ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114328317-51-01/F Helsinki, 14 April 2016

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

For diammonium hexanitratocerate, EC No 240-827-6 (CAS No 16774-21-3), 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 diammonium hexanitratocerate, EC No 240-827-6 (CAS No 16774-21-3), submitted by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study (OECD 414) in rats, oral route, using the analogue substance cerium (III) nitrate.

This decision is based on the registration 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 after 10 February 2016, i.e. 30 calendar days after the end of the commenting period.

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 further examination pursuant to Article 40(1) on 16 February 2015.

ECHA held a third party consultation for the testing proposal from 20 May 2015 until 6 July 2015. ECHA did not receive information from third parties.

On 19 November 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

By 11 January 2016 the Registrant did not provide any comments on the draft decision to ECHA.

On 3 March 2016, ECHA notified the competent authorities of the Member States of its draft decision and invited them to propose amendment to the draft decision under Article 51 of the REACH Regulation. As no amendment was proposed, 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 test pursuant to Article 40(3)(c) and 13(4) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route,

while the originally proposed test for a developmental toxicity study (test method: EU B.31/OECD 414) proposed to be carried out using the analogue substance cerium (III) nitrate is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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.

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 **21 April 2017** 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 proposed to be performed with the analogue substance cerium (III) nitrate (EC No 233-297-2). ECHA has considered first the scientific validity of the read-across hypothesis (section III.0.) before assessing the testing proposed (section III.1.).

A. Tests required pursuant to Article 40(3)

0. Read-across approach

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

According to Annex XI, Section 1.5., there needs to be structural similarity among the substances within a group or category and furthermore, 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 by interpolation to other substances in the group (read-across approach). Furthermore, Annex XI, Section 1.5 lists several additional requirements, including that adequate and reliable documentation of the applied method is to be provided.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant and information submitted by the Registrant to support the grouping and read-across hypothesis

The Registrant has proposed to cover the human health information requirement for a pre-natal developmental toxicity study (Annex IX, 8.7.2.) by performing the test with the analogue substance cerium (III) trinitrate (EC 233-297-2; CAS 10108-73-3) as his source substance to generate data to address by read-across the information requirement for the (target) substance subject to this decision (hereinafter referred to as the registered substance). The Registrant provided a read-across hypothesis driven by the presence and bioavailability of a common metal cation cerium (+III) of both the analogue and the registered substances with the following justification:

"*The substances discussed in this analogue approach are cerium trinitrate and cerium ammonium nitrate. Both substances are water soluble cerium compounds (in pure water) consisting of the same rare earth element (Ce), but different counterparts (nitrate versus ammonium nitrate). Additionally, the oxidation state of cerium is different in these compounds: +IV in cerium ammonium nitrate and +III in cerium trinitrate. Differences in toxicity between different compounds of the rare earth under consideration are dependent on the compounds' inherent properties determining the behaviour in the environment and in living organisms. In this respect, one of the key properties in defining read across strategies is water solubility. For metals, typically the more toxic metal species are released in the medium under consideration (e.g. bodily fluids or environmental media), the more bioavailable/bioaccessible the metal will be. Note that other properties of the substance (e.g. particle size distribution) as well as the characteristics of the receiving compartment (e.g. pH) may also affect bioavailability/bioaccessibility.*

Although cerium ammonium nitrate as well as cerium trinitrate are very soluble in pure water (dissolution accompanied with acidification of the test medium), water solubility is sharply decreased when pH is increased up to environmentally/physiologically relevant pH levels. In environmentally/physiologically relevant aqueous media, dissolved cerium levels (i.e. usually a good measure of bioavailability/bioaccessibility) are dependent on the composition and properties of the medium. For instance, pH and redox potential determine the relative presence of Ce(+IV) (which is not stable in aqueous solutions) and Ce(+III) (which can occur in dissolved state) (Pourbaix diagram, see further). Additionally, complexation of Ce(+III) with phosphates (independent of pH) and pH-dependent formation of Ce(+III) carbonate complexes and Ce(OH)3 will affect the levels of dissolved cerium (reference can be made to Visual MINTEQ v.3.0 modelling performed in the IUCLID endpoint summary for toxicity to aquatic plants as well as in the chemical safety assessment for cerium ammonium nitrate). Because Ce(+IV) cannot occur in dissolved state, any toxicity observed for both tetravalent and trivalent cerium compounds is expected to be due to exposure to bioavailable/bioaccessible Ce(+III). Therefore, read across appears to be possible between these compounds."

To support the proposed read-across approach, the Registrant provided a read-across justification document "*Read across justification for cerium ammonium nitrate*". In this document, the Registrant has provided structures of the analogue and registered substances, an assessment of physico-chemical, environmental fate and toxicity and toxicological properties of the substances, a data matrix presenting physico-chemical properties, environmental fate and toxicity, the results of experimental studies for physico-chemical properties and mammalian toxicity and the classification of the substances. In the technical dossiers and CSR for the registered and analogue substances the Registrant provided experimental studies for human health endpoints.

In addition, the Registrant provided a summary of toxicokinetic data of other cerium compounds "*Toxicokinetic Assessment: Cerium ammonium nitrate*", based on a review of cerium compounds performed by the US EPA (2009).

b. ECHA analysis of the grouping approach and the read-across hypothesis of the Registrant in light of the requirements of Annex XI, 1.5

Firstly, ECHA understands that the Registrant's hypothesis is based on high water solubility of both substances and consequently bioavailability of the common cerium metal in ionic form. The Registrant claims that any toxicity observed for both tetravalent (the registered substance) and trivalent (the analogue substance) cerium compounds is expected to be mainly due to exposure to bioavailable/bioaccessible Ce(+III) cation.

According to the read-across hypothesis, provided by the Registrant, water solubility varies greatly according to pH and is similar for both substances although the time needed to obtain dissolution equilibrium is longer for the registered substance. ECHA notes that the Registrant also explained in the read-across hypothesis that no significant differences were observed in aqueous solubility between these two substances at similar pH levels and consequently bioavailability of both substances is expected to be similar or lower for the registered substance.

The Registrant further explains that the cerium arising from the dissolution of the substances is also dependent on the composition and properties of the medium, on complexation of Ce(+III) with phosphates and carbonates and on particle size distribution. ECHA notes that the Registrant has not adequately explained how the properties of the medium and the complex formation by precipitation impact the dissolution of the substances and how these aspects, together with the different dissolution times, may impact the toxicological properties of the substances.

ECHA therefore concludes that due to uncertainties regarding the dissolution of cerium, the Registrant's claim regarding similar or lower bioavailability for the registered substance compared to the analogue substance has not been verified.

Secondly, the Registrant has provided data (Pourbaix diagram) to support the claim regarding the reduction of Ce(+IV) to Ce(+III)". Based on this analysis, the Registrant claims that Ce(+IV) is not expected to be stable in the aqueous environment and therefore "*adsorption and uptake are most likely only relevant for Ce(+III)*", and concludes that the read-across is justified for environmental endpoints. ECHA notes that the Registrant has not explained how this argument applies for human health endpoints.

Thirdly, the Registrant also states that the reduction of Ce(+IV) to Ce(+III) is expected to be slow and the Ce(+IV) cation of the registered substance is not expected to occur in a dissolved state to a significant extent. ECHA notes that no data has been provided to support the claimed slow rate of reduction in media which are physiologically relevant to human systemic exposure. The Registrant has not adequately explained how this claimed slow rate of reduction supports their read-across hypothesis. ECHA further notes that in respect of the claimed reduction the Registrant makes reference to a report to state that "*experimental data have not demonstrated a change in the oxidation state of the cerium molecule in the body (Berry, 1988, 1989)*". ECHA notes that the claimed reduction of Ce(+IV) to Ce(+III) in the body cannot be verified from the information provided and hence it does not adequately support the read-across hypothesis that "*in the body cerium (+IV) is reduced into better water soluble cerium (+III) which then drives the toxicity*".

ECHA concludes that the Registrant has failed to demonstrate that the reduction of Ce(+IV) to Ce(+III) takes place in physiological conditions relevant to human health. Consequently, the registered and analogue substances might be present in different oxidation states. The Registrant has not addressed how the different oxidation states may affect the toxicological properties of the substances. Therefore, the Registrant's claim that the "*toxicity observed for both tetravalent and trivalent cerium compounds is expected to be due to exposure to bioavailable/bioaccessible Ce(+III)*" has not been verified. Consequently, ECHA considers that based on the information provided by the Registrant, the human health effects of the registered substance cannot be predicted from the properties of the source substance.

Lastly, the Registrant has provided acute oral toxicity, skin and eye irritation/corrosion, skin sensitisation and Ames test conducted with the registered substance. In addition, in the registration dossier for the analogue substance cerium (III) nitrate, the Registrant has provided results of acute oral and dermal toxicity, skin and eye irritation/corrosion, skin sensitisation, Ames test, *in vitro* mammalian cell gene mutation, *in vitro* mammalian chromosomal aberration studies and combined repeated dose toxicity study with reproduction/developmental screening test (OECD 422) conducted with the analogue substance.

ECHA notes that the registered substance is self-classified as acutely toxic (oral, cat 4, LD50 values 300-2000 mg/kg bw), corrosive to the skin and eye, and for skin sensitisation, while the source substance is not classified for acute toxicity (key study acute oral LD50 value 4200 mg/kg bw) or skin sensitisation and is self-classified as irritant to the eye. Both substances do not demonstrate *in vitro* mutagenicity in the Ames test. The Registrant attributes the local adverse effects of the registered substance to the counter anions (NH_4^+/NO_3^-), as they have "*different acidic potency*". However, the Registrant does not expect these differences to alter systemic toxicity and concludes that "*the comparison of those endpoints for which data are available for both compounds, as well as the indications that the substances can be expected to behave similarly in physiologically relevant media and show similar toxicokinetic behaviour, sufficiently supports this read-across strategy (weight of evidence approach)*".

ECHA notes that the experimental data on acute toxicity, skin and eye irriration/corrosion, skin sensitisation provided for both substances are not sufficient to predict similar toxicokinetic behaviour of the substances in respect of assessing the potential for systemic toxicity which is pertinent to the proposed test. More specifically, as there are no studies with repeated dosing on the registered substance available in the registration dossiers, a comparison of the toxicological profiles of the substances after repeated dosing is not possible.

c. Conclusion on the read-across approach

ECHA concludes that the read-across approach cannot be accepted for the reasons set out above. In conclusion, the human health effects cannot be predicted from data for reference substance within the group by interpolation to other substances in the group (read-across approach) as required by Annex XI, 1.5.

ECHA therefore concludes that the criteria of Annex XI, 1.5 are not met, and the read-across approach, as presented by the Registrant, cannot be accepted to meet the information requirements in question.

1. Pre-natal developmental toxicity study

a) Examination of the testing proposal

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.

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 submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414 to be performed with the analogue substance cerium (III) trinitrate (EC No 233-297-2). ECHA does not consider the read-across approach justified as explained above in Section III.0.

ECHA considers that the proposed study type is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

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

For the reasons explained above, the proposed test for a pre-natal developmental toxicity study (test method: OECD 414) via the oral route using the analogue substance cerium (III) nitrate (EC No 233-297-2) is rejected pursuant to Article 40(3)(d) as the provided information on the suggested read-across did not meet the requirements of Annex XI, 1.5. of the REACH Regulation.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

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 has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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. If the registration of the substance covers different grades, the sample used for the new study must be suitable to assess these.

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 Guilhem de Seze, 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.