Helsinki, 23 November 2018

Addressee: [redacted]

Decision number: TPE-D-2114449801-48-01/F
Substance name: [[(phosphonomethyl)imino]bis[hexamethylenenitrilobis(methylene)]]-tetrakisphosphonic acid
EC number: 252-156-6
CAS number: 34690-00-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 8 May 2018
Registered tonnage band: 10-100
Registered jointly: 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.

You are requested to perform:

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

TOXICOLOGICAL AND ECOTOXICOLOGICAL INFORMATION

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance [[(phosphonomethyl)imino]bis[hexamethylenenitrilo-bis(methylene)]]tetrakisphosphonic acid (EC number: 252-156-6), hereafter the 'target substance' or 'registered substance', acronym 'BHMT-H'.

Toxicological information requirements

In relation to the testing proposals for toxicological information requirements subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirements for a repeated dose (90-day) toxicity study (Annex IX, Section 6.8.2,) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

In your testing proposals the test material for the proposed studies was not clearly identified. There is somewhat conflicting information in the CSR and in the IUCLID section 7.5.1 and 7.8.2.

In the CSR three options are offered: the registered substance and two possible analogue substances, a "salt of the same phosphonic acid" or a salt of a structurally analogous phosphonic acid HMDTMP.

In the technical IUCLID dossier there is a "statement regarding stepwise assessment and testing". There you state that the registered substance is a member of a group of analogous aminomethylenephosphonate and other organophosphonate substances, for which several studies on repeated dose toxicity or pre-natal developmental toxicity would be available, without specifying how they contribute to the assessment of the registered substance. You propose to conduct in vitro testing as part of a decision making framework, prior to proceeding with an OECD TG 408 study. However, you also state that no work was initiated. You further state 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.*"

However, then you continue: "*It is proposed to perform the study with the related substance, HMDTMP (4-7K) (Potassium salts of {hexane-1,6-diylbis[nitrilobis(methylene)]}-tetrakisphosphonic acid (4-7:1); EC 701-184-1).* You want to use the results obtained with this substance to predict the properties of the registered substance. This substance is also one of the options for test material identified in the CSR.

ECHA understands that with regard to the above mentioned "stepwise assessment and testing" you did not provide supporting and detailed information. Instead you propose to use the results obtained with the analogue substance to adapt the standard information requirements for your registered substance by using a grouping and read-across approach following Annex XI, Section 1.5. of the REACH Regulation.

Ecotoxicological information requirements

In relation to the testing proposal for ecotoxicological information requirements subject to the present decision, you propose to use the Equilibrium Partitioning Method (EPM) and a confirmatory long term toxicity study with terrestrial invertebrates to fulfil the standard information requirements for Effects on terrestrial organisms (Annex IX, Section 9.4.).

You have provided two testing proposals in IUCLID section 6.3.1 Toxicity to soil macroorganisms except arthropods: One proposes testing the analogue substance [nitrilotris(methylene)]trisphosphonic acid, sodium salt (ATMP xNa, CAS No 20592-85-2, EC No 243-900-0) and the other proposes testing the analogue substance [hexane-1,6-diylbis[nitrilobis(methylene)]]tetrakisphosphonic acid, potassium salt (HMDTMP (4-7 K), CAS No 38820-59-6, EC No 254-135-7). As the latter includes a cross reference to another testing proposal and a read-across justification "from ATMP to HMDTMP", ECHA understands that this testing proposal is not relevant for the registered substance BHMT-H. Therefore ECHA understands that you intend to perform a confirmatory long term toxicity study with terrestrial invertebrates using the analogue substance ATMP xNa, and that you propose to use the results to adapt the standard information requirements for your registered substance by using a grouping and read-across approach following Annex XI, Section 1.5. of the REACH Regulation.

ECHA has considered first the scientific and regulatory validity of your grouping and read-across approach in general before assessing the individual properties in section 1 of this appendix.

Grouping of substances and read-across approach

Description of the grouping and read-across approach

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.

[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.

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 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).

In your testing proposals, you have not provided information on the identity and characterisation of the "*salt of the same phosphonic acid*" proposed for toxicity testing. You provided a category hypothesis for "*BHMT acids*", which explains why data can be read-across from salts and which mentions sodium and potassium salts. You did not provide information which salt is proposed for testing and why it is preferable over the acid.

Furthermore, you have provided a read-across documentation for an "*aminomethylene phosphonates super-category*" in the CSR of the registration. BHMT, HMDTMP and ATMP are identified as members of this category. You use the following arguments to support the prediction of properties of the registered substance from data obtained with substances of the group: you claim that the members of the "*aminomethylene phosphonates super-category*" share a common chemistry incorporating alkyl backbones with one or more tertiary amine centres and multiple methylphosphonate groups present. You continue to explain that the acid and salt forms of a defined phosphonate structure will not behave differently in dilute aqueous conditions. Therefore, for *in vivo* toxicity studies the local pH and ionic conditions within the stomach and gastrointestinal tract dominate the speciation of the phosphonate, irrespective of the form originally dosed.

You also claim that many phosphonate properties are thought to be mediated by complexation of metal ions and/or binding properties of the phosphonate. In this context you consider it reasonable to read across data from analogous phosphonates within the super-category, with similar properties, same phosphonate group count, and similar alkyl chain length linking the complexing functional groups. You further argue that the aminomethylenephosphonates are typically not of high ecotoxicity under neutral conditions, probably due to low bioavailability.

In your documentation of the category for the toxicological properties you further indicate that "*aminomethylene-phosphonates are known to bind to bone in vivo and to hydroxyapatite in vitro*". You consider that for the endpoints under consideration, i.e. sub-chronic toxicity and pre-natal developmental toxicity, "*some toxicological effects could potentially be mediated through this property*". You also justify the selection of HMDTMP as source substance on the basis of the highest Tanimoto score with the registered substance from all the identified category members. You conclude on that basis that "*read-across between BHMT and HMDTMP categories is well justified for properties in which binding to calcium is critical*".

You provide a data matrix for the aminomethylene phosphonates super-category. You conclude for toxicity that in most areas the aminomethylene phosphonates have consistent properties.

ECHA understands that on the basis of structural similarity and similarity in (eco)toxicological properties for some members of the category, you consider it possible to predict the human health and ecotoxicological properties of the registered substance from

[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).

the other members of the phosphonates super-category as proposed in your testing proposals using the analogue substance HMDTMP or ATMP as test material. As an integral part of this prediction, you propose that the source and registered substances have similar properties for the above-mentioned information requirements and particularly that the binding properties and behaviour of these substances towards adsorption to bone is similar. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

ECHA considers that there is insufficient information to support your read-across hypothesis.

Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why the predictions for human health or ecotoxicological properties are reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health or ecotoxicological properties of a substance.

In your documentation of the adaptation you have established elements of structural similarity and outlined structural differences between the members of the category, including the registered substance and the source substance. However, you do not address the reasons why and how a specific property for the registered substance may be predicted on the basis of results obtained with the proposed source substance despite the structural differences.

In your category hypothesis for a "BHMT acid category" in the CSR, you explain that acid and salts do not behave differently in aqueous solutions. Currently there are no data for any human health hazard for the acid or its salts in the registration dossier. ECHA is of the opinion that based on the information provided you have not established why in this specific case a salt would be preferable over the acid, the registered substance. Therefore ECHA rejects a "*salt of the same phosphonic acid*" as test material.

For the aminomethylene phosphonates super-category you claim that all the aminomethylenephosphonates are known to bind to bone *in vivo* and consider this mechanism of action as potentially responsible for sub-chronic toxicity and pre-natal developmental toxicity and therefore HMDTMP could be used as analogue substance. However, no information on the human health related hazard properties of the registered substance is included in the registration dossier, which would allow to establish similarity in toxicological properties for the registered and source substance for the endpoints under consideration. You have also not provided specific supporting information allowing to confirm, characterise and compare the behaviour of the source and target substances with regard to adsorption to bone. Furthermore, there is no evidence that adsorption to bone is the only or the pre-dominant possible mechanism of toxicity.

Similarly for ecotoxicity, you argue that the substances are typically not highly ecotoxic under neutral conditions, probably due to low bioavailability. You describe that behaviour of these substances are dominated by their binding properties and therefore you consider it reasonable to predict the properties of the registered substance from analogous phosphonates within the super-category. However, 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 target and source substances in terrestrial environment. You have also not provided specific supporting information allowing to confirm, characterise and compare the behaviour of the source and target substances with regard to adsorption/desorption and bioavailability of the substances in soil.

As an additional consideration, ECHA further points out that no information on the composition (identification of the constituents, their concentration ranges and typical concentrations) of the proposed source substance is provided in your dossier. Therefore, it is not possible to formally establish structural similarity between the registered substance and the source substance.

As indicated above, on the basis of the information provided in your registration dossier, there is not sufficient support for your proposal that the registered (target) substance and the source substance behave similarly towards adsorption to bone and that they have otherwise similar toxicological properties. Also the proposed prediction for terrestrial toxicity is lacking explanation and supporting evidence that the bioavailability and ecotoxicity of the substances would be similar in terrestrial environment. Therefore ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health or ecotoxicological effects 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. Therefore, ECHA rejects "*salt of the same phosphonic acid*" or "*a salt of a structurally analogous phosphonic acid, HMDTMP*" or "ATMP" as test materials for the proposed studies.

In your comments to the draft decision you indicate that you "*agree with ECHA that the justifications for read-across in the datasets can and should be improved*" with regard to a number of the points raised by ECHA in the draft decision. You expressed your intentions to consolidate the justification of your read-across hypothesis according to which 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 ecotoxicological profiles of the phosphonates under consideration when reviewed in terms of impact on complexation and adsorption behaviour*".

You acknowledge that there are no repeated dose toxicity data available for BHMT-H to support the read-across. However, the dominance of the extremely strong complexation properties of this substance, as with the other organophosphonate complexing agents, means according to you that any toxicity would originate with complexation with metal ions either in the gut or systemically. Toxicity tests on the other organophosphonate complexing agents would 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. Therefore, you do not agree with the testing requested in the draft decision.

You intend to further refine and strengthen your 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: 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).

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 decision 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.
6) ECHA notes that no specific adaptation arguments are made for the information requests for repeated dose toxicity (90-day) according to OECD TG 408 and for the prenatal developmental toxicity test according to OECD TG 414.

ECHA acknowledges your intentions to further refine and consolidate your read-across approach. However, since the outcome of these investigations is unknown, ECHA considers that no conclusion can be drawn on whether the potential updated read-across approach as referred to in your comments will comply with the requirements of Annex XI, Section 1.5 of the REACH Regulation. ECHA will further assess the information provided in an updated dossier in the Dossier Evaluation Follow-Up Process and will come to a conclusion on whether the information provided adequately fulfils the information requirements addressed in this decision.

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[4]).

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. You acknowledge that there are no repeated dose toxicity studies available for the registered substance to support your proposed read-across. And you do not identify, what source study with which results you actually want to use for read-across. ECHA notes that you also do not agree with testing one of the originally proposed source substances, HMDTMP (4-7K).
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 Kd soil values and ecotoxicological data: 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.

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. 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.[4] 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 1907/2006 (penalties for non-compliance) for the period during which the registration dossier was not compliant[5].

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

[4] Only the final decision will be sent to the National enforcement authority so they can consider enforcement actions.
[5] 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

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. You did not specify clearly the test material for the proposed study. You stated: *"It is proposed to perform the study with either the registered substance or a read-across substance, which would be a salt of the same phosphonic acid; or salt of a structurally analogous phosphonic acid, HMDTMP. See Section 5 of the CSR for details of read-across."*

ECHA notes your considerations for alternative methods to fulfil the information requirement for sub-chronic toxicity (90-day) 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 has evaluated your proposal to perform the test with the analogue substances "salt of the same phosponic acid" or "HMDTMP" (CAS number 23605-74-5). Your proposal to use these test materials instead of the registered substance is rejected for the reasons presented in the section on "*Grouping of substances and read-across approach*" above.

Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to aerosols of the registered substance is possible, ECHA points out that the concentrations of the registered substance in solutions are indicated by you to be [redacted] %. Furthermore, no repeated dose toxicity study by the oral route is available. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that a 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.

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.

In your comments to the draft decision, you explain why you prefer "a salt of BHMT" to be tested in vivo. You state that the free acid form is classified as irritant and might have local effects in the gastrointestinal tract, which may cause unnecessary pain to the test organisms. You did not specify, which salt (i.e. which counter ion, which number of counter ions for the phosphonate groups available) you would prefer to test. You also do not provide evidence of local effects in repeated dose toxicity studies for the registered substance. Furthermore you do not provide any evidence on the impact the different possible salt forms may have on the availability of the test substance for uptake.

ECHA considers that toxicity tests have to take into account local effects in the dose setting. If the available data is not sufficient for dose setting, a dose not causing pain or suffering needs to be determined in a dose range finding study. Furthermore, the provided tables for the proposed category members appear to indicate that the toxicity tests with repeated dosing were performed with the acid forms, indicating that there was not an issue with irritation of the gastrointestinal tract. The registration for the substance you mention as an example, had a different set of circumstances (e.g. the substance was classified as corrosive) and furthermore the decision was not adopted due to cease of manufacture.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the 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. You did not specify clearly the test material for the proposed study. You stated: *"It is proposed to perform the study with either the registered substance or a read-across substance, which would be a salt of the same phosphonic acid; or salt of a structurally analogous phosphonic acid, HMDTMP. See Section 5 of the CSR for details of read-across."*

ECHA notes your considerations for alternative methods to fulfil the information requirement for sub-chronic toxicity (90-day) 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 has evaluated your proposal to perform the test with the analogue substances "salt of the same phosponic acid" or "HMDTMP" (CAS number 23605-74-5). Your proposal to use these test materials instead of the registered substance is rejected for the reasons presented in the section on "*Grouping of substances and read-across approach*" above.

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

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.

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 aqueous solution, ECHA concludes that testing should be performed by the oral route.

Since no specific arguments were made for pre-natal developmental toxicity, the considerations on your comments provided under "Grouping and read-across approach" apply for this property as well.

Your comments on the substance to be tested are addressed under section 1 above.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the 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: EU 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 in the data waiving endpoint record: "*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.*

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 Kp (soil-water) 1300 L/kg). 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 ATMP (CAS No CAS 20592-85-2) and thus sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5.

Your proposal to test the analogue substance instead of the registered substance is rejected for reasons presented in the section on "*Grouping of substances and read-across approach*" above.

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.

The requests in the decision were not amended on the basis of your comments (see "Grouping of substances and read-across approach").

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 toxicity to microorganims studies 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 and long-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 invertebrates. While aquatic microorganism effects data are not taken into account in deriving the freshwater PNEC value, it is notable that the data on microorganisms indicate an EC5 at 100 mg/l, which is equivalent to the EC50 for the most sensitive trophic level. 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. See also the endpoint summary for additional considerations on the toxicity to micro-organism from aquatic data*".

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 that 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 requests in the decision were not amended on the basis of your comments (see "Grouping of substances and read-across approach").

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 15 April 2014.

ECHA notes that the tonnage band for one member of the joint submission is 100 to 1 000 tonnes per year.

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: potassium salts of {hexane-1,6-diylbis[nitrilobis(methylene)]}tetrakisphosphonic acid , HMDTMP (4-7K) (EC No 701-184-1, CAS N, N/A) 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.