EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114290609-37-01/F Helsinki, 28 November 2014

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

For 1-isopropyl-4-methylcyclohexane, CAS No 99-82-1 (EC No 202-790-4), 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 1-isopropyl-4-methylcyclohexane, CAS No 99-82-1 (EC No 202-790-4), submitted by [redacted] (Registrant).

- OECD Test Guideline 114 (Viscosity of Liquids);
- OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) in rats, via oral route (gavage). The study would include extensive investigations of the male (including sperm parameters) and female reproductive organs;
- OECD Guideline 414 (Prenatal Developmental Toxicity Study) in rats via oral route (gavage).

This decision is based on the registration dossier as submitted with submission number [redacted] for the tonnage band 100 to 1000 tonnes per year. This decision does not take into account any updates after 4 September 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.

On 11 June 2013, 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 18 February 2014 until 4 April 2014. ECHA did not receive information from third parties.

On 13 June 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.

On 16 July 2014 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Statement of reasons (Section III) whereas no amendments to the Testing required (Section II) were made.

On 4 September 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

The Registrant shall carry out the following proposed/modified tests pursuant to Article 40(3)(a/b) 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. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) 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. It is at the Registrant's discretion to perform the intended additional examinations of the reproductive organs during the testing program;
3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

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.

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 **5 December 2016** an update of the registration dossier containing the information required by this decision. 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.

1. Viscosity (Annex IX, Section 7.17.)

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.

"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 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 OECD Test Guideline 114 (Viscosity of Liquids).

ECHA considers the proposed test appropriate and testing should be performed with the registered substance subject to the present decision.

b) Outcome

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 subject to the present decision: Viscosity of liquids (test method: OECD 114).

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

The Registrant proposed testing by the oral route. In light of the physico-chemical properties of the substance (liquid with low vapour pressure) and the information provided on the uses and human exposure (no uses with spray application), 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 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In the OECD Guideline 422 (28 day) study effects in the kidneys (hyaline droplets and/or casts in the kidney) in all dose groups (LOAEL 111 mg/kg/day) 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-globin-mediated nephropathy. Since humans do not excrete alpha-2u-globin, this mode of action is not relevant to humans. For this reason, ECHA decided to modify the Registrant's testing proposal by including urinalysis (which is optional in paragraph 30 of OECD 408, and the relevant part of Section 1.5.2.2. of EU Method B.26) to investigate kidney function, and a full histopathological examination (paragraph 36 of OECD 408, Section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

In the comments on the draft decision the Registrant has contested the need of performing the requested additional examinations on the mode of action of the registered substance with regard to alpha-2u-globulin mediated nephropathy. The Registrant argues in his comments on the draft decision that similar substances have shown this "mode of action" (e.g. d-limonene).

However, the Registrant failed to provide a rational to justify that the structural similarity leads to a common alpha-2u-globulin mediated nephropathy. Furthermore, the example given, d-limonene, is an unsaturated hydrocarbon while the registered substance is a saturated hydrocarbon. The major metabolite involved in the d-limonene alpha-2u-globulin mediated nephropathy, cis-d-limonene-1,2-oxide, is formed due to the oxidation of the double bound in the molecule's ring. This metabolite cannot be originated from the registered substance. There is no double bound to be oxidised, consequently the epoxide cannot be formed. Therefore the mode of action of the two substances cannot be the same.

The exposure profile of the substance mentioned by the Registrant in the comments to the draft decision is not related to the need of further investigations. The need of performing the additional examination in the OECD 408 were triggered by the findings of the OECD 422 present on the technical dossier of the registerd substance.
ECHA considers that there is the need to unequivocally prove whether effects in the kidneys of male rats, in the requested 90 day study, are due to alpha-2u-globin-mediated nephropathy. If this is not demonstrated, these effects would have to be understood as adverse effects, having an impact in the NOAEL setting.

ECHA considers that performing the immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin would bring clear evidences on the mode of action of the substance.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including additional examinations/parameters, extensive investigations of the male (including sperm parameters) and female reproductive organs. ECHA notes that it is at the Registrant's discretion to perform the intended additional examinations during the testing programme and use the results to ensure the safe use of the substance. However, the Registrant is reminded that the proposed extension of this study is not a standard information requirement in the registration dossier for reproductive toxicity set out in Annex IX, Section 8.7.3. unless the Registrant applies the results from the 90-day study as a valid adaptation according to Annex IX, Section 8.7, column 2.

b) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the modified study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) 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. It is at the Registrant's discretion to perform the intended additional examinations during the testing program.

3. 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 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).

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.

Furthermore, 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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