EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000004988-54-03/F Helsinki, 22 January 2015

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

For [redacted] CAS No [redacted] (EC No [redacted]), 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 [redacted], CAS No [redacted] (EC No [redacted] submitted by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study (OECD 414).

This decision is based on the registration dossier 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 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 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.

The examination of the testing proposal was initiated upon the date when receipt of the complete registration dossier was confirmed on 6 September 2013.

ECHA held a third party consultation for the testing proposal from 22 October 2013 until 5 December 2013. ECHA received information from third parties (see section III below).

On 5 March 2014 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 4 April 2014 the Registrant did not provide any comments on the draft decision to ECHA.

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 proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(b) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

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

The dossier contains some indications that the substance may also be manufactured in grades that meet definition in the EU recommendation for nanomaterials[1]. ECHA reminds the Registrant that the REACH Regulation imposes the determination of hazards and risk irrespective of the form of the substances concerned to ensure a high level of protection of human health and the environment. This includes grades that refer to nanoforms of substances, which may trigger specific hazardous properties and risks, as already highlighted by various institutions, including the European Parliament.[2]

ECHA highlights that failure to report sufficient information on each grade of a substance in the dossier, whether in a specific nanoform of the substance or not may result in these grades not being covered by this registration.

ECHA also notes that the REACH Regulation requires the Registrant to identify the pre-natal development toxicity potential of the substance irrespective of its form, as they may, in principle, entail different hazards. In theory, in order to fulfil that requirement, experimental information is needed on each specific form covered by the dossier of the registered substance. However, the Registrant may take the responsibility to select one or more representative form(s) of the substance in order to address the hazards of the different forms.

In case where more than one form of the substance needs to be tested, the Registrant shall submit a new testing proposal for each additional experimental study planned.

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.

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[1] *Commission Recommendation on the Definition of Nanomaterials of 20 October 2011, 2011/696/EU.*

2 *"Whereas nanomaterials [...] potentially present significant new risks due to their minute size, such as increased reactivity and mobility, possibly leading to increased toxicity in combination with unrestricted access to the human body, and possibly involving quite different mechanisms of interference with the physiology of human and environmental species"*. Recital D of European Parliament Resolution of 24 April 2009 on Regulatory aspects of nanomaterials.

2. 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 **29 January 2016** an update of the registration dossier containing the information required by this decision.

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 and scientific information submitted by third parties.

1. Pre-natal developmental toxicity study

a) Selection of the test material(s)

In section 3.1 of the dossier, the Registrant has included a reference to '[redacted]'. As the carbon coated material is stated to be '[redacted]' and is used as [redacted], the substance may be manufactured in grades that fulfill the EU recommendation for nanomaterial. It is thus unclear whether the dossier covers different forms of the substance.

The purpose of the REACH Regulation is to ensure a high level of protection of human health and the environment. In order to achieve this objective, the REACH Regulation imposes the determination of hazards and risks of substances manufactured or imported into the European Union. The determination of hazards and risks is irrespective of the forms of the substances concerned.

Current scientific knowledge establishes that the risks of nanoforms of substances would require separate assessment. Indeed, the potential risks of nanoforms are not founded on mere hypotheses that have not been scientifically confirmed. These potential risks have been demonstrated by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).[3] The fact that there is still some degree of scientific uncertainty as to the existence or extent of such risks does not, by itself, discharge registrants from characterising nanoforms in order to carry out their duties under the REACH Regulation. Based on the above, the Registrant is compelled to scientifically assess the potentially adverse effects of nanoforms.

It is therefore of utmost importance that the data generated with the test proposed allows the determination of the actual hazards posed by the registered substance, irrespective of its forms. Accordingly, when a registration dossier concerns a substance subject to different forms and phases, which may result in different hazards and risks, the Registrant is compelled to determine the specific hazards and risks relevant for each specific form.

[3] "*There is sufficient evidence that there can be a change in some properties of the material at the nanoscale which is, for instance, due to the increase in surface-to-volume ratio. These nanospecific properties raise concerns over their potential to cause harm to humans and the environment. The chemical reactivity of nanoparticles often relates to the surface area. Consequently, the chemical reactivity per mass dose increases for smaller particles of the same type. This effect may or may not be associated with an increase in biological activity or toxicity*". SCENIHR, Opinion of 8 December 2010 on *Scientific Basis for the Definition of the Term «nanomaterial »*, page 31.

In case the registration dossier covers different forms of the substance, the responsibility to decide which forms of the substance to test falls to the Registrant. Based on the above and on his knowledge of the substance identity, the Registrant may consider it necessary to test all the forms in order to determine their specific hazards. Alternatively, the Registrant may decide to test only one or some of these forms. This approach may fulfil the information requirement only if the Registrant can scientifically justify why he considers a particular form to be representative of the toxicological hazards of other forms and documents that this choice would not lead to an underestimation of the hazards. The Registrant shall also provide adequate information on the characteristics of the tested substance.

If, upon further consideration of the documentation provided, ECHA considers any justification provided inadequate to exclude an underestimation of the hazards, it reserves the right to request additional tests necessary to fulfil the fundamental objectives of the REACH Regulation.

In case where more than one form of the substance is tested, the Registrant shall submit a new testing proposal for each additional experimental study planned.

b) Examination of the testing proposal

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

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. ECHA concludes that 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 according to EU B.31/OECD 414.

The Registrant did not specify the species to be used for testing and did not specify the route 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.

If the testing is performed in relation to nanoforms of the substance, ECHA notes that on September 20, 2013, the Organization for Economic Cooperation and Development (OECD) announced a recommendation applicable to existing regulatory frameworks to manage risks associated with manufactured nanomaterials. A set of tools for testing and assessment are also recommended by OECD.
These tools all come from the body's Series on the Safety of Manufactured Nanomaterials, and are:

- Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials [ENV/JM/MONO(2009)21];
- Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials [ENV/JM/MONO(2012)40];
- Identification, Compilation and Analysis of Guidance Information for Exposure Measurement and Exposure Mitigation: Manufactured Nanomaterials [ENV/JM/MONO(2009)15];
- Important Issues in Risk Assessment of Manufactured Nanomaterials [ENV/JM/MONO(2012)8].

For nanomaterials, these tools should be used in conjunction with existing OECD Test Guidelines, which shall be 'adapted as appropriate to take into account the specific properties of manufactured nanomaterials'.

c) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information:

A third party has proposed a weight-of evidence approach for ECHA to take into account before further tests on vertebrate animals are required. As part of this approach, the third party provided results from pre-natal developmental studies on the read-across substances: Ferrus sulphate (rats, guideline and/or exact study conditions not specified; 1974); Ferric sodium pyrophosphate (rats, guideline and/or exact study conditions not specified; 1975); and Lithium carbonate (rats, mice and rabbit, guideline and/or exact study conditions not specified; 1972, 1979, 1982, 1986, 1988, 1989, and1995). In addition, the third party has provided additional arguments based on toxicokinetics, i.e. assumed low bioavailability for the substance subject to this decision and experience from clinical practice of lithium therapy.

ECHA has taken the information provided into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.2 and 1.5 of the REACH Regulation are met. More specifically, the proposed weight-of-evidence approach based on the information provided by the third party is not sufficient to assume that the substance subject to this decision (including all forms of the substance) has or has not a particular dangerous property after gestational exposure and that the standard information requirement for a pre-natal developmental toxicity study could be adapted. In particular, the third party has not provided sufficient information with regard to the guideline used and/or exact study conditions in order to allow an independent assessment of the

information provided. With regard to the assumed low bioavailability, ECHA notes that the effects observed in the available OECD 408 study on the substance subject to this decision do not support this assumption. With regard to the experience from clinical practice the third party has not linked the exposure in the clinical setting to the plasma concentrations expected in an OECD 414 study. Furthermore, the proposed read-across approach as an element of the weight of evidence justification did not demonstrate how the human health effects of all forms of the registered substance may be predicted from data on the reference substances.

Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfil Annex XI requirements and is therefore not sufficient to allow ECHA to reject the testing proposal. Nevertheless, ECHA acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities. This would require that the Registrant documents, using several independent sources of information, that there is a sufficient weight of evidence leading to the assumption/conclusion that a substance has or has not particular dangerous properties, according to the criteria laid down in Annex XI of the REACH Regulation.

d) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the proposed 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 meets real information needs. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed test, the sample of substance used for the new study(ies) 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 of the same substance to agree to the test proposed (as applicable to their tonnage level) 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(ies) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition and form 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(ies) must be suitable to assess these grades.

If the sample is used to assess different forms of the substance and a representative form is tested, also information as specified below has to be provided:

a) detailed information on the composition of the sample tested: this must include information on the particle size of the tested material;
b) an explanation why the sample tested represents the forms of the registered substance. In particular it should be explained how all the forms with possible

different hazards are represented in the composition of the sample tested;

c) information, based on available knowledge on the known hazards of each form of the registered substance, to demonstrate that testing that sample does not result in an underestimation of the hazards.

Should the sample cover nanoforms, ECHA also notes that the following guidance is recommended to be followed:

- Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials [ENV/JM/MONO(2012)40].

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(ies) 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://echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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