Decision number: TPE-D-0000004410-87-02/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 Dibismuth trioxide, CAS No 1304-76-3 (EC No 215-134-7), 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 jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for Dibismuth trioxide, CAS No 1304-76-3 (EC No 215-134-7), [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 100 to 1000 tonnes per year. ECHA furthermore notes that one or more member registrant manufactures or imports the registered substance at a tonnage 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 third party consultation for the testing proposals from 29 April 2011 until 14 June 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. That draft decision was based on submission number [redacted].

On 19 November 2012 ECHA received comments from the Registrant. On 19 November 2012 the Registrant updated his registration dossier (submission number [redacted]).

ECHA considered the Registrant's comments and update received. On basis of the comments, and the new information in the received update, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

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) of the REACH Regulation using the indicated test method:

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).

Depending on whether the water solubility of the crystalline phases of the substance subject to the present decision would confirm or not confirm the read-across hypothesis of the Registrant, these tests shall be performed:

a) Either on the analogue substance bismuth hydroxide nitrate oxide oxide (CAS No. 1304-85-4: EC No. 215-136-8);

b) Or on each phase of the substance subject to the present decision.

If the Registrant decides not to perform the required tests with each phase concerned by the dossier, he shall demonstrate, in accordance with the specific requirements outlined in Section IV below, that the material used for testing is representative for every phase covered by the dossier, in order to establish the relevant hazards of each of these phases. The information ultimately submitted by the Registrant shall thus demonstrate that the testing of such material does not result in an underestimation of the hazards of any phases covered by the dossier of the registered substance.

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.

ECHA notes that the substance concerned by the registration Dibismuth trioxide, CAS No 1304-76-3 (EC No 215-134-7), only exists in the form of crystalline phases, while the dossier initially submitted (submission number [redacted]) did not specify any phase. Following ECHA's draft decision the Registrant has updated his registration dossier on 19 November 2012 (submission number [redacted]) specifying the different crystalline phases (α-dibismuth trioxide (specified as monoclinic), and ß-dibismuth trioxide (specified as pseudo-cubic or tetragonal) that are covered by the registration.

In addition, the Registrant refers in its dossier to a *"Bi2O3 submicron/nanosize"* grade. The Registrant must be informed that, considering the information provided, ECHA considers that none of the grades reported in the section "4.5 Particle size distribution (granulometry)" of the IUCLID dossier, meet the criteria set out in under the "Commission Recommendation of 18 October 2011 on the definition of nanomaterial". This determination is based on the provided particle size distributions for the different grades of the substance in the above mention section of the IUCLID dossier and despite the reference to a *"Bi2O3 submicron/nanosize"* grade.

ECHA stresses that the evaluation of a dossier can only address the phases or forms (including nanoforms) of a substance that are precisely identifiable from the dossier. Accordingly, the registration of Dibismuth trioxide shall not be considered to cover the phases or forms of the substance which have not been properly identified in the dossier.

Moreover, in relation to the testing proposals subject to the present decision, the Registrant has proposed to use a read-across approach, in accordance with Annex XI, 1.5, and to perform the proposed tests on an analogue substance. To the extent that all proposed testing relies upon the testing of same material, ECHA has considered first the scientific relevance of the test material proposed by the Registrant (preliminary considerations; Section 0, below), before assessing the testing proposed (Section 1 and 2 below).

0. Read-across approach

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 phases or forms of the substances concerned.

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 phases or forms. Specifically, and in view of the considerable difference in the phases or forms of the registered substance, the proposed test shall aim at identifying all the actual human health hazards of the registered substance, and shall preclude underestimation of hazards. Indeed, it should be noted that the difference in phases of the registered substance does not relieve the Registrant from complying with the obligation to identify accurately hazards posed by the substance, irrespective of these phases.

Accordingly, when a registration dossier concerns a substance subject to different phases or forms, which may result in different hazards and risks, the Registrant is compelled to determine the specific hazards and risks relevant for each specific phase or form. This is notably the case for crystalline phases, where differences in the crystalline phase of a substance may result in different toxicity, as is known for example for amorphous and crystalline silicon dioxide.

In that context, the REACH Regulation also promotes alternative methods for the assessment of hazards of substances, including the specific phases of these substances. As a result, the REACH Regulation allows the Registrant to identify the hazards of these specific phases by alternative means offering equivalence to test methods.

In the present case, ECHA notes that 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).

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".

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category such that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) within the group by interpolation.

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. More specifically, in the Chemical Safety Report, the Registrant states that "*Read across between bismuth hydroxide nitrate oxide and dibismuth trioxide 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 understands that the read-across hypothesis assumes that all the crystalline phases of the substance subject to the present decision will exhibit no difference in systemic effects due to exposure to the bismuth ions.

However, ECHA notes that currently the read-across hypothesis is based only on the assumption that the analogue substance (Bismuth hydroxide nitrate oxide) is more soluble than the crystalline phases of the substance subject to the present decision and that, consequently, a higher bioavailability of bismuth ions can be expected for the analogue substance than for the registered substance.

While ECHA recognises the relevance of bioavailability of bismuth ions for the determination of the systemic effects of the various phases of the substance, it concludes that the Registrant's assumption of similar toxicity for these phases and the analogue substance is not supported by the currently available information. This circumstance creates uncertainties that will have to be addressed by the Registrant in order to meet the conditions set out in Annex XI, section 1.5. of the REACH Regulation.

ECHA considers that the read-across hypothesis proposed by the registrant could only be validated following the confirmation of the assumption that the analogue substance (Bismuth hydroxide nitrate oxide) is more soluble than the crystalline phases of the substance subject to the present decision. The determination of the solubility of each of the phases of the substance is therefore a prerequisite to confirm their toxicological profile based on the read-across approach. ECHA considers that generating this additional information on each phase of the substance is therefore an essential condition for the ultimate acceptance of the read-across approach in relation to sub-chronic toxicity and pre-natal developmental toxicity.

In the case where the solubility of the crystalline phases of the substance subject to the present decision would not confirm the read-across hypothesis relied upon by the Registrant, this outcome shall not alter the obligation of the Registrant to meet the standard information requirements. Should the read-across strategy be inadequate, it is the responsibility of the Registrant to submit reliable information or adaptations that do not underestimate the hazards of the crystalline phases of the substance subject to the present decision in relation to the relevant endpoints.

Consequently, based on the available compositional information and supporting information about the underlying chemistry, ECHA considers plausible the read-across hypothesis between the substance subject to the present decision and the analogue substance, under the condition that the Registrant demonstrates that the water solubility of all the crystalline phases of the substance subject to this decision covered in the dossier is lower than the water solubility of the analogue substance.

In any case, 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 and for the relevant phases.

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 requirements for all the crystalline phases for the substance subject to this decision, as proposed by the Registrant. If, upon further consideration, the updated dossier does not satisfy the requirements of this decision and of the REACH Regulation, 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) 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 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.

In accordance with Column 1 of Annex IX, section 8.6.2 of the REACH Regulation the study should be performed via "the most appropriate route of administration, having regard to the likely route of human exposure". Column 2 of Annex IX, section 8.6.2 defines that inhalation route is appropriate if "exposure of humans via inhalation is likely taking into account (...) the possibility of exposure to aerosols, particles or droplets of an inhalable size".

Considering the process categories reported by the Registrant for some of the uses by workers in industrials settings and by professional workers (e.g. PROC 7, PROC 8a, and PROC 8b) inhalation appears to be the most likely route of human exposure. However, from the results of results of a testing programme on dustiness testing coupled with particle size analysis and modelling to predict deposition patterns in the respiratory tract, the Registrant dismisses the exposure of workers to respirable particles of the registered substance, considering the very low predicted deposition of dibismuth trioxide in the pulmonary/alveolar region of the respiratory tract. The Registrant states that even if inhaled, the particles will not reach pulmonary/alveolar region and will be either spat or swallowed.

ECHA notes that the reporting level from the above mentioned testing programme is not so detailed as to allow ECHA to irrevocably exclude or confirm the possibility of exposure of workers to respirable particles. ECHA has therefore not concluded as to whether there is any need for a study by the inhalation route.

It is the Registrant's responsibility to evaluate if there are potential local effects by inhalation or any potential inhalation route specific systemic toxicity, and in the case he finds them relevant, make an additional related testing proposal.

Nevertheless, in view of the information currently provided in the dossier, ECHA accepts the route proposed by the Registrant, i.e. the oral route.

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) 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). Depending on whether the water solubility of the crystalline phases of the substance subject to the present decision would confirm or not confirm the read-across hypothesis of the Registrant, as explained in section III.0. above, the study shall be performed:

c) Either on the analogue substance bismuth hydroxide nitrate oxide oxide (CAS No. 1304-85-4: EC No. 215-136-8);
d) Or on each phase of the substance subject to the present decision.

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 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) 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). Depending on whether the water solubility of the crystalline phases of the substance subject to the present decision would confirm or not confirm the read-across hypothesis of the Registrant, as explained in section III.0. above, the study shall be performed:

a) Either on the analogue substance bismuth hydroxide nitrate oxide oxide (CAS No. 1304-85-4: EC No. 215-136-8)
b) Or on each phase of the substance subject to the present decision.

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.

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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