ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114328185-52-01/F Helsinki, 13 April 2016

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

For 2-Oxepanone, polymer with 1,6-hexanediol, EC No 609-271-5(CAS No 36609-29-7), 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 2-Oxepanone, polymer with 1,6-hexanediol, EC No 609-271-5 (CAS No 36609-29-7), submitted by [redacted] (Registrant).

- 90-day oral repeated dose toxicity study (OECD 408) in rats, oral route using the analogue substance 2-oxepanone, polymer with 1,4-butanediol (EC no 608-670-1).
- Pre-natal developmental toxicity study (OECD 414) in rats, using the analogue substance 2-oxepanone, polymer with 1,4-butanediol (EC no 608-670-1).

This decision is based on the registration 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 23 November 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 proposals for further examination pursuant to Article 40(1) on 4 September 2014.

ECHA held a third party consultation for the testing proposals from 16 October 2014 until 1 December 2014. ECHA did not receive information from third parties.

On 16 September 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 16 October 2015 ECHA received comments from the Registrant agreeing to ECHA's draft decision.

On 21 January 2016 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 tests pursuant to Article 40(3)(c) 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-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats;

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 tests for a sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) proposed to be carried out using the analogue substance 2-Oxepanone, polymer with 1,4-butanediol (EC no 608-670-1) are 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 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.

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 **20 April 2018** 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

0. Read-across approach

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance proposed to be performed with the analogue substance 2-Oxepanone, polymer with 1,4-butanediol CAS No 31831-53-5 (EC No 608-670-1), on the submitted read-across justification. ECHA has considered first the scientific validity of the read-across hypothesis, before assessing the testing proposed (sections III.1 and III.2).

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*". According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

The following analysis presents the Registrant's justification for the proposed read-across approach and hypothesis, together with ECHA's analysis.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant and information submitted by the Registrant to support the grouping and read-across hypothesis

The Registrant has proposed to cover the standard information requirements for a sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by performing the test with an analogue substance 2-Oxepanone, polymer with 1,4-butanediol CAS No 31831-53-5 (EC no 608-670-1). The Registrant has provided the following justification: "*The two substances are expected to have comparable ecotoxicological and toxicological behavior based on physic-chemical and structural considerations*" and "*The substances are structurally similar in that they both contain 6-hydroxyhexanoic acid repeating units. The linking unit is 1,4-butanediol in 2-oxepanone, polymer with 1,4-butanediol and 1,6-hexanediol in 2-oxepanone, polymer with 1,6 hexane diol. The diols differ by two carbons in the aliphatic chain. The substances are therefore sufficiently similar in terms of structure to support the read-across approach*". To support the read-across approach, the Registrant has provided a read-across justification document "*2-oxepanone, polymer with 1,4-butanediol (Capa 2043) and 2-oxepanone, polymer with 1,6 hexane diol (Capa 2047A)*", in which the physico-chemical and structural considerations and conclusions are presented.

b. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

Based on the information provided, ECHA understands that the read-across hypothesis proposed by the Registrant is based on similar physico-chemical properties and structural similarity of the registered and analogue substance. On this basis, the Registrant expects the substances to have "*comparable ecotoxicological and toxicological behaviour*".

The Registrant has provided substance identity data, including the composition of the substances. ECHA notes that the substances have a common core structure, 6-hydroxyhexanoic acid, and non-common structures, *i.e.* 1,4-butanediol and 1,6-hexanediol which differ by two carbons. Furthermore, ECHA notes that the Registrant has concluded that despite the two carbon difference in the aliphatic chain the substances are sufficiently similar to support the read-across approach. In addition, the analytical data provided supports qualitative similarity in composition between the substances.
The Registrant has provided physico-chemical data for both substances in the read-across justification document. Based on the data provided it can be concluded that the substances have similar physico-chemical properties (melting point, freezing point, LogPow and water solubility).

When applying a read-across approach, the likely toxicokinetics of the substances, including the possibility of different metabolic pathways needs to be considered as part of the approach, where relevant. The Registrant has predicted the metabolism of both substances by using the OECD QSAR Toolbox. ECHA notes that the metabolic profile of the substances is different as in addition to a common metabolite, 6-hydroxyhexanoic acid, non-common metabolites are also formed: 4-hydroxybutanoic acid (gamma-hydroxybutyric acid) and 1,6-hexanediol from the analogue and registered substances, respectively. According to the Registrant, "*additional metabolism may occur through sequential oxidation of the terminal alcohol groups to form the corresponding aldehydes and carboxylic acids*". Furthermore, 4-Hydroxybutanoic acid is predicted to be further metabolized to gamma-aminobutyric acid (GABA), succinic semialdehyde and succinic acid. In the case of 1,6-hexanediol, it is "*likely*" to be metabolized to 6-hydroxyhexanoic acid and adipic acid.

ECHA notes that the proposed metabolic pathways are based on predictions and no experimental data has been provided to support the predicted metabolism. In addition, the Registrant has not addressed other relevant aspects of the differences in the metabolic profiles of the substances, such as the rate and completeness of the metabolism or impact of the parent compounds (e.g. before they are metabolised) and possible impacts of other metabolites on the toxicity profiles of the substances. The Registrant has stated that the toxicity of the analogue substance is likely to be due to the non-common metabolite 4-hydroxybutanoic acid. No information has been provided on the potential toxicity of the 1,6-hexanediol, the non-common metabolite of the registered substance and how the toxicity of 1,6-hexanediol compares with that of 4-hydroxybutanoic acid. Thus, reliable data on the impact of the different metabolic profiles of the substances on their toxicity is missing. Therefore, it is not possible to predict the toxicological properties of the registered substance from the data on the analogue substance.

In the read-across justification document, the Registrant states that "*the two substances are expected to have comparable ecotoxicological and toxicological behavior based on physic-chemical and structural considerations*". The Registrant only substantiates this claim by comparing the physico-chemical properties and structural similarities. In addition, human health toxicity data conducted with the registered substance has not been provided and therefore toxicological profiles of the two substances cannot be compared. In the absence of these data ECHA considers that the Registrant's claim cannot be verified.

c. Conclusion on the read-across approach

ECHA notes that there is no information on the impact of the different metabolic profiles of the substances on their toxicity profiles, and no data on toxicity of the registered substance has been provided. Therefore, ECHA concludes that the Registrant has failed to demonstrate that the properties of the registered substance can be predicted from the data obtained from the analogue substance 2-Oxepanone, polymer with 1,4-butanediol.

Based on the data submitted by the Registrant, ECHA concludes that the Registrant has not provided adequate and reliable information to demonstrate that the read-across approach is plausible for the human health endpoints in consideration.
ECHA therefore concludes that the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by the Registrant, cannot be considered plausible to meet the information requirements.

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) via the oral route (EU B.26/OECD 408) to be performed with the analogue substance 2-oxepanone, polymer with 1,4-butanediol (EC no 608-670-1). ECHA does not consider the read-across approach justified, i.e. the testing proposal not to be compliant with the Annex XI, 1.5. provisions, as explained above in section III.0.

ECHA considers that a sub-chronic toxicity study (90 day) via the oral 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 registered substance is not classified as corrosive/irritating to the skin and/or damaging/irritating to the eyes and in light of the physico-chemical properties of the substance (liquid with low vapour pressure), ECHA considers that testing by the oral route is the most appropriate route of administration.

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.

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).

For the reasons explained above in section III.0, the proposed test for a sub-chronic toxicity (90-day) study (test method OECD 408) to be conducted with the analogue substance 2-oxepanone, polymer with 1,4-butanediol (EC no 608-670-1) is rejected pursuant to Article 40(3)(d) as the provided information on the suggested read-across did not meet the requirements of Annex XI, 1.5. of the REACH Regulation.

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

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 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 in rats according to EU B.31/OECD 414 to be performed with the analogue substance 2-oxepanone, polymer with 1,4-butanediol (EC no 608-670-1). ECHA does not consider the read-across approach justified, i.e. the testing proposal not to be compliant with the Annex XI, 1.5. provisions, as explained above in section III.0.

ECHA considers that a pre-natal developmental toxicity study according to the test method EU B.31/OECD 414, is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

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)(c) of the REACH Regulation, the Registrant is requested to carry out the following 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).

For the reasons explained above in section III.0, the proposed test for a pre-natal developmental toxicity study (test method OECD 414) to be conducted with the analogue substance 2-oxepanone, polymer with 1,4-butanediol (EC no 608-670-1) is rejected pursuant to Article 40(3)(d) as the provided information on the suggested read-across did not meet the requirements of Annex XI, 1.5. of the REACH Regulation.

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.

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation E1

[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.