EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114288525-39-01/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 pentan-2-one, CAS No 107-87-9 (EC No 203-528-1), 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 pentan-2-one, CAS No 107-87-9 (EC No 203-528-1), submitted by [redacted] (Registrant).

- Sub-chronic inhalation toxicity study (90-days; OECD 413); and
- Pre-natal developmental toxicity 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 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 9 July 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 received information from third parties (see section III below).

On 30 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 18 July 2014 ECHA received comments from the Registrant on the draft decision.

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

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 of 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. Sub-chronic toxicity study (90-days), inhalation route (Annex IX, Section 8.6.2.; test method: OECD 413) in rats; and

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

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.

1. Sub-chronic toxicity study (90-days)

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 inhalation (OECD 413).

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 inhalation route but did not justify the route selection. In light of the physico-chemical properties of the substance liquid with high vapour pressure (3206 Pa at 20° C) and the information provided on the uses and human exposure *i.e.* uses with spray application, ECHA considers that testing by the inhalation route is most appropriate.

The Registrant did not specify the species to be used for testing. According to the test method OECD 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The Registrant did not provide comments on this endpoint.

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.

<u>Third party information 1 and 2</u>:

Third parties have provided short abstracts and references to two studies conducted with 2-penatanone: [redacted] and A Comparative Chronic Toxicity Study of Methyl n-Propyl Ketone, Methyl n-Butyl Ketone and Hexane. [redacted]

ECHA notes that both of these studies were conducted prior to the introduction of Good Laboratory Practice (GLP) and not conducted according to the current test guidelines. According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA as being appropriate.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2. of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) of the REACH Regulation shall be considered equivalent to data generated by the corresponding test methods referred to in Article 13(3) if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

The information provided by third parties does not address whether these conditions would be met.

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

2. Pre-natal developmental toxicity study

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 did not specify the species to be used for testing. 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 that testing should be performed with the rat or the rabbit as a first species to be used.

The Registrant did not specify the route for testing. Originally ECHA considered that the test should be conducted by the oral route.

In his comments the Registrant agreed that '*the rat is the appropriate species for the study*'. However, the Registrant did not agree with the route of administration and requested that the route of administration is changed to the inhalation route. The Registrant provided the following justification '*For this substance, inhalation is the most relevant route of exposure as the substance is a volatile solvent. Also,* [redacted] *is the Lead Registrant or Co-Registrant for several other substances with similar structures, physical properties and uses, and for all of these, inhalation studies have been conducted or proposed. Thus, an inhalation study would allow for a more relevant analysis of the data in light of the chemical class*'.

ECHA has considered the Registrant's comment. ECHA agrees with the Registrant that inhalation is an appropriate route of exposure. The Registrant argues that inhalation exposure is highly relevant in terms of human exposure (*i.e.* reducing uncertainty in route-to-route extrapolation). Furthermore, ECHA notes that in the available OECD 421 study conducted by the inhalation route the highest dose tested was 5 g/m^3, and this demonstrates that sufficiently high concentrations can be achieved by the inhalation route for adequate evaluation of systemic toxicity.

In addition, the Registrant argues that inhalation studies have been conducted or proposed for other substances with similar structures. ECHA notes that while this is a plausible concern the Registrant has not identified any substances with "similar structures" nor made any claims based on other substances for developmental toxicity in the IUCLID dossier and ECHA cannot evaluate this claim.

Therefore, based on the considerations above, ECHA considers that inhalation is the most appropriate route of administration and has changed the route of administration to inhalation.

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 currently not sufficient to fulfil this information requirement.

Third party information 3:

A third Party has proposed a grouping of substances and 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 a data matrix listing physical chemical properties and results from human health endpoints for two proposed analouge substances (butan-2-one, CAS No. 78-93-3; and hexan-2-one, CAS No. 591-78-6) and the substance subject to the resent decision. The third party proposes to justify the read-across based on '*similar chemical structures, physicochemical properties and toxicity profiles*'.

ECHA has taken the information provided into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. More specifically, the proposed read-across approach is not sufficient to assume that the substance has or has not a particular dangerous property after gestational exposure and that the standard information requirement for a pre-natal developmental toxicity study could be adapted. Firstly, ECHA acknowledges that there is a structural similarity between the proposed analogues and the substance subject to this decision. Secondly, ECHA can not conclude that the substances have '*similar*' physicochemical properties rather that they

follow a regular pattern. Thirdly, with regard to '*similar ... toxicity profiles*'; ECHA notes that the third party has not explained as to how similarity in one toxicological endpoint provides predictive power for another toxicological endpoint. ECHA considers read-across as endpoint specific. Therefore, each adaptation based on read-across is required to have an endpoint specific justification. Finally, both analogue substances have pre-natal developmental toxicity studies available via the inhalation route. Both studies observed developmental effects and have reported NOAECs of 1000 ppm. However, ECHA notes that the NOAECs are based on different developmental effects; '*delayed ossification of interparietal bones and significant increase in the incidence of extra lumbar ribs*' versus '*decrease in the number and weight of live offspring reduced litter size*'. ECHA concludes that the proposed read-across approach did not demonstrate that effects after gestational exposure of the substance subject to the present decision may be predicted from data on the proposed analogue substances.

Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfil Annex XI, Section 1.5. requirements and is therefore not sufficient to allow ECHA to reject the testing proposal. Nevertheless, ECHA acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities.

Third party information 4:

A third party has provided a Reproduction/Developmental Toxicity Screening Test (OECD 421) in the Rat, [redacted]

ECHA notes that this study has been submitted by the Registrant in his techical dossier. Furthermore, ECHA notes that the substance subject the present registration is registered for the tonnage band 100 to 1000 tonnes per annum. For that tonnage band 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. Therefore, the information submitted does not provide a sufficient basis on which to reject the proposed test.

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, inhalation 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.

[redacted]

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