EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114288849-23-01/F Helsinki, 25 November 2014

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

For 5-methylheptan-3-one, CAS No 541-85-5 (EC No 208-793-7), 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 5-methylheptan-3-one, CAS No 541-85-5 (EC No 208-793-7, submitted by [redacted] (Registrant).

1. Sub-chronic toxicity study, inhalation (OECD 413) in rats, on the registered substance; and
2. Prenatal developmental toxicity study by inhalation (OECD 414) in rats, on the registered substance.

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 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.

ECHA received the registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 21 May 2013.

ECHA held a third party consultation for the testing proposals from 3 March 2014 until 17 April 2014. ECHA did not receive information from third parties.

On 18 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.

By 25 July 2014 the Registrant did not provide any comments on the draft decision to ECHA.

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

A. Tests required pursuant to Article 40(3)

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 method and the registered substance subject to the present decision:

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

The Registrant shall carry out the following modified tests 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:

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.

while the originally proposed test for a Sub-chronic toxicity study, inhalation (OECD 413) in rats 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 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 Authorities of the Member States for enforcement.

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 **2 December 2016** 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.

A. Tests required pursuant to Article 40(3)

1. 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 via inhalation (OECD 413).

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

The Registrant proposed testing by inhalation without giving a justification for the chosen route of administration. In this respect, ECHA notes that there are human data on local effects (nose, eye and throat) provided, from which an IOEL of 10 ppm (53 mg/m3) was derived. The Registrant used this value as the acute DNEL for local effects. ECHA considers therefore that local effects on the respiratory tract are addressed and that due to the availability of human data on local effects in the respiratory tract, a 90-day inhalation study in rats would not add significant contribution for a DNEL for local effects. Furthermore, local irritation might limit maximum exposure concentrations. ECHA also notes that the substance is a liquid with a relatively low vapour pressure (270 Pa at 25°C) and the reported uses do not include spray applications. ECHA therefore concludes that high inhalation exposure is not to be expected (exposure estimates in manufacture, industrial use and formulation are up to 10 mg/m³ (DNEL local effects 53 mg/m³); the Registrant indicated that RMMs are in place; in the product, the substance is used in relatively low concentrations of [redacted] to [redacted]%. From the provided information (abstract of the sub-chronic toxicity study (Salocks et al. 1990)), adverse systemic effects on the nervous system were observed with a NOAEL of 82 mg/kg bw/day (subchronic; rat; target organs: neurologic). Quote from the information provided: "*Histopathological examination of sciatic and tibial nerves from high dose rats showed the following effects: axonal swellings, reduced myelin thickness and Wallerian degeneration. All of these effects are diagnostic of gamma-diketone neuropathy.*" Therefore, ECHA concludes that the substance is systemically available after oral administration and that adverse effects on the nervous system are observed at a relatively low NOAEL.

In light of the physico-chemical properties of the substance, and the information provided on the uses, human exposure, and adverse neurological effects after oral administration, ECHA considers that testing by the oral route is most appropriate.

b) 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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) while the originally proposed test for a Sub-chronic toxicity study, inhalation (OECD 413) in rats proposed to be carried out using the registered substance is rejected.

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

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 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 by inhalation.

ECHA considers that the proposed study is not appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation. The Registrant proposed testing by inhalation. However, as outlined above (see III.A.1) oral exposure is the most appropriate route of administration. In this respect, ECHA emphasises that adverse systemic effects were observed after oral administration in the 13-week repeated-dose toxicity study (Salocks et al. 1990). Furthermore, the Registrant has not provided any evidence which might justify a deviation from the oral route (e.g. no evidence of extensive first-pass metabolism). Therefore, ECHA considers that testing should be conducted by the oral route.

The Registrant proposed testing in rats. 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 rabbit as a first species to be used.

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: 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, 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.

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