ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 10 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465864-36-01/F
Substance name: Alcohols, C18-22, distn. residues
EC number: 641-136-6
CAS number: 1160164-88-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/07/2017
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(s) 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:**
   - **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);**
   - **Cohort 1B (Reproductive toxicity) with 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 **19 April 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, Hazard Assessment C4

[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.

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

a) Examination of a 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.

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement as laid down in column 1 of Section 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)[2].

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 EOGRTS according to OECD TG 443, basic design, by the oral route (maximum dose level 1000 mg/kg bw/day) in rats with ten-week premating exposure duration to be performed with the registered substance. You have provided the following justifications, according to the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA Guidance[3]:
For extension of Cohort 1B:
"The substances have uses leading to significant exposure of consumers or professionals. […] The substances are not classified as Mutagen Category 1A or 1B or 2. […] The NOEL of the 90-day subchronic study is not more than 3 times lower than that the NOEL from the 28-day sub-acute study. Therefore, there is no indication that the internal dose for the substance or potential metabolites will reach a steady state in the test animals only after an extended exposure. […] There are no indications based on the available study results that endocrine disruption is a relevant mode of action for the substances, additionally no structural alerts exist. Therefore, based on the above considerations, the registrant does not believe that there is a basis for extending cohort 1B to include the F2 generation."

For inclusion of Cohorts 2A/2B:
"previous studies with the substance do not indicate neurotoxic effects; test animals exposure to the substance have not expressed any behavioural changes in the absence of general toxicity; the substance is not known to have any mode of action associated with neurotoxicity such as cholinesterase inhibition and thyroid toxicity; there are no indications that endocrine disruption is a relevant mode of action for the substance; no structural analogues are known to show neurotoxic effects".

For inclusion of Cohort 3:
" the substance has not caused biologically significant changes in haematology/clinical chemistry and/or organ weight associated with immunotoxicity; the substance has not caused significant effects to immunology organs; the substance is not classified as a

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

(respiratory) sensitizer; there are no indications that endocrine disruption is a relevant mode of action for the substance; no structural analogues are known to show immunotoxic effects".

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.

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

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.

Premating exposure duration and dose-level setting

You proposed that premating exposure duration should be ten weeks. ECHA agrees with your proposal. 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[3]. Ten weeks exposure duration is supported also by the lipophilicity of the substance ($\log K_{ow} > 7.17$) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested premating exposure duration is ten weeks.

You proposed "*using, 1000 mg/kg bw/d, as the highest dose level for the study*". 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 a range-finding study (or range finding studies) is performed and that its results 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 Section 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 the extension of Cohort 1B and provided a justification as specified above.

ECHA considers that the criteria to extend the Cohort 1B are met, because:

- The substance has uses leading to significant exposure of consumers and professionals;
- There are indication that the substance will reach a steady state in the test aninmals only after an extended exposure.

In this respect ECHA notes the following:

- According to ECHA Guidance[3], extended time to reach the steady state may be indicated by available toxicokinetic information, physico-chemical properties and information from (eco)toxicological data. ECHA notes that the substance is very poorly water soluble.
- In addition, an octanol-water partition coefficient (log Kow) value above 4.5 indicates (bio)accumulation potential and that the substance is likely to be poorly absorbed. Your claim that "*any hydrolysis of the ester components will create lower molecular weight species which would be more easily absorbed*" has not been substantiated by experimental data and therefore cannot be confirmed.
- Finally, ECHA notes that as no adverse effects were observed in the submitted 28-day and 90-day studies (as well as in the pre-natal developmental toxicity study), for which you provided equal NOELs (1000 mg/kg bw.day), NOAELs or LOAELs could not been established. Hence, based on available data, it is not possible to conclude that there is no need to have a longer exposure time to cause the toxicity, due to accumulation of a substance or its metabolites.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and to produce the F2 generation.

Species and route selection

You proposed testing by oral route in rats. ECHA agrees with your proposal.

b) Consideration of the information received during third party consultation

ECHA received third party information during the third party consultation. For the reasons explained below the information provided is not sufficient to fulfil this information requirement.

The third party provided their considerations of the necessity of the study and stated that the substance is very likely to be poorly absorbed, of very low bioavailability and low toxicity. Furthermore, the third party 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)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance, as specified above.

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 and/or Cohort 3 if 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[3]. 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) 31 July 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 **2 November 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 did not receive any comments by the end of the commenting period.

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.