated dose

toxicity studies available in the registration dossier that could trigger an extended one-generation reproductive toxicity study.
Therefore, ECHA has rejected the testing proposal for a two-generation reproductive toxicity study.

c) Outcome

ECHA concludes that there is at this stage no information gap for the standard information requirement of Annex IX, Section 8.7.3. Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed test for a two-generation reproduction toxicity study (OECD 416) is rejected.

d) Notes for consideration by the Registrant

The Registrant has proposed to perform a sub-chronic toxicity study (90-day). Once the results from the sub-chronic toxicity study (Section II, 3. above) are available, the Registrant should reconsider the information requirement of Annex IX, Section 8.7.3. If the sub-chronic toxicity study indicates adverse effects on reproductive organs or tissues, or reveals other concerns in relation with reproductive toxicity, a new testing proposal for the present endpoint would – in accordance with the REACH Regulation – have to be submitted, unless compliance with this information requirement is scientifically justified and documented by means of specific or general rules of adaptation.

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. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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[2] by Ofelia Bercaru , Head of Unit, Evaluation, E3

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