Decision number: TPE-D-0000004597-63-03/F Helsinki, 29 August 2014

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

For bismuth trinitrate, CAS No 10361-44-1 (EC No 233-791-8), 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)(d) thereof for bismuth trinitrate, CAS No 10361-44-1 (EC No 233-791-8), submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408) in rats, oral route using the analogue substance bismuth hydroxide nitrate oxide and including evaluation of potential effects to reproduction by examination of additional parameters: "microscopic examination of selected tissues like testes or epididymides as well as monitoring the status of relevant hormones like testosterone in additional blood samples".
- Prenatal Developmental Toxicity Study (OECD 414) in rats, oral route using the analogue substance bismuth hydroxide nitrate oxide.

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 proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 26 June 2013.

ECHA held a third party consultation for the testing proposals from 20 September 2013 until 4 November 2013. ECHA did receive information from third parties (see section III below).

On 10 December 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 45 days of the receipt of the draft decision.

By 24 January 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 additional tests pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408).
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

while the originally proposed tests for a 90-day oral toxicity study (test method: OECD 408) and Prenatal Developmental Toxicity Study (test method: OECD 414) proposed to be carried out using the analogue substance bismuth hydroxide nitrate oxide are rejected pursuant to Article 40(3)(d) of the REACH Regulation.

It is at the Registrant's discretion to perform the intended additional examinations initially suggested to be carried out in the testing of the analogue substances during the testing program as required under 1. and 2. for the substance subject to the present decision.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **5 September 2016** an update of the registration dossier containing the information required by this decision. The timeline has been set to allow for sequential testing as appropriate.

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.

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.

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 and scientific information submitted by third parties.

In relation to the testing proposals subject to the present decision, the Registrant has proposed to use a read-across and grouping approach, in accordance with Annex XI, 1.5., and to perform the proposed tests on an analogue substance as outlined below. ECHA has considered first the scientific validity of the proposed read-across and grouping approach (Section 0 below), before assessing the testing proposed (Section 1 below).

0. Consideration of the read-across approach

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. Towards this end, it is necessary to consider whether programmes of testing proposed by registrants are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting, wherever possible, the use of alternative means, to obtain equivalent information to the prescribed tests for determining health and environmental hazards. In accordance with these objectives, ECHA shall assess whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed tests is sufficiently plausible based on the information currently available.

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 on reference substance(s) within the group by interpolation.

To fulfill the standard information requirements for bismuth trinitrate with respect to the endpoints subchronic toxicity (90-day) and pre-natal developmental toxicity, the Registrant proposed a read-across approach based on testing to be performed on the analogue substance bismuth hydroxide nitrate oxide (also named bismuth subnitrate).

In the present case, ECHA considers that the read-across approach proposed by the Registrant does not give sufficient guarantees that equivalent results to the prescribed information will be provided on the health hazards. More specifically, Section 1.5. of Annex XI of the REACH Regulation sets out the conditions to be met by alternative methods so that equivalent results to the prescribed test may be obtained. The read-across justification provided by the Registrant does not fulfil those conditions in relation to the documentation provided. In particular, it does not enable the toxicological properties of the registered substance bismuth trinitrate to be predicted from data for bismuth subnitrate for the reasons outlined below.

It is a requirement of Annex XI, Section 1.5., that "adequate and reliable documentation of the applied method shall be provided." In the present case, ECHA notes that the documentation submitted is inadequate.

The table in section R.6.2.6.1 "Reporting Format for the analogue approach" of ECHA's Guidance on information requirements and chemical safety assessment, R.6 (May 2008), sets out aspects which must be addressed to justify a read-across hypothesis. In the dossier provided by the Registrant, the following issues were not addressed to a sufficient extent:

Analogue approach justification. The guidance highlights the following: "Based on available experimental data, including basic physico-chemical properties, summarise how these results verify that the read-across is justified. The data should also show that functional groups not common to source and target chemicals do not affect the anticipated toxicity. The available experimental results in the data matrix [...] should support the justification for the read-across."

In the Chemical Safety Report (CSR) the Registrant has attached as appendix 1 a "Justification of read-across approach". This document summarises in a tabular form the physico-chemical properties of seven bismuth compounds, including both bismuth trinitrate and bismuth subnitrate. The Registrant makes the argument that all seven compounds have similar physico-chemical properties but bismuth subnitrate has the highest water solubility and has therefore the highest bioavailability. Under the section of developmental toxicity of the CSR the Registrant makes the additional argument that "bismuth subnitrate is a moderately soluble bismuth substance and yields bismuth and nitrate ions upon dissolution thus read-across from bismuth subnitrate to bismuth nitrate is considered feasible".

ECHA notes that the Registrant has supported the argument of higher water solubility of the proposed analogue substance in the above-mentioned read-across justification table which gives a water solubility of 900 mg/l for the analogue substance bismuth subnitrate and 50 mg/l for the registered substance bismuth trinitrate. In a footnote the Registrant claims, however, that a definitive value for water solubility of the registered substance cannot be established. ECHA notes further that in section "1.3 Physico-chemical properties" of the CSR the Registrant states that the water solubility of the registered substance varies according to several parameters and a range of 50 – 2180 mg/l is given. Due to this variation and the inconsistent information provided on water solubility, ECHA concludes that it is not possible to verify the Registrant's argument that the analogue substance bismuth subnitrate has a higher water solubility and therefore a higher bioavailability than the registered substance bismuth trinitrate.

Data matrix. The Guidance R.6 highlights the following: "Provide a matrix of data (endpoints vs. target and source chemicals) [...]. In each cell in the Data Matrix, the study result type should be indicated in the first line, e.g.: experimental result, experimental study planned, read-across from supporting substance (structural analogue or surrogate), (Q)SAR. If experimental results are available, the key study results should be shown in the Data Matrix." As already pointed out above the Registrant has made the argument that bismuth trinitrate and bismuth subnitrate have similar physico-chemical properties. However, the Registrant has not provided any data matrix or other comparison for the toxicological (or eco-toxicological) properties of these two substances. ECHA notes further that the registered substance bismuth trinitrate is classified as an oxidiser as well as causing serious eye damage while the proposed analogue substance is not classified. This would indicate that the toxicological properties of the two compounds are different. Furthermore the Registrant has not provided any comparison of toxicological differences that might or might not arise from different amounts of nitrate ion produced upon dissolution of bismuth subnitrate in comparison to bismuth trinitrate.

Based on the above, the proposed read-across approach does not satisfy requirements of Annex XI, section 1.5., in terms of documentation of the adaptation argument and consequently does not allow predicting the toxicological and eco-toxicological properties of the registered substance bismuth trinitrate from tests conducted with the analogue substance bismuth subnitrate. Therefore the tests on the analogue substance are not appropriate to fulfil the information requirements of the substance subject to the present decision.

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA rejects the proposals to carry out the tests on the analogue substance bismuth hydroxide nitrate oxide (bismuth subnitrate) as non-compliant with the REACH Regulation.

Nevertheless, it is necessary to consider whether the tests proposed shall be performed in order to meet the information requirements.

1. Repeated dose toxicity study (Annex IX, 8.6.2.)

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 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 provide information for this endpoint.

The Registrant proposed testing by the oral route. The registered substance is a solid with a low fraction of inhalable particles and the exposure estimates indicate low levels of inhalation exposures. In 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 most appropriate.

The Registrant proposed testing in rats. According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including additional examinations/parameters: "microscopic examination of selected tissues like testes or epididymides as well as monitoring the status of relevant hormones like testosterone in additional blood samples". 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 the Registrant applies the results from the 90-day study as a valid adaptation according to Annex X, 8.7., column 2.

b) 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.

A third party provided the following information: "We refer to a recently conducted 90-day oral toxicity study with bismuth citrate. A summary of the study was submitted to the US Environmental Protection Agency. Provided suitable methodology these data can support the registrants' category approach for bismuth chemicals based on similar physicochemical properties and low enteral absorption. Then performing the proposed 90-day oral toxicity study is not required to fulfil the information requirements and additionally is not in the interests of animal welfare."

A third Party has proposed a read-across approach for ECHA to take into account before further tests on vertebrate animals are required. As part of this approach, the third party provided a reference to a 90-day subchronic gavage oral toxicity study in rats by using the read-across substance bismuth citrate, but did not provide the study itself.

ECHA has taken the information provided into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. More specifically, the proposed read-across approach did not provide an adequate and reliable documentation to demonstrate that the toxicological effects of the registered substance after sub-chronic exposure can be predicted from the data existing on the analogue substance due to structural similarity and that the standard information requirement for a sub-chronic repeated toxicity study (90-day) could be adapted.

Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfill 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 that the sub-chronic repeated dose toxicity of the registered substance can be predicted from the data existing on the analogue substance based on structural similarity according to the conditions laid down in Annex XI Section 1.5.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) As explained in Section III.0 above, the read-across approach proposed by the Registrant is to be rejected based on Article 40(3)(d) of the REACH Regulation as non-complint with Annex XI, 1.5. requirements. The study shall therefore be performed using the substance concerned by the present decision, bismuth trinitrate CAS No 10361-44-1 (EC No 233-791-8).

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

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 proposed testing in rats. He proposed testing by the oral route. 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) 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.

A third party provided the following information: "We refer to existing embryo-foetal developmental toxicity studies in rats and rabbits with the analogue chemical bismuth citrate. These studies were performed by a manufacturer of pharmaceuticals who is willing to enter into a discussion with the registrant regarding the suitability of these studies. Provided adequate methodology these data can support the registrants' category approach for bismuth chemicals based on similar physicochemical properties and low enteral absorption. Then performing the proposed pre-natal developmental toxicity study is not required to fulfil the information requirements and additionally is not in the interests of animal welfare."

A third party has proposed a read-across 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 an existing embryo-foetal developmental toxicity studies in rats and rabbits by using the read-across substance bismuth citrate.

ECHA has taken the information provided into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. More specifically, the proposed read-across approach did not provide an adequate and reliable documentation to demonstrate that the toxicological effects of the registered substance after gestational exposure can be predicted from the data existing on the analogue substance and that the standard information requirement for a prenatal developmental toxicity study could be adapted. In addition ECHA notes that the Registrant has included in his registration dossier the study provided by the third party but has assigned it a reliability score of 4 (not assignable) because the study was published only as an abstract and it was not clear if any guideline had been followed.

Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfill 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 that the prenatal developmental toxicity of the registered substance can be predicted from the data existing on the analogue substance based on structural similarity according to the conditions laid down in Annex XI Section 1.5. and that the study available on the analogue substance fulfills the conditions of Annex XI Section 1.1.2. concerning data not carried out according to GLP or the test methods referred to in Article 13(3).

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414). As explained in Section III.0 above, the read-across approach proposed by the Registrant is to be rejected based on Article 40(3)(d) of the REACH Regulation as non-complint with Annex XI, 1.5. The study shall therefore be performed using the substance concerned by the present decision, bismuth trinitrate CAS No 10361-44-1 (EC No 233-791-8).

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 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 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 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. If the registration of the substance covers different grades, the sample used for the new studies 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 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/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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