EUROPEAN CHEMICALS AGENCY

Helsinki, 17 July 2017

Addressee: [redacted]

Decision number: TPE-D-2114366429-38-01/F
Substance name: Tetrahydro-4-methyl-2-(2-methylprop-1-enyl)pyran
EC number: 240-457-5
CAS number: 16409-43-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/03/2017
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is modified and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance, including additional investigations as follows:**
    - **The study protocol shall be modified to include the following additional parameters: additional examinations of male and female reproductive parameters (oestrous cycle, sperm parameters, and reproductive and other certain organs and tissues) that produce respective information as outlined for P parental animals in EU test method B.35, sections 1.5.3., 1.5.4. and 1.5.6. to 1.5.8.**

Your testing proposal is accepted and you are requested to carry out:

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

You 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 to the REACH Regulation.

To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and an adequate and reliable documentation.
You have to submit the requested information in an updated registration dossier by **24 July 2019** . You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

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.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

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.

In your technical dossier you have submitted the following information:

i. A testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26/OECD TG 408.
ii. Key study; Reliability 1 (reliable without restriction); 2012; GLP; according to OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents); Registered substance administered to rats via oral gavage; Doses: 0, 100, 300 and 1000 mg/kg/day; Findings include: "*Histopathology revealed in the left epididymis the presence of immature ducts in the distal corpus and/or cauda epididymis in all mid/ high dose males. Immature ducts increased in severity dose dependently. With increasing severity the immature ducts were accompanied by increasing interstitial edema, which correlated with the significant weight increase found in the high dose group. In only two of five high dose males, additional intraductal granulocytic infiltration was observed in single distended ducts of the cauda with apparent sperm stasis. All of these findings were attributed to treatment and were regarded as adverse.*";
iii. Experimental results; Reliability 4 (not assignable); 1969; non-GLP; non-Guideline (Principle of the test: sub-chronic feeding study in rats; limited documentation); One dose 2.51 or 2.81 mg/kg/day in male and females, respectively.

ECHA notes that the information available on the registered substance does not meet the standard information requirements for Annex IX, Section 8.6.2. because a study conducted according to the OECD TG 407(study ii above) does not generate equivalent information compared to the OECD TG 408; and ECHA considers that the available sub-chronic study is not reliable and does not meet the provisions of Article 13(3) and Annex XI, Section 1.1.2.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration.

The substance is a liquid with low vapour pressure 0.53 hPa at 20° C. The use pattern of the substance includes professional and consumer uses with spray application where available information indicates that human exposure to the registered substance by the inhalation route is likely. However, the available oral sub-acute study on the registered substance indicates a concern for systemic toxicity; *i.e.* adverse effects on the testis that requires further information on repeated dose toxicity by the oral route. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

You proposed testing in rats. According to the test method EU B.26/OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Furthermore, ECHA notes that the Registrant reported in the OECD 407 study that the testis was a target organ for treatment-related adverse effects. ECHA therefore considers that the potential for testicular effects shall be further investigated in the proposed sub-chronic toxicity study (90-days). Additional examinations on reproductive parameters that are normally performed in the two-generation toxicity to reproduction study (test method: EU B.35/OECD 416) can be included into the proposed sub-chronic repeated dose toxicity study (90-days) to investigate this effect. The Registrant shall therefore include the following additional parameters:

- additional examinations of male and female reproductive parameters (oestrous cycle, sperm parameters, and reproductive and other certain organs and tissues) that produce respective information as outlined for P parental animals in EU test method B.35, sections 1.5.3., 1.5.4. and 1.5.6. to 1.5.8.

Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified 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 TG 408). The study protocol shall be modified to include additional clinical pathology and histopathological evaluations (sperm parameters, oestrus cycle), as described above, to further investigate potential effects on reproductive organs.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD TG 414 by the oral route.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with rats. According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

You proposed testing by the oral route.

ECHA agrees that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31/OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6.2.3.2 (December 2016).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 25 May 2013.

ECHA held a third party consultation for the testing proposals from 30 November 2015 until 15 January 2016. ECHA did not receive information from third parties.

This decision does not take into account any updates after **26 May 2017**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

In your comments you agreed to the requests in the draft decision. ECHA took your comments into account and did not amend the requests. However, you highlight that the substance identifiers and substance name used in the draft decision have been changed and updated in the registration dossier, submission, [redacted] on 27 March 2017.

ECHA acknowledges that this registration dossier has completed its adaptation of the substance identifiers as the dossier has been updated with these new identifiers. This has resulted in a change of the EC number from the number 939-429-1 to the number 240-457-5, an inclusion of a CAS number to 16409-43-1 and a change of the substance name from "Reaction mass of (2S-cis)-tetrahydro-4-methyl-2-(2-methyl-1-propenyl)-" to "Tetrahydro-4-methyl-2-(2-methylprop-1-enyl)pyran". ECHA has taken the information concerning the new identifiers, in the updated registration into account, and amended the draft decision in this regard. This change in identifiers does not impact the information requests in this decision. ECHA has not assessed the dossier update for any other changes. The dossier will be assessed in the follow up stage based on the latest update.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your 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.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 or imported by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.