Helsinki, 14 February 2020

Addressee: [redacted]

Decision number: TPE-D-2114495573-37-01/F
Substance name: Sodium salts of [[(phosphonomethyl)imino]bis[ethane-2,1-diylnitrilobis(methylene)]]tetrakisphosphonic acid (1-3 Na:1)
EC number: 701-215-9
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19/09/2018
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for Long-term toxicity on terrestrial invertebrates (Annex X, Section 9.4.4.; 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:

1. **Long-term toxicity on terrestrial invertebrates (Annex X, Section 9.4.4.; test method: Earthworm reproduction test, OECD TG 222)**

   The study is to be conducted using DTPMP (5-7Na) Sodium salts of [[(phosphonomethyl)imino]bis[ethane-2,1-diylnitrilobis(methylene)]]tetrakisphosphonic acid (5-7 Na:1) (EC 701-216-4);

You have to submit the requested information in an updated registration dossier *by **19 February 2021***. You shall also update the chemical safety report, where relevant.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment

[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. Long-term toxicity to terrestrial invertebrates (Annex X, Section 9.4.4.)

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 and X, Section 9.4. of the REACH Regulation. The Registrant must address the standard information requirements set out in Annex IX and X, Section 9.4., for different taxonomic groups: short-term toxicity testing on invertebrates (Annex IX, Section 9.4.1.), long-term toxicity testing on invertebrates (Annex X, section 9.4.4.), short-term toxicity testing on plants (Annex IX, section 9.4.3.) and long-term toxicity testing on plants (Annex X, section 9.4.6.).

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: "*The available evidence for DTPMP and its salts in respect of terrestrial hazard has been considered in the context of the 'soil hazard category' defined in ECHA Guidance (on Information requirements and chemical safety assessment) part R.7c. DTPMP and its salts are considered to be soil Hazard Category 3 due to their high adsorption values and low toxicity to aquatic organisms properties.*

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 DTPMP category. … 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.

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, log Koc(equivalent) value of approximately 4). 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 X, Section 9.4.4.

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[2]. 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[3]- (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

[2] 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.
[3] 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).

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 DTPMP (1-3Na) / Sodium salts of [[(phosphonomethyl)imino]bis[ethane-2,1-diylnitrilobis(methylene)]]tetrakisphosphonic acid (1-3 Na:1) (EC 701-215-9) using data of a structurally similar substance ATMP-xNa / [nitrilotris(methylene)]trisphosphonic acid, sodium salt (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.

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*". 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 DTPMP have been calculated at 600 l/kg and 380 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 is your read-across hypothesis. In the following, ECHA examines your proposal to predict long-term toxicity on terrestrial invertebrates of the registered substance from ATMP acid (CAS 6419-19-8).

Firstly, 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.

Secondly, according to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.2.1.f, (version 1.0, May 2008) "it is important to provide supporting information to strengthen the rationale for the read-across. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals".

ECHA notes that you have not provided an explanation or supporting information to confirm, characterise and compare the behaviour of the source and registered substances with regard to bioavailability of the substances in soil. Furthermore no information on the terrestrial hazard properties of the substances is included in the registration dossier. Consequently, there is no supporting information provided to compare the toxic potential of the substances in soil and strengthen the rationale for the read-across.

Thirdly, ECHA notes that the registered substance is an organic UVCB substance and the reported boundary composition of the registered substance includes 12 constituents. While your read-across justification addresses the prediction from ATMP acid (CAS 6419-19-8) to the DTPMP, which has three amine centres and five methylphosphonate groups, the registered substance contains also other constituents such as [redacted] The contribution of exposure to these constituents to the ecotoxicological properties of the registered substance require specific considerations and an assessment whether the prediction is compromised by some of the constituents. However your read-across justification does not address all the constituents of the registered substance.

In conclusion, 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.

In your comments to the draft decision you agreed that the information currently in the dossier does not fulfil the information requirement, and you intend to perform the requested study on one of the members of the DTPMP category (DTPMP (5-7Na) Sodium salts of [[(phosphonomethyl)imino]bis[ethane-2,1-diylnitrilobis(methylene)]]tetrakisphosphonic acid (5-7 Na:1), EC 701-216-4.).

Furthermore, you indicate that you intend to modify the test design of the requested study by adding iron into artificial soil to minimise the effect of nutrient depletion on earthworm reproduction.

In general ECHA considers that the requested study should be conducted with the test guideline indicated in the decision. However, if there is a reason to deviate from the test guideline, reasons should be well justified and documentation supporting the reasoning should be provided.

Considering the deviation from the test guideline proposed in the comments to this draft decision, the following uncertainties can be noted:

- You refer to OECD GD 23 where the complexation phenomenon is acknowledged. ECHA however notes that the guidance in OECD GD 23 refers to algal growth studies which per se may be more influenced by nutrient depletion than earthworm reproduction.
- You have not given any scientific explanation nor evidence to what extent the earthworm reproduction can be affected by nutrient depletion.
- Similarly, you have not given any scientific explanation nor evidence if the complexation of the test substance with added iron can influence the bioavailability of the test substance and thus the results measuring the intrinsic toxicity of the test substance could be compromised by the modification.

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.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study using DTPMP (5-7Na) Sodium salts of [[(phosphonomethyl)imino]bis[ethane-2,1-diylnitrilobis(methylene)]]tetrakisphosphonic acid (5-7 Na:1) (EC 701-216-4): 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 8 October 2018.

This decision does not take into account any updates after **13 March 2019**, 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 within 30 days of the notification.

ECHA took into account your comments and amended the request(s) but did not change the deadline.

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 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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.