

Helsinki, 22 November 2018

Addressee: [REDACTED]

Decision number: TPE-D-2114449873-37-01/F
Substance name: 4-hydroxy-4-methylpentan-2-one
EC number: 204-626-7
CAS number: 123-42-2
Registration number: [REDACTED]
Submission number: [REDACTED]
Submission date: 22/02/2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

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

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

- 1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
 - **At least two weeks pre-mating exposure duration for the parental (P0) generation;**
 - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
 - **Cohort 1A (Reproductive toxicity);**
 - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.**

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 **30 November 2020**. You also have to update the chemical safety report, where relevant.

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>.

Authorised¹ 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 proposal submitted by you.

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral route to be performed on rat with the registered substance and the basic study design.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). 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.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.

ECHA considers that the proposed study designs requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation.

Premating exposure duration and dose-level setting

You proposed that pre-mating exposure duration for parental (P0) animals should be four weeks and did not provide any further explanation.

According to ECHA Guidance, the starting point for deciding on the length of pre-mating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility. ECHA notes that in this specific case, an extension of Cohort 1B to produce a F2 generation is requested (as outlined below). Hence, 2-week pre-mating exposure duration for P0 animals is sufficient

because the F1 animals of Cohort 1B are mated to produce the F2 generation and, thus, the pre-mating exposure duration will be 10 weeks for these animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals.

Therefore, the requested pre-mating exposure duration is at least 2 weeks and ECHA agrees with your proposed pre-mating exposure duration.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include extension of Cohort 1B referring to the previous ECHA's decision on compliance check issued on 12 June 2014. In 2014, the standard information requirement under Annex X, Section 8.7.3. of the REACH Regulation was a two-generation reproductive toxicity study (OECD TG 416, EU B.35). You considered that the information from the new pre-natal developmental toxicity study (OECD TG 414, 2016) indicates no developmental or other related toxicity. Therefore, you proposed that the information from the mating of Cohort 1B animals to produce a F2 generation is not relevant.

ECHA notes that the uses of the registered substance in the joint submission are leading to significant exposure of consumers and professionals because the registered substance is used by professionals in coating, cleaning products, binders, agrochemical products and polymer processing (PROCs 1, 2, 3, 4, 5, 6, 8a, 8b, 10, 11, 13, 14, 15, 19) and by consumers e.g. in anti-freeze products, biocidal products, polishes, textile dyes, fillers, plasters, modelling clays as well as finger paints.

Furthermore, there are indications for endocrine-disrupting modes of action of the registered substance. Therefore, both the exposure and toxicity conditions of the column 2, Annex X, Section 8.7.3. for triggering an extension of Cohort 1 B to produce a F2 generation are met.

More specifically, in the OECD 422 (1997) study, significant weight increase and histopathological changes in adrenal glands of male and female rats at middle and high dose levels were reported. At the highest dose level, you reported a decreased fertilisation and number of implantations in female rats. No significant maternal toxicity was reported. Similar adverse effects on adrenal glands (increase in organ weight (up to +38%), presence of histopathological changes) were reported in the OECD 408 (2017) study. Furthermore, in the highest dose groups lower mean epidymal sperm counts (-10%) and lower number of oestrus cycles (2.4 vs 3.5 of control) and cycle length (4.7 vs 7.8 days of control) were

observed. ECHA considers these changes are associated with endocrine-disrupting modes of action of the registered substance.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and the registered substance indicates endocrine-disruption modes of action.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed not to include Cohorts 2A and 2B based on the results of the available sub-chronic 90-days study and combined repeated dose toxicity study with the reproduction / developmental toxicity screening test. ECHA agrees that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

You proposed not to include Cohort 3 based on the results of the available sub-chronic 90-days study and combined repeated dose toxicity study with the reproduction / developmental toxicity screening test. ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

Species and route selection

You proposed testing in rats and by oral route. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

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.

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: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);

- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the pre-mating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 22 February 2017.

ECHA held a third party consultation for the testing proposals from 1 September 2016 until 17 October 2016. ECHA did not receive information from third parties.

This decision does not take into account any updates after **4 July 2018**, 30 calendar days after the end of the commenting period.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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.