

Decision number: TPE-D-2114294430-52-01/F

Helsinki, 26 February 2015

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006**For isopropylcyclohexane, CAS No 696-29-7 (EC No 211-792-4), registration number:** [REDACTED]**Addressee:** [REDACTED]
[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 isopropylcyclohexane, CAS No 696-29-7 (EC No 211-792-4), submitted by [REDACTED] (Registrant).

- 90-day oral toxicity study (OECD 413), inhalation route;
- Developmental toxicity / teratogenicity study (OECD 414).

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 30 October 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.

ECHA received the registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 30 May 2013.

ECHA held a third party consultation for the testing proposals from 18 February 2014 until 4 April 2014. ECHA received information from third parties (see section III below).

On 31 July 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 8 September 2014 the Registrant did not provide any comments on the draft decision to ECHA.

On 30 October 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 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 modified test pursuant to Article 40(3)(b) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, 8.6.2.; test method: OECD 413) in rats, 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.

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

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

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 **6 March 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.

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(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.

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. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, 8.6.2.)

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.

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) via inhalation (OECD 413). The Registrant justified (in IUCLID, 7.1.1) the inhalation route stating the following: "*Due to the vapour pressure of 6 hPa inhalation absorption via vapour can be expected to a certain extend. Wherever aerosolization occurs exposure is possible and due to the lipophilic character, the substance has the potential to be absorbed by micellular solubilisation. An acute toxicity study in rats with inhalation exposure for 4 h revealed slight ataxia, slightly reduced muscle tone and slight dyspnoea immediately until 60 minutes or 3 hours after end of exposure indicating inhalation absorption.*" Taking this and the exposure assessment into account, ECHA considers that exposure of humans via inhalation is likely, and therefore, ECHA considers that the inhalation route is appropriate, as is the oral route. ECHA considers that the Registrant's choice of most-appropriate route is acceptable. Based on the observed toxicity during the range finding study the Registrant shall decide whether an aerosol or vapour study are more appropriate study designs to be performed.

Clear adverse/nephrotoxic effects were observed in a toxicokinetics study (14-day exposure; Henningsen et al. 1998) after oral (gavage) administration. In the toxicokinetic study the effects were observed in male rats. The fact that these effects were only observed in male rats indicates that the registered substance may induce alpha-2u globulinmediated nephropathy. Humans do not excrete alpha-2u globulin and this mode of action is not relevant to humans. However the pathogenic mechanism of toxicity leading to hydrocarbon nephropathy in this case remains to be investigated.

For this reason the Registrant's testing proposal is modified to include urinalysis (which is optional in paragraph 38 of OECD 413, and the relevant part of section 1.6.3. of EU Method B.29) to investigate kidney function, and a full histopathological examination (paragraph 45 of OECD 413, section 1.6.3. of EU Method B.29), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

The Registrant did not specify the species nor the tested substance. According to the test method EU B.26/OECD 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat with the registered substance.

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

b) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision under modified conditions: Sub-chronic toxicity study (90-day) in rats, inhalation route (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.

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

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 with the registered substance. 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 did not specify the route of exposure. 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. The substance is a moderate volatile liquid (6 hPa), poorly soluble in water and the toxicokinetic study (Henningesen et al. 1988) in the dossier performed by gavage showed absorption via this route. The Registrant states: "*Oral exposure ensures a good systemic bioavailability of the substance.*" Therefore, ECHA considers these default parameters appropriate and testing should be performed by the oral route (gavage) with the rat or the rabbit as a first species to be used.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has proposed a read-across approach for ECHA to take into account before further tests on vertebrate animals are required. As part of this approach, the third party provided reference to the disseminated dossiers of two potential read-across substances, 1-isopropyl-4-methylcyclohexane (EC 202-790-4), and reaction mass of cis-4-(isopropyl) cyclohexanemethanol and trans-4-(isopropyl) cyclohexanemethanol (EC 939-719-8). These dossiers contain testing proposals for a 90-day repeated dose toxicity study and the pre-natal study, yet to be performed.

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 should assess whether he can justify a read-across as suggested by the third party. If the adaptation can be justified, he should include the adaptation argument with all necessary documentation in the registration dossier. Such update can only be taken into consideration in the decision-making if it is submitted before the draft decision is sent to the Member State Competent Authorities pursuant to Article 51(1) of the REACH Regulation.

ECHA notes that the information provided by the third party is insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. For example, there is no justification showing that the physico-chemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance. Therefore, the information provided by the third party in itself would not be sufficient to adapt the standard information requirement.

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

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 has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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. 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(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.



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