EUROPEAN CHEMICALS AGENCY

Helsinki, 25 October 2017

Addressee: [redacted]

Decision number: CCH-D-2114375720-49-01/F
Substance name: TETRASODIUM N,N-BIS(CARBOXYLATOMETHYL)-L-GLUTAMATE
EC number: 257-573-7
CAS number: 51981-21-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04/04/2013
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Description of the analytical methods (Annex VI, Section 2.3.7.);**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat), oral route with 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **1 November 2018**. You also have to update the chemical safety report, where relevant.

The reasons of 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 Kevin Pollard, Head of Unit, Evaluation E1.

[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.

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Appendix 1: Reasons

1. Description of the analytical methods (Annex VI, Section 2.3.7.)

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

Annex VI, section 2.3.7 of the REACH Regulation requires that each registration dossier contains a sufficiently detailed description of the analytical methods used for establishing the identity of the registered substance. Additionally, Annex VI section 2.2.2 requires that information on optical activity and typical ratio of (stereo)isomers (if applicable and appropriate) needs to be provided to enable the identification of the substance.

Based on the substance identity information provided in IUCLID section 1.1 (EC and CAS entries) and 1.2, the substance subject of this registration refers to the sodium salt of a derivative of the specific isomer L-glutamate. In IUCLID section 1.4 you did not provide information on the optical activity of the substance and no analytical information on how the chirality of the substance has been determined was provided in the registration dossier. In addition the IUPAC name provided in the dossier refers to the generic "tetrasodium 2-[bis(carboxylatomethyl)amino]pentanedioate".

In the absence of analytical information (e.g. chiral chromatography, etc.) that would allow to clearly establish the stereochemistry of the substance, it is not possible to verify that the substance is the derivative of the L-isomer of glutamate.

Therefore, you are requested to provide information on how the stereochemistry of the substance subject to this decision has been determined. This may include the optical activity of the substance itself, or any other analytical method that can confirm the stereochemistry of your substance (e.g. chiral chromatography). The description of the method(s) shall be given in such detail that the method(s) may be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

As for the reporting in the registration dossier, the information requested above shall be attached to section 1.4 of your dossier. You shall ensure that this information is consistent the substance identifiers provided in section 1.1 and 1.2 of your dossier (EC number, CAS number, IUPAC name and structural formula).

Should the information submitted by you as a result of the present decision result in a need to modify the identifier of the substance (*i.e.* your substance is the racemate), the process of adapting the identifiers (EC number and CAS number) will be considered relevant. In that case, ECHA will inform you in due time as to when and how the identifier adaptation process shall be initiated. The process, subject to certain conditions, enable the registrants to adapt the EC identifier of an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you have indicated the availability of a chiral HPLC method to determine the stereochemistry of the substance. You have also indicated that an analysis using that method shows that the registered substance is composed by the optical isomer L in more than [redacted]% m/m and that you would update the registration dossier to provide the results. Following a quick screening of the dossier update submitted on 22 June 2017 (submission No. [redacted]) ECHA points out that the analytical report provided appears to fulfil the requirements "A. VI - 2.3.7. Description of the analytical methods (Annex VI, 2.3.7)" and thus addressing the information requirements in the draft decision. However, as mentioned in Appendix 2 below, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation and ECHA will only examine the information provided after the deadline set in the adopted decision has passed.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rabbits by the oral route using the registered substance as test material with a Klimisch score of 1 ([redacted] 2012).

In the technical dossier you have provided a study record for a two-generation reproductive toxicity study (OECD TG 416) in rats with the registered substance including additional investigations "*to fulfill the requirements of the OECD 414 guideline*". You have considered "*the study result of the F0-generation and F1-pups*" to equivalently cover information generated from the pre-natal developmental toxicity study according to OECD TG 414 in rats. More specifically, on day 4 of lactation the offspring were externally examined and one male and one female offspring (if possible) were investigated for skeletal examination (excluding ossifications). At weaning, the thoracic and abdominal tissues and organs were examined macroscopically and the cranium externally. However, this study does not provide the information required by Annex X, Section 8.7.2., because of low statistical power of skeletal examinations (only two offspring per litter), limited examinations, failure to investigate all foetuses/pups due to potential cannibalism by the dam, deaths and random culling.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation, you have explained that the available two-generation reproductive toxicity study included additional examination on developmental toxicity that equivalently cover the information generated from an OECD TG 414 study in rats. Based on the results of the two-generation reproductive toxicity study you conclude that the registered substance is not toxic to reproduction or development in the rat. You also provided more information on the results of the available prenatal developmental toxicity study in the rabbit to support your conclusion of no treatment-related abnormalities.

ECHA acknowledges your comments; however, the available two-generation reproductive toxicity study does not provide the information required by Annex X, Section 8.7.2., for the reason indicated in this section above and therefore cannot exclude with certainty respective adverse effects and a residual concern remains.

Therefore, the information provided does not meet the information requirement of Annex IX, Section 8.2. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a non-rodent species (rabbit). According to the test method EU B.31./OECD 414, the rat is the preferred rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rat as a second 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 5.0, December 2016) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rat) by the oral route.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 22 February 2017.

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 amended the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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.