EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 27 January 2021

Addressees
Registrants of Amphoacetates C8-C18 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
11/12/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C7-C17 odd-numbered, C17-unsatd. alkyl) derivs. and sodium hydroxide and chloroacetic acid
EC number: 931-291-0
CAS number: NS

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***2 November 2023***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Pre-natal developmental toxicity study in a second species (rabbit), oral route, also requested, and specified, at B.1 below (triggered by Annex IX, section 8.7.2);

B. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rabbit), oral route;

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, 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) without extension to mate the Cohort 1B animals to produce the F2 generation.

You must report the study performed according to the above specifications. Any expansions of the study design must be scientifically justified.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII to IX of REACH, if you have

registered a substance at 100-1000 tpa;

- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information they are required to submit to fulfil the information requirements for their registration.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons for the requirements applicable to all the Registrants subject to Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted.

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

A pre-natal developmental toxicity (PNDT) study for a first species is a standard information requirement in Annex IX, Section 8.7.2. to REACH. Column 2 of the same Section provides that the decision on the need to perform a PNDT study on a second species at Annex IX level is based on the outcome of the first test and all other relevant and available data.

The dossier contains a PNDT study in rats. You have identified a need to perform a PNDT study in a second species and submitted a testing proposal for a PNDT study in rabbit according to OECD TG 414.

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. Furthermore, you have not classified the Substance as Repr. 1B based on the results of the pre-natal developmental toxicity study in a first species, and, therefore, a pre-natal developmental toxicity study in a second species cannot be adapted according to the third paragraph of column 2, section 8.7., Annex IX.

ECHA agrees with your consideration that, based on the outcome of the first test and all other relevant available data, there is a need for a PNDT study on a second species already at Annex IX. The cardiovascular/abdomen malformations (all dose groups) and lung findings (low and mid dose) seem treatment related despite no clear dose-response. Such malformations are rare and above historical controls.

ECHA considers that the proposed study fulfils the information requirement.

In your comments to the draft decision you agree to perform the pre-natal developmental toxicity study in rabbit via the oral route.

For the examination of your testing proposal and the reasons for the specification of the study design, see the reasons given in Appendix B.1.

Appendix B: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

This decision is based on the examination of the testing proposals you submitted.

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

Pre-natal developmental toxicity (PNDT) studies on two species is a standard information requirement under Annex X, Section 8.7.2 to REACH.

You have submitted a testing proposal for a PNDT study in a second species (rabbits) according to OECD TG 414 with the Substance.

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 have not classified the Substance as Repr. 1B based on the results of the pre-natal developmental toxicity study in a first species, and, therefore, a pre-natal developmental toxicity study in a second species cannot be adapted according to the third paragraph of column 2, section 8.7., Annex X.

ECHA considers that the proposed study is suitable to fulfil the information requirement.

In your comments to the draft decision you agree to perform the pre-natal developmental toxicity study in rabbit via the oral route.

Species

You proposed testing with the rabbit as a second species. The study in the first species was carried out with rats. The rat or the rabbit is the preferred species under the OECD TG 414[2]. ECHA therefore agrees with your proposal to perform the study with the rabbit as a second species.

Route

You did not specify the administration route for the study.

The oral route is the most appropriate route of administration to investigate reproductive toxicity[5].

Under Article 40(3)(a) of REACH, you are requested to carry out the proposed test with the Substance.

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

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to REACH. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443. You have provided the following justification and specification of the study design according to the criteria described in Column 2 of Section 8.7.3, Annex IX/X: *"As there are no indications that the substance has immunotoxicological or neurotoxicological properties, the basic study set-up is considered adequate."*

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.

The proposed study design requires modification to fulfil the information requirement.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You did not propose premating exposure duration. 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 R.7a.

In order to be compliant and not to be rejected due to too low dose levels, the study must include a highest dose level which must 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. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no existing 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.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

In your comments to the draft decision you agree on performing EOGRTS basic design.

Species and route selection

You did not specify either the route or the species to be tested. ECHA considers that the oral route is the most appropriate route of administration, since the substance to be tested is a liquid, and according to the test method OECD TG 443, the rat is the preferred species.

Outcome

Under Article 40(3)(a) of REACH, you are requested to carry out the proposed test with the Substance.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, 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 the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant

information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annexes IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[3].

In your comments to the draft decision you state that *"that the prenatal study and the EOGRTS are planned sequentially with the prenatal study in the rabbit starting first. If the prenatal study in the rabbit confirms developmental toxicity, then the substance will have to be classified for developmental toxicity. As classification for developmental effects (cat. 1B) is a valid waiver for further testing of developmental toxicity, classification in this category would justify omitting the developmental neurotoxicity cohort element from the EOGRTS design"*.

Classification as Repro 1B for developmental effects on the basis of findings detected in a PNDT study would alleviate the need to include the Cohorts 2A and 2B in the design of the EOGRTS. However, the current request does not include developmental neurotoxicity cohorts (Cohorts 2A and 2B) and therefore there are currently no triggers to include the Cohorts 2A and 2B in the design of the requested EOGRTS. As indicated above, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during conduct of this study. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study.

[3] ECHA Guidance R.7a, Section R.7.6.

Appendix C: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 12 December 2019.

ECHA held a third party consultation for the testing proposals from 23 March 2020 until 7 May 2020. ECHA did not receive information from third parties.

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

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

ECHA took into account your comments and amended the request(s).

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

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 your Member State(s).

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[4].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[6]

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[7]

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.