EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114291540-52-01/F Helsinki, 19 December 2014

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

For 2,2-dimethyl-3-oxopropyl dodecanoate, CAS RN 102985-93-3 (EC No 468-880-2), 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 jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for 2,2-dimethyl-3-oxopropyl dodecanoate, CAS RN 102985-93-3 (EC No 468-880-2), submitted by [redacted] (Registrant).

- Viscosity (OECD 114);
- 90-day oral toxicity study in rats, by oral route (OECD 408 - *"will include additional investigation on sexual organs to support the test proposal/strategy. In addition a recovery group will be included in the study"*);
- 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 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.

The examination of the testing proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 02 January 2014.

ECHA held a third party consultation for the testing proposals from 18 February 2014 until 04 April 2014. ECHA received information from third parties (see section III below).

On 23 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 30 July 2014 the Registrant did not provide any comments on the draft decision to ECHA.

On 04 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 tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

A. Tests required pursuant to Article 40(3)

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; 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.; 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 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.

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 January 2017** 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 and scientific information submitted by third parties.

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 an OECD Test Guideline 114 (Viscosity of Liquids) test. ECHA considers the proposed test appropriate and testing should be performed with the registered substance.

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: Viscosity of liquids (test method: OECD 114).

2. Repeated dose toxicity study (Annex IX, Section 8.6.2.)

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 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) with the following justification: *"experimental study planned",* and that *"the study will be available in 2015 or later depending on ECHA decision."* After indicating the test guideline proposed, the Registrant indicated that *"this oral 90-day toxicity study on rats will include additional investigation on sexual organs to support the test proposal/strategy for reproductive toxicity. In addition a recovery group will be included in the study."*

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. After balancing the arguments related to the properties of the substance (liquid with very low vapour pressure, with no apparent

concerns for respiratory tract, expected to be rapidly degraded after oral intake) and the information provided on the uses and human exposure (i.e., 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 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including additional "*investigation on sexual organs to support the test proposal/strategy for reproductive toxicity. In addition a recovery group will be included in the study.*" ECHA notes, that it is at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance. However, the Registrant is reminded that the proposed extension of this study does not fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex X, Section 8.7.3. unless the Registrant applies the results from the 90-day study as a valid adaptation according to Annex X, Section 8.7, column 2.

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 indicated that: "*based on registration data the substance displays a "low toxicity profile". A review on more than 40 low toxicity chemicals has shown that the results of the 28-day study are predictive of low toxicity in the 90-day repeated dose toxicity study. Under these circumstances the proposed test is not expected to add toxicologically meaningful information suggesting that it may be waived in a weight-of-evidence approach.*"

ECHA acknowledges that the third-party has proposed a weight-of-evidence approach for the Registrant to consider before further tests on vertebrate animals are undertaken.

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 1.2. Therefore, the Registrant should assess whether they can justify weight of evidence as suggested by the third party. If the adaptation can be justified, they 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.

However, ECHA notes that the information provided by the third party is insufficient for demonstrating that the conditions of Annex XI, Section 1.2. of the REACH Regulation are met. ECHA observes that the third party has proposed a weight of evidence approach based on a database search applying certain selection criteria. The third party claims that this general weight of evidence approach can be used to predict the sub-chronic toxic properties of a substance based on observed "low toxicity" in a sub-acute (short-term repeated dose) toxicity study if the substance fulfils certain other criteria described as a "low toxicity profile". However, ECHA notes that this predictive weight of evidence approach has shortcomings that prevent its application. First of all, ECHA notes that a weight of evidence approach requires substance-specific justification and cannot be addressed with a generic weight of evidence approach which e.g. does not explain whether it is applicable to the registered substance. Secondly, the proposed approach seems to be not robust with a limited predictive power; it is based on eighteen substances with a "low toxicity profile" including two substances for which the prediction was not correct. Thirdly, ECHA notes that the proposed general weight of evidence approach is not appropriate to conclude that a substance will not have an effect in a sub-chronic toxicity study based on results of a sub-acute toxicity study. The study design of sub-acute toxicity studies and sub-chronic toxicity studies differ in relevant key parameters affecting the uncertainty and relevance of the information obtained from these studies. For example, the reduced number of animals used in a sub-acute toxicity study (5 animals per sex and dose) compared to the sub-chronic toxicity study (10 animals per sex and dose) results in a lower statistical power of the sub-acute toxicity study to detect effects. Similarly, the duration of exposure in a sub-chronic toxicity study (90 days) covers a prolonged period of the animals' lifespan as compared to the sub-acute toxicity study (28 days). As a consequence of these differences in the study protocols, a sub-chronic toxicity study (90-day) may detect effects which were not observed in a sub-acute toxicity study (28 days). Therefore, the information provided by the third party is not sufficient to adapt the standard information requirement.

In addition, the third party has not either demonstrated that any of the other possible adaption arguments have been met, also in relation of low toxicity: the third party has not demonstrated that the substance is unreactive, insoluble and not inhalable and that there is no evidence of absorption, coupled with limited human exposure.

This would require the Registrant to demonstrate, using several independent sources of information, that there is a sufficient weight of evidence leading to the assumption or conclusion that their substance has or not a particular dangerous property, according to the criteria laid down in Annex XI of the REACH Regulation.

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, via oral route (test method: EU B.26/OECD 408).

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 with the following justification: *"No data on developmental toxicity is available. Thus, a new study with the test substance according to OECD 414 is proposed. The substance will be administered orally on rats".*

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/rabbits, 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

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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Leena Ylä-Mononen
Director of Evaluation