EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114306458-49-01/F Helsinki, 31 July 2015

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For guanidinium phosphate (1:1), EC No 226-551-9 (CAS No 5423-22-3), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for guanidinium phosphate (1:1), EC No 226-551-9 (CAS No 5423-22-3), submitted by [redacted] (Registrant):

- Testing proposal: 90-day oral toxicity study (OECD 408), in rodents, oral route, with the analogue substance guanidinium hydrochloride.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates submitted after the deadline for updating (7 May 2015) communicated to the Registrant by ECHA on 31 March 2015.

This decision does not imply that the information provided by the Registrant in his 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.

ECHA received the registration dossier containing the above-mentioned testing proposal for examination pursuant to Article 40(1) on 5 July 2013.

ECHA held a third party consultation for the testing proposal from 16 May 2014 until 30 June 2014. ECHA received information from third parties (see section III below).

On 8 August 2014, ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 12 September 2014, ECHA received comments from the Registrant on the draft decision. On 18 September 2014, the Registrant updated his registration dossier with the submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update. On the basis of this information, Section II was amended. The Statement of Reasons (Section III) was

changed accordingly.

On 11 June 2015, ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test method and the analogue substance guanidinium hydrochloride (EC 200-002-3, CAS 50-01-1):

- Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408)

Note for consideration by the Registrant:

The Registrant 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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request in this decision, or to fulfil otherwise the information requirement with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **9 November 2015** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance and scientific information submitted by third parties.

A. Tests required pursuant to Article 40(3)

0) Grouping of substances and read-across approach

Article 13(1) and 13(3) of the REACH Regulation allows that information on intrinsic properties of substances may be generated by means other than tests, including information from structurally related substances (grouping or read-across), "provided that the conditions set out in Annex XI are met".

The criteria for read-across are set out in Annex XI, section 1.5.

In the updated dossier the Registrant has proposed a testing approach for sub-chronic toxicity using an analogue as test (source) substance guanidinium hydrochloride (EC 200-002-3, CAS 50-01-1). The Registrant stated: *"Based on the rationale attached in section 13, these data can be read across to guanidinium phosphate."* ECHA notes that in the updated registration dossier the Registrant has provided a rationale and justification for the analogue read-across approach.

According to the Registrant, the read-across hypothesis is based on the "*chemical nature, similar physico-chemical properties and comparable toxicity profile"* of the substances. The Registrant has provided a read-across justification document, including a data matrix covering the physicochemical and toxicological properties.

In the document, the Registrant argued that the structural differences (i.e. hydrochloride and phosphate) are not expected to result in different toxicity profiles for sub-chronic toxicity. This is based on the following main arguments: "*Phosphate is abundantly present in the environment and in the human body.*" "*The main difference between the target substance guanidinium phosphate (1:1) and the analogue substance guanidinium hydrochloride is that the latter is classified for skin and eye irritancy. This is most probablty related to the acidity of the hydrochloride-part of the substance. In contrast, guanidine phosphate will dissociate into a guanidine-ion and a phosphate-ion, and has been shown not to be irritating to skin or eye. As these irritating effects of guanidine hydrochloride are local effects, and are regarded to be not relevant for systemic toxicity, the difference in irritating properties between the two substances does not influence the read across of the endpoints proposed.*"

According to Annex XI, Section 1.5, the similarities of the read-across substances may be based on a common functional group. Based on the data submitted, ECHA considers that the Registrant has provided sufficient data to demonstrate that the toxicity of guanidinium phosphate is expected to be driven by guanidinium ion, thus meeting the criteria of Annex XI, 1.5.

In conclusion, although ECHA considers the proposed read-across and grouping approach as plausible, a final decision on the validity of the approach will only be possible when the conditions set out in Annex XI are eventually met for the relevant endpoint. As long as the result of the test proposed by the Registrant is not available, ECHA considers that the read-across and grouping approach, although plausible, is still under development.

ECHA emphasises that it is the Registrant's responsibility to amend and substantiate the read-across justification according to Annex XI, 1.5. and to use all relevant available data once the new test data becomes available.

Following the update of the dossier based on the present decision, ECHA will determine whether the documentation provided is sufficient to satisfactorily address the information requirement of Annex IX for the registered substance as proposed by the Registrant. If, upon further consideration, the proposed approach does not satisfy the conditions set out in Annex XI, ECHA reserves the right to request the information necessary to fulfil the information requirement.

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

a) Examination of the testing proposal

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.

The Registrant initially submitted a testing proposal for a sub-chronic toxicity study (90-day) to be carried out on the registered substance, including "*a reproduction/developmental toxicity screening test (comparable to OECD 422, but with extended exposure period)*". However, in the dossier update of 18 September 2014 (submission number [redacted]) after ECHA had notified him of the draft decision, the Registrant removed the testing proposal from the endpoint study record and instead selected "study scientifically unjustified". In the same record, he stated that "*The 90d study is preliminary waived based on the expected availability of a chronic study for the substance analogue guanidinium hydrochloride ("90-days Repeated Dose Oral Toxicity Study in Wistar Rats with Guanidinium hydrochloride including a 28 Day Recovery Period and Fertility Parameters" (as of Study plan)). This study is expected to become available in 2015."* The same read-across approach is present in his comment to the draft decision.

ECHA notes that the Registrant has expressed an intention of testing an analogue substance to meet the information requirements for the presently registered substance. ECHA has to examine in the context of the testing proposal examination any intention of testing, including testing of an analogue substance, to ensure that the proposed strategy of generation of data is tailored to the relevant information needs for the endpoint and the dossier under the assessment. Therefore, the decision-making process of the testing proposal was continued and ECHA informed the Registrant of this on 5 March 2015.

Based on ECHA's preliminary considerations (see Section 0 above), the Registrant's proposed read-across approach is considered plausible.

The Registrant proposed testing by the oral route. In light of the properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate.

The Registrant did not specify the species to be used for testing. According to the test method EU B.26/OECD 408, the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

b) Consideration of the information received during third party consultation

ECHA received third-party information concerning the testing proposal during the third-party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

ECHA acknowledges that two third parties have proposed a read-across approach for the Registrant to consider. In particular, one of the third parties has proposed that "[t]he Agency and the registrant may consider read-across to guanidinium hydroxide and inorganic phosphates. A comparable approach has been chosen for the registration of

guanidinium nitrate and accepted by the Agency. Sub-chronic toxicity studies with the aluminium sodium salt of phosphoric acid in dogs resulted in limited systemic effects (renal congregations at high doses >1000 mg/kg bw/d which were attributed to the phosphate ion). The risk assessment for guanidinium phosphate may therefore predominantly rely on data obtained with guanidinium hydroxide (ongoing study)."

ECHA notes that it is the Registrant's responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5. Therefore, the Registrant should assess whether he can justify a read-across as suggested by the third party. If the adaptation can be justified, he should include the adaptation argument with all necessary documentation in the registration dossier.

ECHA notes that the information provided by the third party is currently insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. For example, no study summaries of the sub-chronic studies were provided and, therefore, ECHA cannot assess whether the read-across studies are adequate; i.e. ECHA cannot assess whether the results of the read-across studies (a) are adequate for the purpose of classification and labelling and/or risk assessment; (b) have adequate and reliable coverage of the key parameters; and (c) cover an adequate exposure duration. Therefore, the information provided by the third party in itself would not be sufficient to adapt the standard information requirement.

c) Outcome

On the basis of the above, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the analogue substance guanidinium hydrochloride (EC 200-002-3, CAS 50-01-1): Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408).

The Registrant is reminded that this decision does not take into account any updates submitted after 7 May 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

B. Deadline for submitting the required information

ECHA notes that a sub-chronic toxicity study on guanidinium hydrochloride (the source substance) has already been requested in the adopted compliance check decision TPE-D-0000003916-66-02/F on the substance guanidinium nitrate, addressed to another registrant. The deadline set out in that decision is 8 October 2015. The Registrant intends to refer to the results of that study, as he stated in his comment to the draft decision. ECHA therefore aligned the deadline for the current decision with the timeline set for the generation of guanidinium hydrochloride. In any case, the minimum timeline should be set at least three months from the date of this decision, so as to allow the possibility of lodging an appeal – three months being the relevant time period specified in Article 92(2) of the REACH Regulation.

Therefore, the deadline set in this decision for submitting the information should be the same as the previous adopted decision or three months from the date of this decision, whichever is later.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new study meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed test, the sample of substance used for the new study must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the test proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new study 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new study must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the study to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals.The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Leena Ylä-Mononen, Director of Evaluation

[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.