Helsinki, 23 November 2018

Addressee
[redacted]

Decision number: TPE-D-2114449802-46-01/F
Substance name: Potassium salts of [hexane-1,6-diylbis[nitrilobis(methylene)]]tetrakisphosphonic acid (4-7:1)
EC number: 701-184-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11 January 2018
Registered tonnage band: 100-1000

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 proposals are accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the registered substance.**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

While your originally proposed test for Long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4.1., column 2; test method: Earthworm reproduction test, OECD TG 222) using the analogue substance ATMP xNa/ [nitrilotris(methylene)]trisphosphonic acid, sodium salt (CAS 20592-85-2; EC 243-900-0) is rejected, you are requested to perform:

3. **Long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4.1., column 2; test method: Earthworm reproduction test, OECD TG 222) using the registered substance.**

You are additionally requested to perform:

4. **Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD TG 216) using the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **30 November 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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 submitted by you.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. 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 a sub-chronic toxicity study (90 day) by the oral route according to OECD TG 408 with the registered substance, "*only in the event that no read-across from existing available reliable studies is possible*."

ECHA requested your considerations for alternative methods to fulfil the information requirement for sub-chronic toxicity (90-day): oral. 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.

ECHA notes that you stated, that the registered substance is a member of a category and that "*within this group there are some existing studies available for the sub-chronic oral repeated dose toxicity endpoint*". You referred to a data matrix attached to section 13 of the technical dossier and concluded that "*... it may be the case that an appropriate read-across of a specific existing reliable study within this analogue group is sufficiently well justified, or that a weight-of-evidence approach is shown to be appropriate based on read-across data across the group. In this situation, the Registrant will update the dossier without delay to include such read-across data with justification to support the read-across,and the testing proposed herein will then no longer be required.*"

Whilst the data matrix provided in the technical dossier lists repeated dose toxicity studies conducted with substances included in the grouping approach developed for other endpoints, ECHA observes that you did not identify an appropriate source study, you did not provide a read-across or weight of evidence justification for the property sub-chronic toxicity (90-day), and there are no data on the registered substance which would allow comparison of toxicity profiles for repeated dose toxicity. As no update has been submitted by you "*without delay*" or since the latest submission mentioned above, ECHA understands that you have not been able to find a justifcation to support read-across. ECHA therefore concludes that there is no valid adaptation available for this endpoint in your dossier and that you propose testing with the registered substance.

You proposed testing by the oral route. The registered substance is a solid manufactured in an aqueous solution of very low vapour pressure. Uses with industrial and professional spray application are reported in the chemical safety report. However, the reported concentrations are low (<[redacted]%). Therefore, ECHA considers that the proposed study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You did not specify the species to be used for testing. According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Whilst no read-across adaptation was included in the dossier submission subject to this decision for this information requirement, ECHA observes that you have expressed in your comments to the draft decision intentions and plans to develop such an adaptation. According to the information provided in your comments, the hypothesis of this new read-across approach is based on the "*nutrient complexation, adsorption and therefore chemical behaviour dominate the effects in some tests, and that the structural differences may impact on the toxicological or exotoxicological profiles of the phosphonates under consideration when reviewed in terms of impact on complexation and adsorption behaviour*".

You intend to further refine and strengthen this read-across approach by investigating and elaborating in a step-wise manner on the following aspects:

1. Discussion of aminoethylene and bis phosphonates structural similarities and differences: you propose to provide a review report on the registered phosphonates. You claim that for phosphonates the driving behaviour is complexation and binding to metals and minerals. You provide data on complexations strength for phosphonates in a table.

2. Discussion of metal complexation and adsorption: you propose to provide *in vitro* studies on metal complexation since you consider that "*complexation determines the toxicological properties of these substances*". You state that such studies are difficult to conduct and provide a laboratory statement in this regard.

3. Discussion of toxicological data: you have summarised available data for some phosphonates in a draft data matrix. You claim that there is no evidence of adverse effects except for those on blood and bone. You provide a draft report on the "*biochemistry of iron uptake and transport in the mammalian body: factors relevant to the toxicology of a series of phosphonates complexing agents*".

4. Discussion of ecotoxicological data and Kd soil values (see under request section 3.)

5. Timeline and summary: You provide a timeline of activities to validate the read-across proposal and develop additional studies. Part of the timeline proposes interactions with ECHA. In summary you propose the step-wise strategy presented below, anticipating that completion of this strategy would require 27 months.

1) Identify whether further long-term toxicity data is required, and if so identify the substance with which to conduct further testing;
2) Conduct an OECD TG 414 study with one substance, and compare the results to the existing available data on phosphonates;
3) Conduct an OECD TG 408;
4) Determine whether additional studies are required, based on the results of new studies.
5) In parallel to 2 above, you propose to identify the most representative substances in the organophosphonate complexing agent group with which to conduct OECD TG 222 and OECD TG 216 studies.

Furthermore, you refer in your comments to the ongoing testing proposal examination for similar endpoints on the analogue substance [[(phosphonomethyl)imino]bis-

[hexamethylenenitrilobis(methylene)]]-tetrakisphosphonic acid (BMHT-H) (EC No 252-156-6; CAs No 34690-00-1). You consider that for both BMHT-H and HMDTMP (4-7K), i.e. the substance subject to this decision, that the "*dominance of the extremely strong complexation properties of this substance (BMHT-H), as with the other organophosphonate complexing agents, means that any toxicity would originate with complexation with metal ions either in the gut or systemically. Toxicity tests on the other organophosphonate complexing agents support this assumption. Therefore, conducting new toxicity tests to investigate the toxicity of another strongly complexing substance would not be a good use of laboratory animals*".

ECHA acknowledges your intentions. However, since the outcome of these investigations is unknown, ECHA considers that no conclusion can be drawn on whether this new read-across approach as referred to in your comments will comply with the requirements of Annex XI, Section 1.5 of the REACH Regulation.

Nevertheless, ECHA has evaluated the information provided in your comments and in the documents attached to your comments and makes the following preliminary observations:

1. Discussion of aminoethylene and bis phosphonates structural similarities and differences: Currently your claim that the driving behaviour for the toxicity of phosphonates is complexation and binding to metals and minerals is lacking supporting data and you want to develop such data in further *in vitro* studies. ECHA notes that currently a well-founded hypothesis is not available explaining how and why a grouping and read-across approach is justified for the information requirements under evaluation.

   You have provided tables with proposed category members and their structures. According to your comments, the common feature shared by all category members appears to be the complexation property of the substances. ECHA notes that the proposed group members exhibit clear structural differences, with some members not having amine functions in their structure or including cyclic chains. Based on the information provided, the grouping of substances does not define unambiguously the applicability domain of this category. Information on the applicability domain is necessary to outline possible structural differences among the category members and constitutes a set of inclusion and exclusion rules establishing the molecular structure(s) that a substance must have to be part of the category and describing the accepted structural differences within the category. You have not defined these inclusion and exclusion criteria, such as branching, number of phosphonate groups, number of nitrogens in the structure, or chain lengths connecting the functional groups. According to ECHA Guidance on information requirements and chemical safety assessment (version 1, May 2008), Chapter R.6, such criteria should be described in order to identify the range of values within which reliable estimations can be made for the members of the category and to define the borders of the category.

   You indicated in your comments that you anticipate that "structural differences may impact on the toxicological and ecotoxicological profiles of the phosphonates under consideration". In this context, if the category approach is further developed, it is particularly important to ensure that the data density across the group of substances allows for a determination of such impact. The data used in a data matrix to support a group-approach must be adequate and reliable (see RAAF[2]).

[2] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

2. Discussion of metal complexation and adsorption: ECHA notes that the proposed *in vitro* studies may be helpful to identify intrinsic properties of the substances with regard to metal complexation and useful to explain mechanistically adverse effects observed in *in vivo* studies. However, the adverse effects caused by such mechanism have to be quantified, in order to define a reliable DNEL for risk management. It cannot be assumed that observed *in vivo* effects of the substances are solely described by complexation data, but the toxicokinetic properties of the substances determining the uptake, distribution and excretion will have a high impact. Furthermore, other mechanisms of toxicity may be acting.

3. Discussion of toxicological data: ECHA notes that only one study of the presented information on repeated dose toxicity is available in the dossier and therefore the other information cannot be assessed by ECHA with regard to adequacy and reliability. The information in the table generally does not allow to conclude on the value of the presented information. At face value, the results in the data matrix for repeated dose toxicity appear to provide evidence of differences in the level of toxicity and do not support a claim of similar toxicity or of a regular pattern. The results appear to stretch from "issue with osteosarcoma" over a "NOAEL of about 82.5 – 92.3 mg/kg bw" to "no effects" for the substances listed in the matrix. In your comments you mention that there is a one-generation reproductive toxicity study available for the free acid form of the registered substance. ECHA points out that the presence of such study type is not a valid adaptation for the conduct of a repeated dose toxicity study according to OECD TG 408 or a pre-natal developmental toxicity study according to OECD TG 414. You do not identify, what source study with which results you actually want to use for your read-across approach.

   ECHA also stresses that the information provided in the report on "the biochemistry of iron uptake..." elaborates on the physiological processes involving iron and does not contain toxicity data. It provides very limited insights on the actual consequences of interferences and disruptions of the physiological processes caused by exposure to phosphonates and only reports on the modification of iron toxicokinetic properties after administration of ATMP.

4. Discussion of ecotoxicological data and Kd soil values: see under request section 3.

5. Timeline: ECHA notes that currently the dossier is not in compliance with the REACH standard information requirements discussed in this decision. ECHA observes that based on the observations made above a valid adaptation according to the appropriate provisions of Column 2 of the REACH Annexes or according to Annex XI is currently not available.

ECHA notes that your strategy includes a proposed interaction with ECHA. ECHA considers that Articles 50 and 51 of the REACH Regulation provide sufficient opportunities for commenting and interactions with registrants. However, if you decide to rely on the adaptation described in your comments, ECHA will check the information provided in accordance with Article 42(1) of the REACH Regulation to determine whether the above mentioned shortcomings are addressed. If, after the check of the information provided, ECHA considers that the information is non-compliant ECHA will inform the respective Member State competent authority (MSCA) and National enforcement authority (NEA) of this.[3] They may consider enforcement actions to secure the implementation of the present decision and exercise the powers reserved to them under Article 126 of Regulation No

[3] Only the final decision will be sent to the National enforcement authority so they can consider enforcement actions.

1907/2006 (penalties for non-compliance) for the period during which the registration dossier was not compliant[4].

In summary, ECHA therefore considers that in your comments you did not provide an appropriate source study, you did not provide a valid read-across approach or weight of evidence justification for the property sub-chronic toxicity (90-day), and there are no data on the registered substance which would allow comparison of toxicity profiles for repeated dose toxicity.

The requests in the decision were accordingly not amended on the basis of your comments.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408).

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

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. 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 a pre-natal developmental toxicity study according to OECD TG 414 with the registered substance, *"only in the event that no read-across from existing available reliable studies is possible."*

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). 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.

ECHA notes that you stated, that your registered substance is a member of a category and that "*within this group there are some existing studies available for the sub-chronic oral repeated dose toxicity endpoint*". You referred to a data matrix attached to section 13 of the technical dossier and concluded that "*... it may be the case that an appropriate read-across of a specific existing reliable study within this analogue group is sufficiently well justified, or that a weight-of-evidence approach is shown to be appropriate based on read-across data across the group. In this situation, the Registrant will update the dossier without delay to include such read-across data with justification to support the read-across,and the testing proposed herein will then no longer be required.*"

Whilst the data matrix provided in the technical dossier lists multiple pre-natal developmental toxicity studies conducted with substances included in the grouping approach developed for other endpoints, ECHA observes that you did not identify an appropriate source study, you did not provide a read-across or weight of evidence justification for the property pre-natal developmental toxicity, and there are no data on the registered

[4] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA

substance which would allow comparison of toxicity profiles for pre-natal developmental toxicity. As no update has been submitted by you "*without delay*" or since the latest submission mentioned above, ECHA understands that you have not been able to find a jusitifcation to to support read-across. ECHA therefore concludes that there is no valid adaptation available in your dossier for this endpoint and that you propose testing with the registered substance.

In IUCLID section 7.8.2 there is a developmental toxicity study conducted with ATMP-H/ [nitrilotris(methylene)]tris(phosphonic acid) / 6419-19-8 / 229-146-5, 22.4 % active acid in water ([redacted] 1979). The guideline is indicated as "other: FDA guidelines for reproductive studies for evaluation of drugs for human use, segment II teratology", GLP was not followed. In the absence of any justification why and how the study results contribute to the assessment of the pre-natal developmental toxicity of the registered substance, ECHA considers the study results as not relevant for the evaluation of this testing proposal.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You did not specify the species to be used for testing. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You did not specify the route for testing. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid manufactured in an aqueous solution , ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

3. Long-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1., column 2)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annex IX, Section 9.4. of the REACH Regulation. The Registrant must address the standard information requirements set out in Annex IX, Section 9.4., for different taxonomic groups: short-term toxicity testing on invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity testing on plants (Annex IX,

Section 9.4.3.). Furthermore, Annex IX, Section 9.4., column 2 specifies that long-term toxicity testing shall be considered by the Registrant instead of short-term, in particular for substances that have a high potential to adsorb to soil or that are very persistent.

The information on "long-term toxicity to invertebrates" 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 a long-term toxicity test to invertebrates (Earthworm Reproduction Test (*Eisenia fetida/Eisenia andrei*), OECD TG 222) with the following justification: "*According to the soil hazard category 3 approach for screening assessment, the PNECsoil has been calculated from PNECfreshwater on the basis of the equilibrium partitioning method and a confirmatory long term toxicity to terrestrial organisms has been proposed for the HMDTMP category:*
The risk characterisation ratio (RCR) based on PNECsoil derived from the equilibrium partitioning method is <1.
The long term terrestrial toxicity study proposed is the earthworm reproductive toxicity test (OECD TG 222) because the aquatic data indicate that vertebrate and invertebrate studies are relatively comparable, while algal data is not used in the hazard assessment.
The study is proposed to conducted with the analogous substance ATMP sodium salt, a neutralised form of ATMP, and read-across to the HMDTMP category members in terms of active acid content. Both substances are aminomethylenephosphonic acids, see Sections 7.0 and 1.4 of the CSR for read-across justifications and category hypothesis."

According to Section R.7.11.5.3., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), substances that are ionisable or have a log K_{ow}/K_{oc} >5 are considered highly adsorptive, whereas substances with a half-life >180 days are considered very persistent in soil. According to you, the substance has a high potential to adsorb to soil (ionisable substance, logK_{oc} of approximately 5). Therefore ECHA agrees that a need for long-term testing is indicated and the proposed test is appropriate to fulfil the information requirement of Annex IX, Section 9.4.1., column 2.

Furthermore, based upon the available aquatic toxicity information and the physico-chemical properties of the substance, and in relation to Section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), ECHA considers that the substance would fall into soil hazard category 3. In the context of an integrated testing strategy for soil toxicity, the Guidance advocates performing an initial screening assessment based upon the Equilibrium Partitioning Method (EPM), together with a confirmatory long-term soil toxicity test. The PNECscreen is calculated through EPM on the basis of aquatic toxicity data only. ECHA notes that the strategy pursued by you is based on this approach.

In your testing proposal you have proposed testing on an analogue substance and thus sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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. 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 (read-across approach). ECHA considers that the

generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[5]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[6]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance HMDTMP-xK, Potassium salts of {hexane-1,6-diylbis[nitrilobis-(methylene)]}tetrakisphosphonic acid (4-7:1) (CAS 38820-59-6; EC 254-135-7) using data of a structurally similar substance ATMP xNa/ [nitrilotris(methylene)]-trisphosphonic acid, sodium salt (EC) (CAS 20592-85-2; EC 243-900-0) (hereafter the 'source substance').

You have provided a read-across documentation as a separate attachment to the testing proposal to justify the prediction. Furthermore you have provided a general description of the grouping for Aminomethylenephosphonates structural analogues in the CSR section 1.4.2.

[5] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.
[6] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

In the read-across documentation of the CSR you define the applicability domain of the aminomethylenephosphonates group as: "*The aminomethylenephosphonates are registered phosphonates which share a common chemistry incorporating alkyl backbones with one or more tertiary amine centres and multiple methylphosphonate groups present.*" You further describe that *"Both acid and certain salt forms of these phosphonates are substances for REACH registration."*

Although you consider the Aminomethylenephosphonates a group of structural analogues you state that "*These can be considered to be a group or family of structurally-analogous substances, within which many properties are generally consistent but in general do not follow predictable trends.*" You have attached also a separate data matrix document in your technical dossier, listing multiple ecotoxicity studies conducted with substances included in the grouping approach.

In the separate justification document attached to the testing proposal, you use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: The substances are "*structural analogues*" and they "*generally possess similar physicochemical properties and are not readily biodegradable and not bioaccumulative*". You further justify that "*the read-across is supported by similar aquatic ecotoxicity*".

You also describe the behavior of the substances in the environment in general terms. You state that "*the fate and behaviour of these substances and their ions are dominated by abiotic dissociation / complexing, irreversible adsorption to surfaces, and less by degradation processes, and they will partition strongly to the solid phase of the soil. The Ksoil-water values for ATMP and HMDMTP have been calculated at 600 l/kg and 1480 l/kg respectively, based on measured Ksediment-water in a study from Michael 1979.*"

As an integral part of this prediction, you propose that the source and registered substance(s) are structural analogues and have similar physicochemical, environmental fate and ecotoxicological properties. ECHA considers that this information is your read-across hypothesis.

Your proposed adaptation argument is that the similarity in chemical structure, and in some of the physico-chemical, fate and ecotoxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure, and in some of the physico-chemical, fate and ecotoxicological properties does not necessarily lead to predictable or similar ecotoxicological properties in other endpoints or environmental compartments. Your justification has not established why the prediction is reliable for the terrestrial toxicity for which the read-across is proposed.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance. In particular ECHA notes that no information on the terrestrial hazard properties of the substances is included in the registration dossier, which would allow to establish similarity in ecotoxicological properties for the registered and source substance in terrestrial environment. You have also not provided specific supporting information allowing to confirm, characterise and compare the behaviour of the source and

registered substances with regard to adsorption/desorption and bioavailability of the substances in soil. The registered and source substances are adsorptive, and you reported that they have differing Ksoil-water values (*"ATMP and HMDMTP have been calculated at 600 l/kg and 1480 l/kg"*), which may influence their bioavailability and uptake during terrestrial toxicity tests. The substances have clear structural differences: the source has one amine center while the registered substance has two amine centers connected by a hexane chain. You have not considered in your documentation why the obvious structural difference and differences in substance properties does not affect the predicted property.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the effects on soil organisms of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of ecotoxicological properties.

The earthworm reproduction test (OECD TG 222) proposed is considered capable of generating information appropriate for the fulfilment of the information requirements for long-term toxicity testing to terrestrial invertebrates.

In your comments to the draft decision you expressed your intentions to consolidate the justification of your read-across hypothesis. The general arguments and grouping are addressed under section 1 above.

You further included a discussion of ecotoxicological data and Kd soil values: you state that the aquatic toxicity data available indicates in general that the substances have low ecotoxicity. You attached a data matrix and one page summary for available ecotoxicological studies. You argue that HEDP has the most severe aquatic toxicity effects (long-term study with *Daphnia magna* with a 28-d NOEC 6.75 mg/l, as active acid) than all the substances in the group and the OECD TG 222 with *Eisenia fetida* study available for HEDP resulted in a NOEC of 500 mg/kg and an LD50 >1000 mg/kg, thereby indicating its low ecotoxicity in terrestrial environment. You further argue that the differences in adsorption, which may affect bioavailability of the substance in soil, are considered to be similar enough in terms of chemical behaviour in the environment (phosphonate pore water concentrations from 0.08% to 0.3% across the phosphonates).

ECHA notes that information on adsorption and pore water partitioning may be helpful to identify intrinsic properties of the substances with regard to bioavailability. However, concentrations in pore water alone do not explain the uptake of substances, as well as their distribution and excretion from the organisms. Furthermore, soil is a highly complex exposure medium with properties that can vary greatly between soil types, hence bioavailability should also be described in relation to soil properties.

Apart from your claim that the differences in adsorption are considered to be similar enough in terms of chemical behaviour in the environment, you do not provide an explanation why read-across predictions are possible within the proposed category. ECHA notes that the aquatic long-term toxicity and terrestrial toxicity information, which you claim to indicate low ecotoxicity of the category members in terrestrial environment, is not available as

robust study summaries in the dossier. Therefore this information cannot be assessed by ECHA with regard to adequacy and reliability. Furthermore, at face value, the results in the data matrix appear to provide evidence of differences in the level of toxicity in aquatic compartment, in the chronic *Daphnia* studies, and thus they do not support a claim of similar toxicity. The NOEC value of 6.75 mg/L from the 28-d study with *Daphnia magna* on HEDP also does not support your claim of low ecotoxicity. ECHA further points out that this chronic *Daphnia* data seem to be available only for two substances, HEDP and ATMP, which does not allow a comparison of the toxicity profiles across the proposed category.

You acknowledged that there is a lack of terrestrial toxicity data and therefore additional OECD TG 222 and TG 216 studies are needed to support the read-across and confirm that complexation and adsorption can be used to predict behaviour and ecotoxicity of aminomethylene phosphonates. You do not describe how you intend to identify the substances for which you will perform the terrestrial toxicity tests.

In conclusion, on the basis of your comments the request in the decision was not amended.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study using the registered substance subject to the present decision: Earthworm reproduction test (OECD TG 222) while your originally proposed Earthworm reproduction test (OECD TG 222) using the analogue substance ATMP xNa/ [nitrilotris(methylene)]trisphosphonic acid, sodium salt (EC) (CAS 20592-85-2; EC 243-900-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

4. Effects on soil micro-organisms (Annex IX, Section 9.4.2.)

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annex IX, Section 9.4. of the REACH Regulation. The Registrant must address the standard information requirements set out in Annex IX, Section 9.4., for different taxonomic groups: short-term toxicity testing on invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity testing on plants (Annex IX, Section 9.4.3.).

You have sought to adapt the information requirement for "effects on soil micro-organisms". You provided the following justification for the adaptation: "*In accordance with Column 2 of REACH Annex IX, there is no need to further investigate the effects of this substance in terrestrial microorganisms because, as indicated in guidance R.7.11.6 (ECHA 2016), the quantitative chemical safety assessment (conducted according to Annex I of REACH) indicates that the Risk Characterisation Ratio is below 1, therefore the risk is already adequately controlled and further testing is not justifiable. The substance is involatile and highly adsorbing and low toxicity was observed in short-term aquatic tests, and there is no reason to expect effects in the terrestrial compartment that were not expressed in the aquatic compartment. Based on the short-term aquatic data set, the most sensitive trophic level is fish. The soil hazard category 3 (ECHA 2014, guidance part R7(c) Table R.7.11—2) has been derived for the category. According to the screening assessment for soil hazard category 3 substances, a PNECsoil has been calculated from the aquatic data on the basis of the equilibrium partitioning method and a confirmatory long term toxicity study with terrestrial invertebrates has been proposed for the structural analogue (ATMP category).*

The PNEC derived by Equilibrium Partitioning has been derived for the purpose of deriving a chemical safety assessment and the risk characterisation ratios are below 1. Details on how the PNEC and the risk characterisation ratio have been derived can be found in IUCLID Section 6.0 and Chapters 9 and 10 of the Chemical Safety Report, respectively".

ECHA understands that you intend to use the Equilibrium Partitioning Method (EPM) and confirmatory terrestrial invertebrate testing to adapt the information requirement Effects on soil microorganisms. The EPM is based on PNECaquatic and as PNECaquatic does not take into consideration any toxicity data on microorganisms, ECHA considers that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method. Therefore the potential adaptation possibility outlined in column 2 of Annex IX, Section 9.4. does not apply for the present endpoint.

Therefore, your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes that the proposed test which ECHA accepted under point (3) above is not sufficient to address this standard information requirement. ECHA concludes that the effects on soil microorganisms need to be ascertained by performing a relevant test.

To address this endpoint, either a nitrogen transformation test (test method: EU C.21/OECD TG 216) or a carbon transformation test (test method: EU C.22/OECD TG 217) could be performed. According to Section R.7.11.3.1, Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), ECHA considers the nitrogen transformation test (EU C.21/OECD TG 216) suitable for non-agrochemicals. For agrochemicals the carbon transformation test (EU: C.22/OECD TG 217) is also required.

The request in the decision was not amended on the basis of your comments (see section 3. above for further details).

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following additional test using the registered substance subject to the present decision: Soil microorganisms: nitrogen transformation test, EU C.21/OECD TG 216.

Notes for your consideration

As the Guidance advocates performing an initial screening assessment based upon the EPM, together with a confirmatory long-term soil toxicity test (the long-term toxicity to terrestrial invertebrates test, specified above), which you are requested to carry out by the present decision, ECHA considers that at this stage it is not possible to determine whether a test will be required to fulfil the standard information requirement in Section 9.4.3. of Annex IX of the REACH Regulation.

Therefore, once results of the requested toxicity test on terrestrial invertebrates are available, you should consider whether there is a need to investigate further the effects on terrestrial organisms in order to fulfil the information requirements of Section 9.4 of Annex IX, and if necessary, submit testing proposals for additional terrestrial toxicity tests. If you conclude that no further investigation of effects on terrestrial organisms is required, you should update your technical dossier by clearly stating the reasons for adapting the information requirement of Annex IX, Section 9.4.3. of the REACH Regulation.

ECHA emphasises that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method and therefore the potential adaptation possibility outlined for the information requirement of Annex IX, Section 9.4.3. does not apply for the present endpoint.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 11 January 2018.

ECHA held a third party consultation for the testing proposals from 31 January 2018 until 19 March 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **8 August 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 did not amend the request(s).

ECHA notes that you request in your comments that the decision on the registered substance and on another testing proposal on: [[(phosphonomethyl)imino]bis-[hexamethylenenitrilobis(methylene)]]-tetrakisphosphonic acid (BMHT-H) are treated in combination, since both substances are claimed to be members of the same category. ECHA confirms that the draft decisions on these testing proposal examinations will be processed and referred to the Member States Competent Authorities at the same time.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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 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.