ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114343357-48-01/F Helsinki, 21 September 2016

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

For trimanganese tetraoxide, CAS No 1317-35-7 (EC No 215-266-5), 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 trimanganese tetraoxide, CAS No 1317-35-7 (EC No 215-266-5), submitted by [redacted] (Registrant).

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 21 July 2016, 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 8 July 2013.

On 29 August 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 September 2013 ECHA received comments from the Registrant on the draft decision. On 21 October 2013 the Registrant updated his registration with the submission number [redacted]

ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex X, Section 8.7.3. The compliance check requirement to submit information of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) has been removed from this draft decision due to the legislative amendments to the REACH Regulation regarding Annex X, Section 8.7.3. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning the information requirement of Annex X, Section 8.7.3.

However, ECHA Secretariat did consider further the Registrant's comments and updates concerning the information requirement of Annex IX, Sections 8.7.2. On the basis of all this information and change of scope, ECHA may, in accordance with Article 41 of the REACH Regulation, initiate a further compliance check of the registration dossier with respect to this information requirement. Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 21 July 2016 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. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1) (a) and (b), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes IX, X 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:

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

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 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **28 September 2017** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two generation reproductive toxicity study (Annex X, Section 8.7.3). As this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a) (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes IX and X of the REACH Regulation.

1. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the updated dossier, the registrant have provided the following endpoint study records for this endpoint:

1) An experimental study, marked as weight of evidence, entitled "Effects of chronic manganese (Mn_3O_4) exposure on selected reproductive parameters in rats." Laskey *et al.,* 1982. Journal of Toxicology and Environmental Health 9:677-687", indicated with reliability score of 4 (study 1);
2) An experimental study, marked as weight of evidence, entitled "Chronic ingestion of Mn_3O_4 by young rats: tissue accumulation, distribution and depletion. Rehnberg *et al.,* 1981. Journal of Toxicology and Environmental Health 7:236-272", indicated with reliability score of 2 (study 2);
3) An experimental study, marked as weight of evidence, entitled "Effect of dietary manganese level on tissue manganese, iron, copper and zinc concentrations in female rats and their fetuses" Järvinen R *et al.,* 1975 Medical Biology 53: 93-99. The study was performed on the analogue substance manganese sulfate (study 3);
4) An experimental study, marked as weight of evidence, entitled "Maternal and developmental toxicity of manganese in mice", Sanchez *et al.,* 1993, Toxicology Letters, 69: 45-52 (study 4); and
5) An adaptation in accordinace with Annex XI, Section 1 indicating that the requested study is not scientifically justified.

Furthermore, the Registrant in its comments on the draft decision provided arguments stating that the study should be adapted based on a weight of evidence argument in accordince to Annex XI, section 1.2. The comments indicated that the most appropriate route of exposure for this substance is the inhalation route, rather than the oral route based on the uses of the substance. Furthermore, the comments indicated that due to the low bioavailability of the substance via the inhalation route, and due to limited workplace exposure, absence of specific reproductive toxicity effects based on the available studies, and animal welfare, the study is not scientifically necessary in accordance with Annex XI, section 1.2 (Weight of Evidence).

However, ECHA notes that the Registrant's adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2 for the following reasons:

- In the technical dossier the registrant has provided a study record for 4 studies (studies 1-4 above). However, studies 1, 2 and 3 do not provide the information required by Annex IX, Section 8.7.2., because they do not provide adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method (OECD TG 414). Specifically, studies 1 and 2 do not include exposure of females during pregnancy, cesarean section and examinations of gross, viceral and skeletal alterations of the pups. In the case of study 3, the examination of the fetuses includes external examination, skeletal examination "skeletal staining" and determination of Mn, Fe, Cu and Zn concentrations in the body, but no examination of the soft tissue alterations, as required by OECD TG 414. Furthermore, in study 3, five fetuses taken at random underwent skeletal staining. OECD TG 414 by contrast requires that "for rodents, approximately one half of each litter should be prepared and examined for skeletal alterations. The remainder should be prepared and examined for soft tissue alterations".

- Moreover, study 4 on the analogue substance manganese chloride was performed via the subcutaneous route of exposure. ECHA notes that the subcutaneous route of exposure is not a normal route of exposure in such studies, and there are some deviations in this study compared to the OECD 414 guideline. The study nevertheless may be considered as a worst case scenario in this case, since exposure by the subcutaneous route to this more soluble form of manganese likely results in a higher exposure to manganese cations compared to oral or inhalation exposure to the less soluble trimanganese tetroxide. ECHA notes, however, that the results of this study indicate that the substance does have effects in the study. The NOAEL for embryotoxicity was 2 mg/kg/bw/day and the NOAEL for maternal toxicity was 4 mg/kg/bw. Mortality was observed in the top dose of the study (16 mg/kg/bw). In addition, there was a significant increase in the number of late resorptions in the 4, 8 and 16 mg/kg/bw dose groups. Furthermore, the test substance had an effect on foetal body weights and a dose response relationship was observed. These effects suggest that the substance has significant effects in a pre-natal developmental toxicity study. These results may lead to the opposite conclusion (i.e. that the substance does have effects in the PNDT study that may require classification and labelling). These effects may lead to the classification and labelling of the substance, although ECHA notes that as the subcutaneous route was used, there may be some questions about the relevance of this particular route of exposure.

- Finally, ECHA acknowledges that in his comments to the draft decision, the Registrant indicates that the inhalation route may be the most appropriate route of exposure based on the particle size of the substance. But at the same time, the information available on the solubility of the substance in artificial gastric fluid and artificial alveolar fluid suggests that the oral route would maximise the exposure to manganese. The study on absorption of manganese ([redacted] showed that for the registered substance, 13% of the manganese may be extractable in artificial gastric fluid, whereas only 0.000047% would be extractable in artificial alveolar fluid. This would suggest that the oral route of exposure may be a better route of exposure for this PNDT study.

As highlighted above, each of the four studies individually do not provide adequate and reliable coverage of the key parameters foreseen to be investigated by the relevant study for this endpoint. In addition, contrary to the Registrant's conclusions, ECHA considers that study 4 provides evidence that manganese may have effects in a pre-natal developmental toxicity study. Finally, the information available on the solubility of the registered substance indicates that the oral route may be a more appropriate route of exposure for this study. On this basis ECHA considers that the Registrant has not demonstrated that there is sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance has or has not effects in a pre-natal developmental toxicity study. Therefore, the Registrant's adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2, and the adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first 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 4.1, October 2015) R.7a, chapter 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.

Regarding the route of exposure, ECHA observes that while the Registrant considers that the inhalation route may be a more realistic route of exposure for workers, the solubility of the registered substance is significantly lower in artificial lung fluid compared to simulated gastric fluid (0.000047% vs. 13%). This indicates that the oral route is the best route of exposure for the prenatal developmental toxicity study. ECHA therefore considers that the study should be performed by the oral route in order to maximise exposure of the developing foetuses to the registered substance.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

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; 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.

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.

If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

IV. Adequate identification of the composition of the tested material

In relation to the information required by the present decision, the sample of substance used for the new studies 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 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies 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.

Authorised[2] by Ofelia Bercaru , Head of Unit, Evaluation E3.

[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.