

Helsinki, 23 November 2021

Addressees

Registrants of JS_Diytterbium trioxide listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision

25/09/2018

Registered substance subject to this decision, hereafter 'the Substance'

Substance name: Ytterbium (III) oxide

EC number: 215-234-0

CAS number: 1314-37-0

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)**DECISION ON TESTING PROPOSAL(S)**

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by **30 November 2022**.

The requested information must be generated using the Substance unless otherwise specified.

We note that in the dossier there is reference to nanoparticles in the analytical report, under the analytical information section, in the context of the Atomic absorption spectroscopy method description. This indicates that the Substance can be possibly manufactured or imported in the European Union in nanoforms by any addressee of the present decision. However, the REACH Regulation (as amended by Regulation Commission Regulation (EU) 2018/1881) sets out explicit information requirements for nanoforms of substances. Manufacturers and importers of nanoforms must have fulfilled these specific information requirements by 1st January 2020. As far as the registration dossier currently submitted on the Substance does not cover any nanoform(s), the information required in the present decision relates only to information required on non-nanoforms.

Based on the above, the information requested in this decision must be generated using exclusively non-nanoforms of the Substance.

A. Information required from the Registrants subject to Annex VIII of REACH

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

Your originally proposed test using the Substance is rejected, according to Article 40(3)(d):

In vivo mammalian erythrocyte micronucleus test (EU B.12./OECD TG 474)

The reasons for the request(s) are explained in the following appendix entitled "Reasons to request information required under Annex VIII of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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, has to 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>.

Approved¹ under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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 A: Reasons to request information required under Annex VIII of REACH

This decision is based on the examination of the testing proposals you submitted.

1. In vivo mammalian alkaline comet assay

Under Annex VIII Section 8.4., column 2 of REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

Your dossier contains positive results for the *in vitro* mammalian chromosomal aberration test, which raise the concern for chromosomal aberrations.

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for an *In vivo* mammalian erythrocyte micronucleus test to be performed with the Substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity *in vivo*. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA agrees that an appropriate *in vivo* follow up genotoxicity study is necessary to address the concern identified *in vitro*.

1.2. Test selection

ECHA notes that the proposed test is generally appropriate to investigate effects on chromosomal aberrations *in vivo* (ECHA Guidance R.7a, Section R.7.7.6.3. and Figure R.7.7-1). But, as set out in the ECHA Guidance, the mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) is suitable to follow up a positive *in vitro* result on chromosomal aberration only if the Substance or its metabolite(s) will reach the target tissue.

However, based on the available studies in the dossier, including the OECD TG 422 study, there was no systemic toxicity observed with the Substance. Therefore, based on the information provided in the dossier, it is highly uncertain whether the Substance or its metabolite(s) will reach the target tissue. According to OECD TG 474 "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*".

As further set out in the ECHA Guidance the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) is also suitable to follow up the positive *in vitro* result for chromosomal aberrations. Moreover, it enables the generation of information regarding potential genotoxic effects at the site of contact.

In your comments to the draft decision you state that "*the absence of systemic toxicity in the OECD TG 422 may be an indication but is certainly not direct experimental evidence for the non-exposure of the target tissue to the test substance.*"

By contrast, ECHA considers that already the indications for the non-exposure of the target tissue to the Substance justify the consideration of alternative and more appropriate means to generate new information. According the ECHA Guidance R.7a (p. 573), "*for substances*

inducing gene mutation or chromosomal aberration in vitro, and for which no indication of sufficient systemic availability has been presented”, “an alternative strategy involving studies to focus on tissues at initial sites of contacts with the body should be considered”.

In your dossier and in your comments you have not shown that there is “sufficient systemic availability” with the Substance.

Furthermore, you also refer to a document published by ECHA (2018)² presenting the three approved *in vivo* genotoxicity test guidelines where you indicate that “it is possible to apply specialised test methods, and that these may not have recognised, internationally valid, test guidelines”. In fact you claim that “an *in vivo* micronucleus test on organs others than bone marrow, e.g. to allow investigation at sites of contact (stomach, duodenum), are methods that have been investigated and discussed³ and that should not be excluded a priori from the spectrum of possible relevant follow-up tests”. In the ECHA document, the text that you quoted is followed by this sentence: “the validity and utility of such tests and the selection of protocols should be assessed by appropriate experts or authorities on a case-by-case basis”. ECHA acknowledges that efforts are ongoing to develop and validate the MN test using tissues other than the erythrocytes. However, these new tests have not been formally validated, as yet, and the process of development of an OECD test guideline for these tests has not yet been started. Thus, in your particular case, ECHA considers that it is not appropriate to request the MN test on other tissues under REACH.

For all these reasons, ECHA remains of the opinion that this is the most appropriate validated test to address the concern identified *in vitro* for your Substance.

In your comments you further mention the negative *in vitro* results obtained with other insoluble rare earth substances for genetic toxicity testing. ECHA considers that, in your dossier and in your comments, you did not provide any documentation to demonstrate how data on other insoluble rare earth substances can be useful to cover the information requirement for your Substance.

Finally, you suggest conducting preliminary investigations in order to take a scientifically founded decision on the most suitable test, such as, investigation of exposure of target organs to the Substance to investigate the systemic and tissue exposure of the Substance following oral administration. ECHA notes that any additional investigations can be performed at your discretion, as long as it does not interfere with the performance and timeline of the comet assay requested in this decision.

Therefore, based on the above, we consider that the comet assay is the most appropriate *in vivo* follow-up test to address the concern identified *in vitro* for the Substance.

1.3. Specification of the study design

According to the test method OECD TG 489, the test must 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.

² https://echa.europa.eu/documents/10162/21650280/oecd_test_guidelines_genotoxicity_en.pdf/56ab5788-0103-4716-8903-59ab0c942efe

³ Yoshifumi Uno, Takeshi Morita, Mirjam Luijten, Carol Beevers, Shuichi Hamada, Satoru Itoh, Wakako Ohyama, Hironao Takasawa, Micronucleus test in rodent tissues other than liver or erythrocytes: Report of the IWGT working group, Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 783, 2015, Pages 19-22, ISSN 1383-5718, <https://doi.org/10.1016/j.mrgentox.2015.03.001>

In line with the test method OECD TG 489, the test must be performed by analysing tissues from 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 analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

Germ cells

You may consider to collect the male gonadal cells from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells. 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.

1.4. Outcome

Your testing proposal is rejected under Article 40(3)(d) of REACH. Under Article 40(3)(c) you are requested to carry out the additional test with the Substance, as specified above.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries⁴.

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

The Test material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
 - the boundary composition(s) of the Substance,
 - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test material must contain that constituent/ impurity.
2. Information on the Test material needed in the updated dossier
 - You must report the composition of the Test material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
 - The reported composition must include all constituents of each Test material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers⁵.

⁴ <https://echa.europa.eu/practical-guides>

⁵ <https://echa.europa.eu/manuals>

Appendix C: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 21 August 2020.

ECHA held a third party consultation for the testing proposal(s) from 23 November 2020 until 7 January 2021. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance⁶ and other supporting documentsEvaluation of available information

Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping

Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)⁷

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)⁵

Physical-chemical properties

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment

Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing

Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents⁸

⁶ <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

⁷ <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

⁸ <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[REDACTED]	[REDACTED]	[REDACTED]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.