EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000005298-66-02/F Helsinki, 3 October 2014

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For disodium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-), CAS No 15375-84-5 (EC No 239-407-5), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for disodium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-), CAS No 15375-84-5 (EC No 239-407-5), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex VIII, Section 8.4.3. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant and other joint registrants for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

This decision is based on the registration 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 submitted after 12 June 2014, 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

The compliance check was initiated on 14 May 2013.

On 12 June 2013 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 27 June 2013 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 2014 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 proposals for amendment were submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annex VIII of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

- In vitro gene mutation study in mammalian cells (Annex VIII, 8.4.3.; test method: EU B.17/OECD 476).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **12 October 2015**.

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

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements. The scope of the present decision is the *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3. of the REACH Regulation).

Mutagenicity, *in vitro* gene mutation study in mammalian cells.

In accordance with Articles 10(a)(vii), 12(1)(e) and with Annex VIII, section 8.4.3. of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells is required if there is a negative result in the *in vitro* studies specified under Annex VII, section 8.4.1 and Annex VIII, section 8.4.2. The registration dossier reports negative results for both *in vitro* studies. Therefore the REACH Regulation requires that information on *in vitro* gene mutation in mammalian cells (Annex VIII, 8.4.3.) is provided in the dossier. The Registrant has not provided this standard information so consequently there is an information gap and it is necessary to provide information for this endpoint.

In its comments and the update, the Registrant is proposing to use REACH Annex XI, Section 1.5. to adapt the standard information requirement with two published mammalian cell gene mutation assays carried out on proposed read across substances: a mouse lymphoma assay with L5178Y cells, test substance Na_3EDTA (NTP, 1984) and another mouse lymphoma assay with L5178Y cells, test substance Na_2EDTA (Whittaker, 2001).

Additionally, the Registrant refers to the lack of genotoxicity reported in the end point study records for *in vivo* mouse micronucleus results (reliability 2). The substances used were disodium EDTA dehydrate (Cas: 6381-92-6, Russo et al, 1992) and another ([redacted], 2000) in which apparently disodium ethylenediamine tetraacetate was used (CAS: 139-33-3). Three other studies which investigated chromosomal aberration and aneuploidic effects of these same substances were reported as reliability 4. Two of these studies reported as positive for genotoxicity.

The Registrant considers that the registered substance is a part of a larger category of aminocarboxylic acid-based chelants. The Registrant has included a separate document "*Justification in support of cross-reading within the Aminocarboxylic acid-based chelants chemical category*" (March 2013) where the category and the read across approach is justified in more detail. In the category justification, the key element is that the category members have identical functional groups. The presence of multiple carboxylic acid groups on the amine gives chelants their metal ion chelating property. According to the Registrant, this property is the important feature to consider in assessing the mammalian toxicity of chelants and in justifying their consideration as a category. With regard to the genetic toxicity, the category document explains that the positive findings seen in some of the category members genotoxicity studies "*have been generally attributed to the threshold mechanisms of pH changes and the chelation of critical nutrient metals such as zinc rather than direct DNA reactivity.*" In summary, the Registrant bases its read across justification for the registered substance on two characteristics, common functional groups and their ability to disturb functioning of enzymes involved in DNA synthesis.

Under REACH Annex XI, Section 1.5 substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. The Annex additionally states that the study results should "have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)".

ECHA considers that the study by NTP (1984) used an appropriate protocol (mouse lymphoma assay) and has adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3) for investigating *in vitro* mammalian cell gene mutation property. The study from 2001 used too low testing concentration, because the highest dose did not demonstrate sufficient cytotoxicity. The provided tests had a negative outcome. All other studies, e.g., Russo et al, (1992) and [redacted], (2000) did not address the correct parameters (*in vitro* mammalian mutagenicity study) but rather investigated the ability of disodium ethylenediamine tetraacetate to cause chromosomal aberrations or aneuploidic effects.

The justification and hypothesis presented by the Registrant is plausible with regard to the sameness of the organic part of the molecule and that the category members have identical functional groups. It is plausible that the chelating property of these substances plays a role in their genotoxicity and that the positive findings could be related to this. However, ECHA notes that the Registrant's hypothesis or the submitted tests do not account for the possible role in mutagenic effects of manganate which is present in the registered substance. The source substances (Na_2EDTA, Na_3EDTA) in the mouse lymphoma assay contain only sodium ions. The dossier does not contain any information explaining why the genotoxicological properties of sodium are predictive to manganate. ECHA further notes that there is evidence available of manganate mutagenicity and carcinogenicity (Assem et al, 2011). Assem et al concluded that "genotoxicity profile of Mn suggest that it is weakly mutagenic and genotoxic." For example, a positive result in a mouse lymphoma mutagenicity test *in vitro* was quoted.

Consequently, the justification and hypothesis presented by the Registrant is not plausible with regard to the sameness of the *inorganic* part of the molecule of the category members. The Registrant's justification fails to show that the toxicological properties of the inorganic elements are likely to be similar or follow a regular pattern as a result of structural similarity in order that may be considered as a group, or 'category' of substances.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: EU B.17./OECD 476).

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by the Registrant and other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. The Registrant is reminded of his responsibility and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In relation to the information required by the present decision, 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 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 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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on 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.

Leena Ylä-Mononen
Director of Evaluation