EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000003782-71-03/F Helsinki, 23 June 2014

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

For bismuth vanadium tetraoxide, CAS No 14059-33-7 (EC No 237-898-0), 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 bismuth vanadium tetraoxide, CAS No 14059-33-7 (EC No 237-898-0) submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex VIII, Section 8.4.3. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant and other joint registrants for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

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 6 March 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 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 4 April 2013.

On 13 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.

On 2 September 2013 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 6 March 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. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annex VIII of the REACH Regulation the Registrant shall submit the following information using the indicated test method and the registered substance subject to the present decision:

- *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.; test method: EU B.17/OECD 476).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **30 June 2015.**

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. The scope of the present decision is the *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3. of the REACH Regulation).

Mutagenicity, *in vitro* gene mutation study in mammalian cells.

In accordance with Articles 10(a)(vii), 12(1)(e) and with Annex VIII, section 8.4.3. of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells is required if there is a negative result in the *in vitro* studies specified under Annex VII, section 8.4.1 and Annex VIII, section 8.4.2. The registration dossier reports negative results for both *in vitro* studies. Therefore, the REACH Regulation requires that information on *in vitro* gene mutation in mammalian cells (Annex VIII, 8.4.3.) is provided in the dossier. ECHA notes furthermore that a cytogenicity study (be it *in vitro* or *in vivo*) cannot be used for in vitro or *in vivo* mammalian cell gene mutation information requirements. Cytogenicity studies and gene mutation studies are corresponding to two different endpoints and two distinct mechanisms of genotoxicity: cytogenicity studies detect structural and numerical chromosome aberrations whereas gene mutation studies detect gene or point mutations. ECHA concludes that the Registrant has neither provided the standard information nor adapted the requirement of Annex VIII, Section 8.4.3 of the REACH Regulation. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant, in the commenting phase, claimed that ECHA had not given consideration to Annex XI, 1.1.2. of the REACH Regulation. ECHA, however, emphasises that it is the duty of the registrant to provide adequate and reliable documentations and to build the necessary premises for the adaptations in order for ECHA to be able to assess it pursuant to the relevant provisions of the REACH Regulation. The Registrant had not referred to or reasoned this adaptation possibility in the registration dossier.

This notwithstanding, ECHA acknowledges that in his comments the Registrant sought to justify an adaptation of the standard information requirement with a weight of evidence approach (Annex XI, 1.2).

The Registrant states in his comments that the vertebrate studies with bismuth vanadium tetraoxide in the dossier such as acute oral and inhalation studies, studies with repeated administration (oral 28 day, inhalation 14, 28 and 90 day studies), an *in vitro* genotoxicity study in bacteria, an *in vitro* chromosomal aberration study and an *in vivo* micronucleus test with i.p. administration are proof of bismuth vanadium tetraoxide being "nontoxic". With reference to Annex XI, section 1.1.2 (2) (adequate and reliable coverage of key parameters) ECHA would like to point out that while the above mentioned toxicity studies may be evidence of low general toxicity they are not relevant for the assessment of mutagenicity and can therefore not contribute to a weight of evidence argument. Furthermore, ECHA notes that the key parameters of an *in vitro* gene mutation study in mammalian cells are not covered by the *in vitro* micronucleus test, an *in vitro* chromosomal aberration study and the *in vivo* micronucleus test listed by the Registrant.

The Registrant further argues that the substance is of low bioavailability pointing to the results of acute oral and inhalation studies and the fact that it did not elicit toxic effects in the oral 28 day study up to the limit dose and in inhalation studies with maximum exposures of 1200 mg/m^3. The Registrant also refers to results of the water solubility studies. For water solubility two key studies were submitted. "[redacted] (2007)" conducted according to OECD 29 and report a solubility of < 0.1 ug/l at 20 °C and pH 5.5-8. Zintl et al (1924) report a solubility of 0.1 -100 mg/l (slightly soluble) and a moderate solubility in nitric and sulphuric acids. However, no other study details are given.

Although the water solubility results show relatively low solubility and results of the toxicity studies may indicate low bioavailability, it is evident from the bioavailability investigation performed by [redacted] (1995) that, in addition to exposure to the lungs, bismuth reaches the kidneys, i.e., is systemically available. The Registrant has not explained why this is not relevant. Furthermore, low solubility is not a limiting factor for testing according to OECD TG 476 *In Vitro Mammalian Cell Gene Mutation Test*. According to the guideline "*Relatively insoluble substances should be tested up to or beyond their limit of solubility under culture conditions. Evidence of insolubility should be determined in the final treatment medium to which cells are exposed. It may be useful to assess solubility at the beginning and the end of the treatment, as solubility can change during the course of exposure in the test system due to presence of cells, S9, serum, etc.*"

The Registrant also makes the case that the relevant factor with regard to this endpoint is soluble vanadium(V)-compounds and that the "available data for bismuth vanadate revealed non-bioavailability *in vivo* supported by negative *in vitro* and *in vivo* chromosomal mutagenicity and negative mutagenicity in bacteria". He also refers to a negative result from a read across substance in a mammalian cell gene mutation study *in vitro* (mouse lymphoma) with a soluble vanadate (vanadium pentaoxide). The Registrant has not included this study in the dossier or given an explanation why this substance should be suitable as a read across source, i.e., why Bismuth contained in the registered substance is not relevant for this endpoint.

Therefore, as none of the data referred to would in itself provide information equivalent to the test requested (Annex XI, 1.1.2.) nor would the different sources of information seen jointly lead to a justified weight of evidence argument, the adaptation argument submitted in the comments is not adequately justified.

Therefore, pursuant to Article 41(1) and 41 (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: EU B.17./OECD 476).

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by the Registrant and other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. The Registrant is reminded of his responsibility and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In carrying out the study required by the present decision it is important to ensure that the particular sample of substance tested 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 study must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the study 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.

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