Decision number: TPE-D-0000002923-72-03/F Helsinki, 13 February 2014

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

For Bismuth, CAS No 7440-69-9 (EC No 231-177-4), 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 proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12 (1)(e) thereof for Bismuth CAS No 7440-69-9 (EC No 231-177-4), by [redacted] (Registrant).

- Repeated Dose 90-Day Oral Toxicity in Rodents (OECD Guideline 408) in rats with additional examinations/parameters to evaluate potential effects on reproduction, using the analogue substance bismuth hydroxide nitrate oxide (CAS No 1304-85-4; EC No 215-136-8);
- Prenatal Developmental Toxicity Study (OECD Guideline 414) in rats, oral route using the analogue substance bismuth hydroxide nitrate oxide (CAS No 1304-85-4; EC No 215-136-8).

This decision is based on the registration dossier 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 after 31 October 2013, 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 present dossier at a later stage.

On 1 December 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a public consultation for the testing proposals from 15 April 2011 until 30 May 2011. ECHA did not receive information from third parties.

On 18 October 2012 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 19 October 2012 the Registrant did not provide any comments on the draft decision to ECHA.

On 31 October 2013 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 to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the analogue substance bismuth hydroxide nitrate oxide CAS No 1304-85-4 (EC No 215-136-8):

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408). It is at the Registrant's discretion to perform the intended additional examinations during the testing program; and
2. Pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **13 February 2016** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. 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. 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.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance.

In relation to the testing proposals subject to the present decision, the Registrant has proposed using the read-across approach, in accordance with Annex XI, 1.5, and to perform the relevant tests on another substance than the registered substance. ECHA has considered first the scientific validity of the proposed read-across approach (Section III.1 below), before assessing the testing proposed (Sections III.2 and III.3 below).

0. Read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

The Registrant proposed to carry out both the Repeated Dose 90-Day Oral Toxicity in Rodents (OECD Guideline 408) and the Prenatal Developmental Toxicity Study (OECD Guideline 414) by using the analogue substance bismuth hydroxide nitrate oxide (CAS No 1304-85-4; EC No 215-136-8). The Registrant has justified the read-across approach based on the assumption that bismuth ion concentrations are the most relevant parameter to evaluate bismuth toxicity.

In the Chemical Safety Report, the Registrant states that "*Read across between bismuth hydroxide nitrate oxide and bismuth metal is considered feasible without restriction with the following rationale: Bismuth substances dissociate in water to Bi3+and the anionic counter-ions and it can be assumed that potential effects are caused by Bi3+. In addition, bismuth is absorbed rapidly after oral dosing evident by an increased bismuth concentration in blood, even though the absorption rate is very low".*

ECHA notes that both studies proposed by the Registrant will address systemic effects due to exposure to the bismuth ions. Bismuth hydroxide nitrate oxide (read-across substance) is more soluble than the registered substance. Consequently a higher bioavailability of bismuth ions can be expected for the read-across substance than for the registered substance. Testing with the read-across substance proposed by the Registrant is thus expected not to underestimate the health hazards of the registered substance as they will be addressed in both studies.

ECHA considers that the justification given demonstrates that it is plausible that the requirements of Annex XI, section 1.5 in conjunction with article 13(1) and Annex IX, third introductory paragraph, of the REACH Regulation may be met. Specifically, adequate and reliable documentation of the applied read-across approach has been provided, and ECHA considers that there appears to be a scientific justification that effects for repeated dose toxicity and pre-natal developmental toxicity studies could be predicted from data for the substance bismuth hydroxide nitrate oxide through the read-across approach. However, a final conclusion on the validity of the suggested approach to adapt the standard information requirement will only be possible when it has been demonstrated on the basis of test results that the conditions set out in Annex XI section 1.5 are met for the particular endpoints.

Therefore, ECHA emphasises that it is the Registrant responsibility to amend and substantiate read-across justification according to Annex XI, section 1.5 and to use all relevant available data, when the results of the tests are available.

Following the update of the dossier based on the present decision, ECHA will decide whether the evidence provided is sufficient to satisfactorily address the information requirement for the substance subject to this decision as proposed by the Registrant. If, upon further consideration, the proposed approach does not satisfy the conditions set out in Annex XI, ECHA reserves the right to request the information necessary to fulfil the information requirements.

1. Sub-chronic toxicity study (90-day)

a) Examination of the testing proposal

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

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, section 8.6.2. 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 generate the data for this endpoint.

The Registrant proposed testing with bismuth hydroxide nitrate oxide (CAS No. 1304-85-4: EC No. 215-136-8).

The Registrant proposed testing by the oral route. In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including evaluation of potential effects on reproduction. ECHA notes, that it is at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance. However, the Registrant is reminded that the proposed extension of this study does not fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex X, 8.7.3. unless Annex X, 8.7. column 2 adaptation is applied.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using bismuth hydroxide nitrate oxide. It is at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance.

2. Pre-natal developmental toxicity study

a) Examination of the testing proposal

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

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, 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 proposed testing with bismuth hydroxide nitrate oxide (CAS No. 1304-85-4: EC No. 215-136-8).

The Registrant proposed testing by the oral route and in rats. 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 as a first species to be used.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414 using the analogue substance bismuth hydroxide nitrate oxide.

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all 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.

IV. Adequate identification of the composition of the tested material

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies 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 evaluation of the testing proposal. 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 tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests 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 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 grades registered to enable the relevance of the studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. 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/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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