Helsinki, 31 January 2017

Addressee: [redacted]

Decision number: TPE-D-2114352306-54-01/F
Substance name: praseodymium(III,IV) oxide
EC number: 234-857-9
CAS number: 12037-29-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 12.03.2015

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

You are requested to perform:

1. **Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4., column 2; test method: EU B.58./OECD TG 488); in transgenic mice or rats, via the oral route, on the following tissues: liver and glandular stomach using the registered substance, or**

   In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum using the registered substance

   while your originally proposed test for an unscheduled DNA synthesis (UDS) test with mammalian liver cells in vivo (OECD TG 486) is rejected.

You 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **1 August 2018**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

1. **Transgenic rodent somatic and germ cell gene mutation assays or In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)**

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.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro* mammalian cell gene mutation assay ([redacted] 2013) performed according to the OECD TG 476 with the registered substance that shows positive results. The positive results indicate that the substance is inducing gene mutations under the conditions of the test.

An appropriate *in vivo* genotoxicity study to follow up the concern on gene mutations is not available for the registered substance but shall be proposed by the Registrant. Consequently, there is an information gap and you proposed to generate information for this endpoint.

Hence, you have submitted a testing proposal for an unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* (OECD TG 486).

ECHA notes that the proposed test is not an appropriate test to further investigate effects on gene mutations *in vivo* as described in the ECHA Guidance document on information requirements and chemical safety assessment R.7a, chapter R.7.7.1. and figure R.7.7-1 (July 2015).

The test method proposed to be used is listed in the ECHA Guidance as an option for the *in vivo* testing as a follow up to positive in vitro results. However, the ECHA Guidance indicates that the UDS test is an indicator test measuring DNA repair of primary damage in liver cells and does not constitute a surrogate test for gene mutations *per se*. The guidance further specifies that the UDS test is sensitive to some, but not all, DNA repair mechanisms and concludes that while a positive result in a UDS test is indicative of induction of DNA damage in liver cells, it is not sufficient information on its own to conclude on the induction of gene mutation by the substance. According to the ECHA guidance, the selection of the UDS test instead of other tests such as the transgenic rodent somatic and germ cell gene mutation (TGR) assays or the comet assay should be justified and supported by substance specific considerations. In the absence of substance specific consideration supporting the selection of the UDS, and taking into account the limitations of the UDS test, this assay does not appear to be the most appropriate study to follow-up on the positive *in vitro* results.

ECHA further notes that according to the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.7.6.3 (July 2015), the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up positive *in vitro* result for gene mutation. Hence, ECHA considers that those tests are appropriate to address the concern. Therefore, ECHA provides you the choice to perform one of those tests.

You did not specify the species to be used for testing. You did not specify the route for testing.

According to the test method (EU B.58/OECD TG 488), the TGR assay shall be performed in transgenic mice or rats and the substance is usually administered orally. According to the test method EU B.58./OECD TG 488, the test shall be performed by analysing tissues from the liver as slowly proliferating tissue and primary site of xenobiotic metabolism, and glandular stomach as rapidly proliferating tissue and site of direct contact.

According to the test method (OECD TG 489), the comet assay shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate. According to the test method OECD TG 489, the test shall be performed by analysing tissues from the liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the substance, and probable different local absorption rates of the substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to sample both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

In the initial draft decision issued to you, ECHA highlighted that testing by the oral route of administration could be considered but concluded that the inhalation route is the most appropriate route of administration for testing on the basis of physico-chemical properties of the substance subject to this decision and based on information on the uses of this substance reported in the dossier. Following the arguments proposed by two Member States Competent Authorities in their proposals for amendments, and reassessment of the findings with a view to the particle size distribution of the substance subject to this decision and the need to maximize the exposure of the first site of contact, ECHA has amended this decision and considers that the oral route is the most appropriate route for conducting the proposed tests.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out one of the following studies with the registered substance subject to the present decision:

- Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice or rats, oral route, on the following tissues: liver and glandular stomach; or
- *In vivo* mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver and glandular stomach and duodenum

while your originally proposed test for an unscheduled DNA synthesis (UDS) test with mammalian liver cells in vivo (OECD TG 486) is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

You are reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

In case you decided to perform the TGR assay, you may consider collecting (see OECD TG 488, paragraph 33) and storing male germ cells for potential further analysis of germ cell mutagenicity in case positive result(s) are obtained from the somatic cells.

In case you decided to perform the comet assay, you may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 23 May 2013.

ECHA held a third party consultation for the testing proposal(s) from 18 September 2014 until 3 November 2014. ECHA did not receive information from third parties.

This decision does not take into account any updates after **3 August 2016**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments. ECHA did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-51 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. 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.

2. 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.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their legal entity compositions. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the compositions of the substance as actually manufactured or imported by each registrant including elements such as morphology. Finally there must be adequate information on the composition for the sample tested and compositions registered to enable the relevance of the test(s) to be assessed.

4. ECHA notes that praseodymium (III,IV) oxide is also known to be manufactured/imported in forms that may fulfil the EU recommendation for nanomaterial[2]. However, there is no pertinent indication of nanomaterial forms of praseodymium (III,IV) oxide in the information included in the registration dossier. ECHA did therefore not consider nanomaterial forms of praseodymium (III,IV) oxide in its assessment.

[2] Commission Recommendation on the Definition of Nanomaterials of 20 October 2011, 2011/696/EU, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF