ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2018

Addressee
[redacted]

Decision number TPE-D-2114453827-38-01/F
Substance name: Reaction mass of 3-isopropyl-6-methylenecyclohexene and (4R)-1-methyl-4-(prop-1-en-2-yl)cyclohexene and (4S)-1-methyl-4-(prop-1-en-2-yl)cyclohexene
EC number: 939-009-8
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/07/2017
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 following testing proposal is accepted and you are requested to carry out:

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

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) using the registered substance is rejected, you are requested to perform:

2. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 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 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 ***17 June 2021***. 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 Kevin Pollard, 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.

Appendix 1: Reasons

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

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

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 OECD TG 414.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

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 the rat as a first species. According to the test method 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 the rat or rabbit as a first species.

You did not specify the route for testing. ECHA considers 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 6.0, July 2017) Chapter R.7a, Section 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.

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: 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* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

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

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.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

You proposed testing by the oral route. However, ECHA considers that the inhalation route is the most appropriate route of administration because exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and the possibility of exposure to aerosols of inhalable size as described in Annex IX, Section 8.6.2., column 2 of the REACH Regulation. More specifically, the registered substance is liquid at ambient temperature and formation of vapours can be assumed due to the reported vapour pressure of 144 Pa at ambient temperature.

Furthermore, uses such as spray application (PROC 7 and PROC 11) may generate aerosols of inhalable size, and uses such roller application or brushing (PROC 10) may also impact in the generation of vapours. In addition, there are relevant human inhalation exposures from some of the wide dispersive uses described in the technical dossier and chemical safety report. Thus, inhalation exposure estimates for PROC 7, PROC 11 and PROC 10 are significant even after applying risk management measures, *i.e.* leading to risk characterisation ratios up to [redacted]. In particular, ECHA notes that for exposure scenario 17 you have reported risk characterisation ratios for inhalation exposure that are higher than 1 and thus showing that the risks in those tasks are not controlled. In addition, high concentration ([redacted] or higher) of the registered substance in the mixture used is described for the contributing scenarios within exposure scenarios 12, 13, 17, 18, 20 and 21. ECHA also notes that you described for uses by consumers high concentrations up to [redacted] and [redacted] for the exposure scenario in fragranced products, coatings and inks, respectively.

Furthermore, there might be a potential for local respiratory tract effects following inhalation exposure because the substance is self-classified as Skin Irrit. 2, which raises a concern that needs to be addressed.

In your comments to the draft decision you state that "*the substance is not concerned by all the uses described in the previous version of the CSR.*" More specifically, you state that the "*only two main industrial uses are to be considered: formulation and use as monomer*", and that therefore "no formation of aerosols is anticipated because the substance is not

concerned by PROC generating aerosols (PROC 7, 10 and 11)." Furthermore, you consider "*exposure to vapour is expected to be insignificant*" in the remaining relevant uses of your registered substance considering the operational conditions and used concentrations.

ECHA notes that you have not provided a CSR on behalf of the joint submission members and it is not clear to ECHA if the change in your uses concern also member(s) of your joint submission. The above indicated uses (covering PROC 7, 10 and 11) have been reported by member(s) of your joint submission. Therefore, as the lead registrant of the joint submission for this substance, you are expected to share the relevant requirements and reasoning of the enclosed draft decision with the members of your joint submission. ECHA also expects you to coordinate your response and any testing with them.

You indicated that it is your intention to provide ECHA the updated version of your chemical safety report (CSR) describing the updated and more accurate uses of your substance. However, ECHA did not receive a dossier update by 5 March 2018 and, as indicated in the notification letter of the draft decision, ECHA does not take any dossier updates into account beyond this date during the decision making process for this draft decision. However, the latest dossier update will be taken into account in the follow-up evaluation according to Article 42 of REACH after the deadline of this decision.

Therefore, ECHA considers that a study performed by the inhalation route with the registered substance is most appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In the reproduction/developmental toxicity screening test according to OECD TG 422 present in your registration dossier, adverse effects including increased incidence and severity of cortical hyaline droplet accumulation were observed in the kidneys of male rats and not in female rats. The fact that these effects were only observed in male rats may indicate that the registered substance may induce alpha-2u-globulin-mediated nephropathy, as you also recognised in your registration dossier. ECHA accordingly considers that the kidney is a target organ of the registered substance. Since humans do not excrete alpha-2u-globulin and this mode of action is not relevant to humans, the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment. For these reasons, ECHA considers that urinalysis is required to investigate kidney function (which is optional in paragraph 38 of OECD TG 413). Additionally, a full histopathological examination (paragraph 45 of OECD TG 413), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.
Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD TG 413) including 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, while your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) is rejected according to Article 40(3)(d) of the REACH Regulation.

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on this draft decision, you requested an extension of the timeline to 30 - 33 months. You sought to justify this by stating "[...] *the proposed deadline of 24 months seems to be quite short considering the limitations of the sample and laboratory availabilities Therefore, the inhalation route is not considered as a significant route of exposure and the sub-chronic toxicity study (90-day; OECD TG 408) is proposed to be conducted by oral route instead of inhalation route. A deadline of 30 to 33 months for the update of the dossier with the requested studies would be more appropriate.*"

Upon request from ECHA, you provided documentary evidence from your selected testing laboratory, with indicative timeline of 54 months including pre-study chemistry, preliminary toxicity trails, acute inhalation study, preliminary inhalation study and definitive inhalation study.

Considering the indicative timeline, the decision making step and the current standard timeline which ECHA uses for this endpoint, ECHA has modified the deadline of the decision from the original 24 months to 30 months, from the date of the decision.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 12 July 2017.

ECHA held a third party consultation for the testing proposals from 1 September 2017 until 16 October 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **5 March 2018**, 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.

ECHA took into account your comments and did not amend the requests, but amended the deadline in the decision.

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.