EUROPEAN CHEMICALS AGENCY

Helsinki, 09 June 2020

Addressees
Registrants of ATMP-H_acid_JS listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
18 February 2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Nitrilotrimethylenetris(phosphonic acid)
EC number: 229-146-5
CAS number: 6419-19-8

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***14 September 2022***.

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, with the Substance or the analogue substance [nitrilotris(methylene)] trisphosphonic acid, sodium salt (EC 243-900-0, CAS 20592-85-2) 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.

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. 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 that they must submit to fulfil the information requirements for their registration.

The Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix C 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. The timeline has been set to allow for sequential testing where relevant.

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.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[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 requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage above 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

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

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) 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.

You have provided a three-generation reproduction study of CP 42902 in rats ([redacted] 1979a).

We have assessed this information and identified the following issue(s):

To be considered compliant and enable concluding if the Substance is a reproductive toxicant, the study has to meet the requirements of OECD TG 443 as specified in REACH. The following key parameter(s) of this test guideline include

- highest dose level should aim to induce some systemic toxicity,
- examination of key parameters for sexual function and fertility,
- examination of key parameters for pre/peri/postnatal developmental toxicity,
- examination of key parameters for endocrine modes of action,
- examination of key parameters for systemic toxicity.

Too low dose level selection
The highest dose level in the provided study did not induce any systemic toxicity and you have not shown that the aim was to induce toxicity. Therefore, the dose level selection was too low, and the study does not fulfil the criterion set in OECD TG 443 and ECHA Guidance R7a.

No examination of key parameters for sexual function and fertility
In the provided study, functional fertility in P0 (parental generation) has not been examined, sperm parameters have not been analysed in P0 generation, oestrus cyclicity has not been investigated in P animals and histopathology of the gonads (P0 and F1 (first offspring generation)) is missing.

No examination of key parameters for pre/peri/postnatal developmental toxicity
In the provided study, prenatal and peri/postnatal developmental toxicity has not been examined as required in OECD TG 443.

No examination of key parameters for endocrine modes of action
In the provided study, investigations of endocrine modes of action, such as oestrous cycle, endocrine (including reproductive) organ weights and histopathology, anogenital distance, nipple retention, sexual maturation (vaginal opening and preputial separation, time from vaginal opening to first oestrous cycle) and thyroid hormone measurements have not been performed as required in OECD TG 443.

No examination of key parameters for systemic toxicity
In the provided study, investigations for full clinical chemistry (P0 and F1), full haematology (P0 and F1) and full histopathology of organs and tissues (P0 and F1) have not been performed as required in OECD TG 443.

Based on the above, the information you provided does not fulfil the information requirement.

In your comments to the draft decision you acknowledge that the provided study does not meet the requirements of OECD TG 443 and agree to conduct the EOGRT study according to OECD TG 443.

However, in your comments you consider that there are scientifically justifiable and animal welfare reasons why carrying out the study is not necessary for both the Substance and the corresponding sodium salt. You propose to test only one of the substances and use read-across between the Substance (acid form) and the sodium salt form in order to minimise further testing.

ECHA has noted a similar data gap in its compliance check for [nitrilotris(methylene)] trisphosphonic acid, sodium salt (EC 243-900-0, CAS 20592-85-2) and considers that an EOGRT study according to OECD TG 443 is needed to fill that data gap.

ECHA accepts that the sodium salt of Nitrilotrimethylenetris(phosphonic acid) dissociates into phosphonic acid and a metal counter-ion (sodium), and that information obtained on the acid or salt (source substance) can be used to predict properties of the other form (target substance). Therefore, ECHA considers that the testing of one substance and subsequent read-across to the other substance will be sufficient to address the information requirement of an EOGRT study under Annex X, section 8.7.3 of REACH.

Therefore, the EOGRT study according to the test method OECD TG 443 shall be performed with either the Substance or the analogue substance [nitrilotris(methylene)] trisphosphonic acid, sodium salt (EC 243-900-0, CAS 20592-85-2).

If the study is performed on the analogue substance your registration dossier must contain a read-across justification in line with the considerations set out above and in your comments to the draft decision.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility. Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[1]

In order to be compliant and not to be rejected due to too low dose levels, 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. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above. If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

Cohorts 1A and 1B

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

Species and route selection

The study must be performed in rats with oral[2] administration under OECD TG 443.

In your comments you ask ECHA to confirm which method of oral administration is most appropriate.

The route of oral administration should be chosen according to OECD TG 443, depending on the characteristics of the compound.

Accordingly, it is for the laboratory contracted by you for testing the substance to determine and justify the most appropriate method of oral administration of the substance on the basis of the characteristics of 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 the 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., Annex 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].

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[3] ECHA Guidance R.7a, Section R.7.6.

Appendix B: Procedural history

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.

The compliance check was initiated on 29 March 2019.

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 within 30 days of the notification.

ECHA took into account your comments and amended the request.

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 C: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further 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 the Member States.

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 shall 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 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]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

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]

Physical-chemical properties
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.

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[8]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[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
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

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

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.