ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114320455-57-01/F Helsinki, 07 March 2016

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

For 3-methylbutanone, CAS No 563-80-4 (EC No 209-264-3), 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 proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for 3-methylbutanone, CAS No 563-80-4 (EC No 209-264-3), submitted by [redacted] (Registrant).

- 90-day inhalation toxicity study (OECD 413) in rats, using 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 16 May 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 registration dossier containing the above-mentioned testing proposal for further examination pursuant to Article 40(1) on 1 August 2012.

ECHA held a third party consultation for the testing proposal from 14 August 2014 until 29 September 2014. ECHA received information from third parties (see section III below).

On 10 March 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.

On 13 April 2015 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. On basis of this information, the deadline in Section II was not amended. The Statement of Reasons (Section III) was changed accordingly.

On 29 October 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.

Subsequently, a proposal for amendment to the draft decision was submitted.

On 04 December 2015 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 14 December 2015 ECHA referred the draft decision to the Member State Committee.

By 4 January 2016 the Registrant did not provide any comments on the proposal for amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 18 January 2016 in a written procedure launched on 8 January 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 modified test pursuant to Article 40(3)(b) and 13(4) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

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

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 in this decision, or to fulfil otherwise the information requirement 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 **14 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.

In the draft decision communicated to you the time indicated to provide the requested information was 18 months from the date of adoption of the decision. In your comments on the draft decision of 13 April 2015, you requested an extension of the timeline to 24 months. You sought to justify this request by referring to your experience with the development of immunohistochemical techniques in general and claiming that the immunohistochemical staining for alpha-2u globulin (a2u) is a non-standard exercise for commercial testing laboratories. Also, according to you, the signal intensity for a similar ketone (MiBK) is much lower than a common positive control (such as D-limonene). Thus, an assay method that can separate a true signal from non-specific background is required. Therefore an additional 6 months was requested. However, you have not provided any evidence from testing laboratories confirming the need of the requested additional time.

You also indicated that if purification of the a2u protein and synthesis of a2u antisera are required, then the requested time period would be one year. ECHA notes that antisera/antibodies to a2u protein are commercially available from many suppliers. Thus, there is no evidence that purification of the a2u protein and synthesis of a2u antisera are required. Therefore, ECHA has not extended the deadline of the decision.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance and scientific information submitted by a third party.

Test required pursuant to Article 40(3)

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 inhalation (OECD 413) route.

ECHA considers that the proposed study via inhalation route is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation because the proposed route is the most appropriate route of administration having regard to the likely route of human exposure due to the following reasons: the substance is a liquid with relatively high vapour pressure and the information provided on the uses and human exposure indicate human exposure to vapours. Therefore, ECHA considers that testing by the inhalation route is most appropriate.

In the repeated dose toxicity study via inhalation route (OECD 412) hyaline droplet formation in the proximal renal tubular epithelium in all male groups was observed. The increase in the severity of this finding was statistically significant in the males of the mid- and high-exposure groups. The fact that these effects were only observed in male rats indicates that the registered substance may induce alpha-2u-globulin-mediated nephropathy. Since humans do not excrete alpha-2u-globulin, this mode of action is not relevant to humans. No information is available on whether or not alpha-2u-globulin was present in the hyaline droplets in the kidneys of the exposed males. ECHA therefore decided to modify the Registrant's testing proposal by including the need to perform urinalysis (which is optional in paragraph 38 of OECD 413) to investigate kidney function and a full histopathological examination (paragraph 45 of OECD 413), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin and to determine its relevance to humans.

In your comments on the draft decision, you have proposed a read-across approach to address the alpha-2u globulin (a2u) induction by using data from a similar ketone, Methyl isoButyl Ketone (MiBK) (EC No 203-550-1). According to you, MiBK and 3-Methylbutanone (MiPK) generally share similar toxicological profiles, and their chemical structures differ by only one additional carbon. Also, induction of a2u is considered to be a common phenomenon for many low molecular weight solvents in general ([redacted]).

ECHA notes that no toxicological data and assessment of the similarity of toxicological properties of the analogue and registered substances and how this is linked with assumed similar properties concerning a2u nephropathy has been provided by you. In the absence of these data ECHA considers that your claim is not verified.

Furthermore, ECHA considers that the one carbon difference may be significant for the toxicokinetic and toxicological properties of the substances. You have not addressed why this difference would not affect the potential a2u nephropathy property. In addition to the parent compounds, the possibility of different metabolites should be taken into account as the property may be linked to metabolites.

ECHA considers that you have failed to provide adequate and reliable documentation as required by Annex XI, Section 1.5 of the REACH Regulation. Therefore, ECHA is not in a position to evaluate the proposed read-across approach which could allow it to be established that the relevant properties of the registered substance can be predicted from those of the analogue substance. The proposed read-across has therefore to be rejected as not acceptable. Accordingly, it is necessary to perform testing on the registered substance.

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 a third party is not sufficient to fulfil this information requirement.

Third party information:

A third party has indicated that for an Annex VIII dossier, a sub-chronic toxicity (90-day) study is not a standard information requirement according to Annex VIII of the REACH Regulation and the preconditions which would trigger an inhalation 90-day study are not met.

ECHA notes that the substance is registered for the tonnage band 100 to 1000 tonnes per year (Annex IX dossier). For that tonnage band 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. Therefore, the test proposed by the Registrant is necessary to fulfil the information requirements.

c) 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: 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.

Note for consideration by the Registrant:

ECHA stresses that – as indicated in Section II above – you may under your own responsibility improve the adaptation. In doing so, you should address the deficiencies discussed above. More generally, for a read-across to be acceptable, it must meet the requirements of Annex XI, 1.5, including that there needs to be a clear and robust justification for the proposed approach. Please see the ECHA guidance on Chapter R.6: QSARs and grouping of chemicals (http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf) and practical guide (http://echa.europa.eu/documents/10162/17250/pg_report_readacross_en.pdf).

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 study meets 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 test, the sample of substance used for the new study 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 test 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 study 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 study 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 study 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 Ofelia Bercaru, Head of Unit, Evaluation E3.

[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.