~~Confidential~~

Helsinki, 27 November 2020

Addressees
Registrants of HMDTMP (4-7Na) listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
29 March 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Sodium salts of [hexane-1,6-diylbis[nitrilobis(methylene)]]-tetrakisphosphonic acid (4-7 Na:1)
EC number: 947-369-2
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 ***3 June 2021***.

The requested information must be generated using the analogue substance: Potassium salts of [hexane-1,6-diylbis[nitrilobis(methylene)]]tetrakisphosphonic acid (4-7:1); EC number: 701-184-1.

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

1. Sub-chronic toxicity study (90-day), oral route (Annex VIII, Section 8.6.1, Column 2; test method OECD TG 408) in rats;

2. Pre-natal developmental toxicity study (Annex VIII, Section 8.7.1, Column 2; test method OECD TG 414) in rats, oral route.

Conditions to comply with the requests

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 Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

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.

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 on general considerations

Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

You propose to provide information on the standard information requirements of the Substance on

- Short-term repeated dose toxicity study (28 day) (Annex VIII, Section 8.6.1) and
- Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1),

by adapting according to Column 2 provisions in Annex VIII, and by grouping and read-across under Annex XI, Section 1.5, from information on the analogue substance Potassium salts of [hexane-1,6-diylbis[nitrilobis(methylene)]]tetrakisphosphonic acid (4-7:1), EC number: 701-184-1 on

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2), and
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2).

Annex XI, Section 1.5 specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category (addressed under 'Scope of the grouping'). Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3,4].

Scope of the grouping of substances

You have formed a group (category) of 'HMDTMP'. You identify the members of the HMDTMP category in the read-across documentation provided in Section 1.4.1 of the CSR.

You provide the following reasoning for grouping the substances in HMDTMP category: "*The category hypothesis is that all the members are various ionised forms of the same parent acid.*"

You define the structural basis for the grouping as all sodium and potassium salts of [hexane-1,6-diylbis-[nitrilobis(methylene)]tetrakisphosphonic acid.

A. ECHA's analysis of the grouping

According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.4.1, (version 1.0, May 2008) a category hypothesis should address "*the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint. These rules, can be described as the applicability domain for an endpoint and provide a means of extending the category membership to chemicals not explicitly included in the current definition of a category.*"

[2] ECHA Guidance R.6
[3] RAAF, March 2017
[4] RAAF UVCB, March 2017

Furthermore, according to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.1.2, (version 1.0, May 2008) "*a category evaluation does not necessarily result in all the individual substances included in the category evaluation being registered to the Agency, although the data from these substances will be included in the category report in support of the registration.*"

Based on your description of the structural basis of your grouping/category approach, ECHA understands that the category members are all sodium and potassium salts of HMDTMP acid and the acid itself.

ECHA considers your category as well defined with clear inclusion/exclusion criteria for category membership.

ECHA assessed your proposed predictions on this basis.

Prediction for toxicological properties

B. Your category hypothesis and information you provided

You have provided the following reasoning for the prediction of toxicological properties: The members of the HMDTMP category are various ionised forms of the HMDTMP acid (CAS No. 23605-74-5). In aqueous conditions of defined pH a salt will behave no differently to the parent acid, at identical concentration of the particular speciated form present and will be fully dissociated. A similar situation arises *in vivo* for systemic toxicity studies, where the local pH and ionic conditions within the stomach, GI tract etc. dominates the speciation of the phosphonate, irrespective of the form originally dosed. In the present context, the effect of the alkaline metal counter-ion (sodium or potassium) will not be significant in respect of the properties under consideration.

C. ECHA's analysis of your predictions in light of the requirements of Annex XI, Section 1.5.

ECHA understands that you base your hypothesis on the fact that the category members will convert into the same HMDTMP anion at physiological conditions, and as a result all substances will have the same toxicological properties. ECHA considers this a reasonable assumption and that it is substantiated by sufficient evidence and accepts that predictions can be made between the category members for systemic toxicity.

Conclusions on the grouping of substances and read-across approach

As explained above, you have established that relevant properties of the Substance can be predicted from data on the analogue substance. ECHA agrees with your read-across hypothesis. However, we emphasise that any final determination on the validity of your read-across adaptation will only be possible when the information on requested studies will be available in the dossier.

Appendix A: Reasons for the requirements applicable to all the Registrants subject to Annex VIII of REACH

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

1. Sub-chronic toxicity study (90-day)

Examination of the testing proposal

A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1).

The short-term toxicity study (28 days) does not need to be conducted, if a reliable sub-chronic (90 days) or chronic toxicity study is available, provided that an appropriate species, dosage, solvent and route of administration were used (Annex VIII, Section 8.6.1, column 2).

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route, according to OECD TG 408 with the analogue substance: Potassium salts of [hexane-1,6-diylbis[nitrilobis(methylene)]]tetrakisphosphonic acid (4-7:1); EC number: 701-184-1 (hereinafter HMDTMP-(4-7)K).

ECHA notes that there is a data gap for this endpoint.

As explained in the Appendix on general considerations, ECHA considers that a study performed with the analogue substance HMDTMP-(4-7)K would be adequate for predicting the properties of the Substance.

In a decision dated 23 November 2018 (decision number TPE-D-2114449802-46-01/F) ECHA requested submission of the information on the OECD TG 408 study for the analogue substance HMDTMP-(4-7)K by 30 November 2020.

With a view to ensuring that generation of information is tailored to real information needs, and to prevent unnecessary testing of vertebrate animals, ECHA agrees with your testing strategy, as far as the following is given.

Study design

The ongoing study on the analogue substance HMDTMP-(4-7)K is performed in rats by the oral route. According to OECD TG 408, the rat is the preferred species and the most appropriate route of administration is the oral route (ECHA Guidance R.7a, Section R.7.5.4.3).

Your testing proposal is accepted under Article 40(3)(a) and you are required to provide the data generated on the analogue substance.

Since the proposed read-across approach has been accepted, and no additional vertebrate animal testing should be required, ECHA considers that 6 months from the date of the final decision provide sufficient time to submit the requested information.

2. Pre-natal developmental toxicity study

Examination of the testing proposal

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or in vitro methods that the

Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

The study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) is already available (Annex VIII, Section 8.7, Column 2, first paragraph, fourth indent).

You have submitted a testing proposal for a PNDT study, in the rat, by the oral route, according to OECD TG 414 with the analogue substance HMDTMP-(4-7)K.

ECHA notes that there is a data gap for this endpoint.

As explained in the Appendix on general considerations, ECHA considers that a study performed with the analogue substance HMDTMP-(4-7)K would be adequate for predicting the properties of the Substance.

In a decision dated 23 November 2018 (decision number TPE-D-2114449802-46-01/F) ECHA requested submission of the information on the OECD TG 414 study with HMDTMP-(4-7)K by 30 November 2020.

With a view to ensuring that generation of information is tailored to real information needs, and to prevent unnecessary testing of vertebrate animals, ECHA agrees with your testing strategy, as far as the following is given.

Study design

The ongoing study on the analogue substance HMDTMP-(4-7)K is performed on rats. Under OECD TG 414 the rat or the rabbit are the preferred species (ECHA Guidance R.7a, Section R.7.6.2.3.2).

The ongoing study on the analogue substance HMDTMP-(4-7)K is performed by the oral route which is the most appropriate route of administration to investigate reproductive toxicity (ECHA Guidance R.7a, Section R.7.6.2.3.2).

Your testing proposal is accepted under Article 40(3)(a) and you are required to provide the data generated on the analogue substance.

Since the proposed read-across approach has been accepted, and no additional vertebrate animal testing should be required, ECHA considers that 6 months from the date of the final decision provide sufficient time to submit the requested information.

Appendix B: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 19 December 2019.

ECHA held a third party consultation for the testing proposals from 27 January 2020 until 12 March 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 did not receive any comments within the notification period.

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 testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registration 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'[5].

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"[6].

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

5. List of references of the ECHA Guidance and other guidance/ reference documents[7]

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)[8]

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.

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

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 fulfilled
[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.