EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000003916-66-02/F Helsinki, 8 October 2013

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

For guanidinium nitrate, CAS No 506-93-4 (EC No 208-060-1), 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 proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for guanidinium nitrate, CAS No 506-93-4 (EC No 208-060-1), by [redacted] (Registrant):

- 90-day oral toxicity study (OECD 408), oral route using the analogue substance guanidinium hydrochloride;
- Developmental toxicity / teratogenicity study (OECD 414), using the analogue substance guanidinium hydrochloride.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 1 August 2013, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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.

On 17 July 2012, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 25 September 2012 until 12 November 2012. ECHA did not receive information from third parties.

On 1 February 2013 ECHA received comments from the Registrant to ECHA's draft decision. In his comment the Registrant indicated his intention to address issues outlined in the draft decision and to submit an updated dossier.

On 2 April 2013 the Registrant updated his registration dossier.

ECHA considered the Registrant's comments received and the updated registration dossier. On that basis, Section II was amended and the Statement of Reasons (Section III) was changed accordingly.

On 1 August 2013 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 to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the analogue substance guanidinium hydrochloride, CAS No 50-01-1 (EC No 200-002-3):

- Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408).
- Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to the column 2 provisions of the respective Annex and those contained in Annex XI of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **8 October 2015** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. Column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance.

In relation to the testing proposal subject to the present decision, the Registrant has proposed to use read-across approach in accordance with Annex XI, 1.5, and to perform the tests on another substance than the substance subject to the present decision. In its evaluation, ECHA has considered firstly the scientific validity of the proposed read-across approach (Section III.1 below), and secondly assessed the testing proposed (Sections III.2 and III.3 below).

1. Read-across approach (preliminary considerations)

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), *"provided that the conditions set out in Annex XI are met"*.

According to the Registrant, use of read-across approach is possible and he proposes to test another substance, guanidine hydrochloride, to meet the information requirements for the endpoints of sub-chronic toxicity and pre-natal developmental toxicity for the substance subject to the present decision.

According to the rules for adaptation set out for grouping or read-across in Annex XI, Section 1.5. of the REACH Regulation, application of the group concept requires that human health effects (among others) *"may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach)."*

The Registrant provides the following justification:
"Guanidine hydrochloride and guanidine nitrate dissociate in biological fluids to yield the guanidine ion and the respective anion. Therefore it is reasonable to discuss the systemic intrinsic properties of the ions separately. The chloride ion is a naturally occurring essential ion in human beings with well-known metabolism and mechanisms of action as described in standard textbooks on pharmacology and physiology. Systemic effects of guanidine hydrochloride are expected to be based on the guanidine ion. The physiological processing of the guanidine ion is expected to be independent of the individual source. Therefore read-across from guanidine hydrochloride for effects of the guanidine ion is considered valid. The effects of the nitrate ion will be discussed separately by read-across. This strategy is supported by a quite similar toxicological profile of both substances, as shown in acute toxicity, irritation, sensitization and genotoxic studies".

In its original draft decision ECHA concluded on the basis of the submitted dossier at the time that the information provided by the Registrant did not sufficiently support the proposed read-across from the source substance guanidine hydrochloride to the target substance (that is the substance subject to the present decision) guanidinium nitrate for the endpoints involved, as the hypothesis was not sufficiently supported by data and thus did not fully meet the requirements of Annex XI, Section 1.5.

In the dossier update submitted after receiving the draft decision, the Registrant submitted robust study summaries for acute oral, inhalation and dermal toxicity, skin and eye irritation, and skin sensitisation studies, and an Ames test conducted with the read-across substance guanidinium hydrochloride. In addition, the Registrant provided information on classification and labelling of both substances. The human health effects of the chloride ion and nitrate were summarised in the read-across justification document attached to the updated dossier. In addition, a pre-natal developmental toxicity (OECD 414) and a combined repeated dose toxicity study with the reproduction/developmental toxicity

screening test (OECD 422) conducted on potassium nitrate were provided. Furthermore, information from published reviews was provided: a two-year study published in the WHO Food additive series, and a summary of the repeated dose toxicity studies published in OECD SIAR (Nitrates category).

ECHA has analysed the comments and the updated dossier in light of the requirements of Annex XI, 1.5. Based on the data provided it can be concluded that guanidinium nitrate and guanidinium hydrochloride have quite a similar toxicological profile for acute toxicity, eye irritation and *in vitro* mutagenicity as claimed by the Registrant. The data further supports the claim that systemic effects of guanidinium hydrochloride are expected to be based on guanidine ion as with the highest guanidinium hydrochloride dose of 500 mg/kg bw/day = 250 mg nitrate/kg bw/day it is unlikely that possible adverse effects in repeated dose toxicity testing and pre-natal developmental toxicity testing would be driven by nitrate. This is supported by the NOAELs from the studies conducted with nitrate: from the chronic toxicity study 370 mg/kg bw/day as a nitrate, 920 mg/kg bw/day as a nitrate from the OECD 422 study, and 1214 mg/kg bw/day as a nitrate from the pre-natal developmental toxicity study.

According to Annex XI, Section 1.5 (1), 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 is expected to be driven by guanidinium ion thus meeting the criteria of Annex XI, 1.5 (1).

ECHA concludes that the read-across hypothesis can be considered plausible as the underlining toxicological information is complete and relevant and supports the hypothesis, and the Registrant may be able to predict the relevant properties of the substance subject to the present decision by using the results of the proposed tests on the read-across substance. Therefore, the results of the proposed tests can be considered adequate for the purpose of classification and labelling and/or risk assessment. Furthermore, as the adequate and reliable documentation of the applied method has been provided, ECHA concludes that the criteria of Annex XI, 1.5 are met.

Following the update of the dossier submitting the information required in the present decision, ECHA will determine whether the documentation provided is sufficient to satisfactorily address the information requirements of Annex IX 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 requirements for the substance subject to the present decision.

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

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 has therefore submitted a testing proposal for sub-chronic toxicity study (90-day, test method: EU B.26/OECD 408) to fulfil the information requirement. The Registrant proposes that the test is to be performed on another substance guanidinium hydrochloride.

ECHA for the reasons stated above agrees with the Registrant that information from a test is necessary in order to fulfil the missing data requirement. Furthermore, for the reasons outlined in section III.1 above, ECHA considers the proposed read-across approach as submitted by the Registrant is plausible. Therefore, in order to meet the standard information requirement of Annex IX, section 8.6.2., the Registrant is requested to perform the test on the analogue substance guanidinium hydrochloride, CAS No 50-01-1 (EC No 200-002-3).

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

The Registrant did not specify the species to be tested. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the following study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the analogue substance guanidinium hydrochloride.

3. Pre-natal developmental toxicity study

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 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.

The Registrant has therefore submitted a testing proposal for pre-natal developmental toxicity study (test method: EU B.31/OECD 414) to fulfil the information requirement. The Registrant proposes that the test is to be performed on another substance guanidinium hydrochloride.

ECHA for the reasons stated above agrees with the Registrant that information from a test is necessary in order to fulfil the missing data requirement. Furthermore, for the reasons outlined in section III.1 above, ECHA considers the proposed read-across approach as submitted by the Registrant as plausible. Therefore, in order to meet the standard information requirement of Annex IX, section 8.7.2., the Registrant is requested to perform the test on the analogue substance guanidinium hydrochloride, CAS No 50-01-1 (EC No 200-002-3).

The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the analogue substance guanidinium hydrochloride.

When considering the need for a testing proposal for a pre-natal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

IV. Adequate identification of the composition of the tested material

It is important to ensure that the particular sample of substance tested in the new studies 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade registered to enable the relevance of the studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. 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://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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