[If applicable: MSC identifiers]

Helsinki, 10 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453298-41-01/F

Substance name: Octene, hydroformylation products, high-boiling
EC number: 271-237-7
CAS number: 68526-89-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/11/2017
Registered tonnage band: [redacted]

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 accepted and you are requested to carry out:

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:

- **Ten 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); and**
- **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

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 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 you submitted and scientific information submitted by third parties.

Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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.

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 Section 8.7.3., Annex X of the REACH Regulation, whereas column 2 defines when the study design needs to be expanded.

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 the basic design of the extended one-generation reproductive toxicity study according to OECD TG 443 in rats, via oral route, with a 2-week premating exposure duration with the following justification and specification of the study design: "*in the absence of any hints for effects on the immune system or CNS, neither cohorts 2A/2B nor cohort 3 are required*" and "*none of the criteria to extent the study to the F2 generation are met*".

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

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.

After having received your comments on the draft decision, ECHA considers that the proposed study design does not require modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation (see below).

In your comments on the draft decision, you explained why the extension of Cohort 1B and the DNT Cohorts 2A/ 2B are not needed:

- Extension of Cohort 1B: Whereas ECHA maintains its position that the uses of the substance lead to significant exposure of consumers and professionals, ECHA considers that the mild thyroid effects seen in the 28-day and 90-day studies are likely to be secondary to the observed liver effects. ECHA also considers that the 11% and 12% increase in absolute adrenals weight in low and mid dose, respectively, may be attributable to the rather low absolute weight in the controls (51.5 mg versus more than 57 mg in low and mid dose) and it is acknowledged that the weight changes are within the historical control values.

- DNT Cohorts 2A/2B: As outlined above, the thyroid effects are likely to be secondary to the observed liver findings. Furthermore, ECHA agrees that the minimal changes in absolute brain weight (no clear dose dependency, effect not observed in females) are likely to not be treatment related. As shown by the historical control data, the lowest value obtained was basically equal to the mean value of the historical controls (2.091 g vs. 2.089 g, respectively).

Based on your comments, ECHA has removed the requests for extension of Cohort 1B and inclusion of Cohorts 2A/2B.

Premating exposure duration and dose-level setting

You proposed 2 weeks for the premating exposure duration, due to the absence of effects on sperm parameters or estrous cycle in the OECD TG 408 study conducted with the registered substance. ECHA does not agree with your reasoning, and a 10-week premating exposure duration is required.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance[2].

In your comment on the draft decision, you explained that a 2-week premating exposure duration is sufficient referring to the OECD TG 443 and the results of the 90-day study in which no effects on sperm motility, sperm morpholgy, or head count in the cauda epididymis or testis were observed. ECHA notes however, that to ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance[2], the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility. Furthermore, ECHA notes that the sperm parameters measured in the provided 90-day study do not cover all aspects of possible toxicological effects on sperm which might influence fertility parameters. Hence, the premating exposure duration must be 10 weeks.

You proposed that the dose level setting will be based on a range-finding study comparable to the OECD TG 422 and that the available studies were performed up to the limit dose of 1000 mg/kg bw/day. ECHA agrees with your considerations that the dose level setting should be based on an adequate dose-range finding study, such as an OECD TG 422 study.

In this respect, ECHA emphasises that 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.

Species and route selection

You proposed testing by oral route, in rats. ECHA agrees with your proposal. According to the test method OECD TG 443, the rat is the preferred species, and the oral route is the most appropriate route of administration since the substance to be tested is a liquid with low vapour pressure.

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[2] ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. The third party provided considerations of the study design and stated that the basic study design (Cohorts 1A and 1B without extension) "*is considered to be appropriate in the absence of any triggers or conditions necessitating the inclusion of additional cohorts or a further generation*". However, the third party did not provide any scientific data which would fulfil this information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the study with the registered substance, as specified above.

Notes for your consideration

No triggers for the extension of Cohort 1B and inclusion of Cohorts 2A/2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) have been identified. However, you may expand the study by extending Cohort 1B and including Cohorts 2A/2B and 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[2].

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.

Deadline to submit the requested information in this decision

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 the draft decision you requested an extension of the timeline to 36 months due to the need for an initial planning phase, palatability and dose range finding studies. You also provided a corresponding statement from the laboratory. ECHA notes that any palatability or range-finding studies may be initiated at any time, and therefore you do not need to await the adopted decision. Hence, ECHA has only partially granted the request and set the deadline to 30 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 24 November 2017.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 7 June 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **12 September 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 amended the requests and the deadline.

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.