~~Confidential~~

Helsinki, 09 November 2023

Addressee
Registrant of JS_Lanthanum trichloride 2 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
13/09/2013

Registered substance subject to this decision ("the Substance")
Substance name: Lanthanum chloride, anhydrous
EC/List number: 233-237-5

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***16 August 2027***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020)

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

Information required from all the Registrants subject to Annex VIII of REACH

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

4. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested in a parallel decision for this jointly submitted dossier (Annex VIII, Section 8.6.1.).

5. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats

6. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203)

The reasons for the decision are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

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0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical and toxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Predictions for toxicological properties

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance(s):

Source substance 1	Lanthanum nitrate hexahydrate ([redacted]%), CAS No. 6487-39-4.
Source substance 2	Lanthanum carbonate ([redacted]%), CAS No. 587-26-8.
Source substance 3	Lanthanum carbonate octahydrate ([redacted]%), CAS No. 6487-39-4
Source substance 4	Lanthanum oxide (purity not known), CAS No. 1312-81-8

7 You provide the following reasoning for the prediction of toxicological properties:

- *"It is supposed that environmental and toxicological effects can be attributed mainly to the Lanthanum cation."*
- *"Lanthanum chloride is an inorganic salt of a weak base, which is highly water soluble and nearly completely dissociates in solution."*
- *"Lanthanum nitrate, its hydrate and Cerium chloride, are highly water soluble. Since these substances are also salts of weak bases, they dissociate in the same manner as Lanthanum chloride."*
- *"Even though Lanthanum carbonate, its hydrate and Lanthanum oxide are practically insoluble in water, they dissociate in the acidic environment of the upper gastrointestinal tract and free Lanthanum ions occur."*

8 ECHA understands that your read-across hypothesis is based on the formation of common (bio)transformation products. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issues with the predictions of toxicological properties:

0.1.1.1. Missing supporting information

10 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

11 Supporting information must include toxicokinetic information on the formation of the common compound to compare properties of the Substance and source substances.

12 As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s), i.e. the target and the source substances dissociate in the upper gastrointestinal tract to release free Lanthanum ions. In this context, information characterising the rate and extent of the (bio)transformation/dissolution of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds as well as to Lanthanum ion itself.

13 However, you have not provided any experimental information, about the (bio)transformation of the Substance nor of the source substance(s) to support your claims regarding formation of a similar common compound with a similar bioavailability.

14 In the absence of this information, you have not provided supporting evidence establishing that the proposed common (bio)transformation product is formed as assumed in your read-across hypothesis. Therefore, you have not provided sufficient supporting information to scientifically justify your read-across hypothesis.

0.1.1.2. Read-across hypothesis contradicted by existing data

15 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information must strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

16 The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

17 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substances cause the same type of effect(s).

18 However, the results of the information obtained with the insoluble source substances such as lanthanum carbonate or lanthanum oxide vary from the ones obtained with the target. Specifically, an OECD 408 study with Lanthanum carbonate in the dossier, found no adverse treatment-related effects up to the highest dose used in the study (974.2 mg/kg bw/d for males and 1489 mg/kg bw/d for females). Also a 3-generation study with Lanthanum oxide reported no effects up to the highest dose (91.8 mg/kg bw/d). By contrast, in a one

generation study with lanthanum chloride in the dossier, a LOAEL of 10 mg/kg bw/day (nominal) was determined based on neurological assessment: more jerking and freezing behaviour, less vigorous in visual placing response. A developmental study with Lanthanum chloride also found deficits in the domains of neurobehavioral development, brain chemistry and learning and memory abilities.

19 The available set of data on the Substance and on the source substances indicate differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effect(s). However, you have not supported and scientifically justified why such differences in the toxicological properties do not affect your read-across hypothesis.

0.1.1.3. Adequacy and reliability of source studies

20 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) be adequate for the purpose of classification and labelling and/or risk assessment;
(2) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;
(3) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

21 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections 8.4.1., 8.7.1., and 8.7.3. Therefore, no reliable predictions can be made for these information requirements.

0.1.2. Conclusion on the read-across approach

22 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

0.2. Assessment of weight of evidence adaptations

23 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

24 Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

25 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

26 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they

together provide sufficient weight to conclude on the corresponding information requirement.

27 Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.

28 You have not included a justification for your weight of evidence adaptation for each of the relevant information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.

29 In spite of this critical deficiency, common to all information requirements under consideration, ECHA has nevertheless assessed the validity of your adaptation.

30 The common deficiency is set out here, while the specific ones are set out under the information requirement concerned in the Sections below.

0.2.1. Reliability of the read across approach

31 Section 0.1 of the present Appendix identifies deficiencies of the read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

32 An in vitro gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

1.1. Information provided

33 You have adapted this information requirement by using a Grouping of substances and read-across approach based on experimental data from the following substances:

(i) an OECD 471 (1992) with the analogue substance Lanthanum nitrate 6*H2O, CAS number 6487-39-4.

1.2. Assessment of the information provided

1.2.1. Read-across adaptation rejected

34 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

1.2.2. The provided study does not meet the specifications of the applicable test guideline

35 To fulfil the information requirement, a study must comply with OECD TG 471 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the test is performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101);
b) 2-Aminoanthracene should not be used as the sole indicator of the efficacy of the S9-mix.;
c) the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory.

36 However, the following specifications are not according to the requirements of the OECD TG 471:

a) the test was performed with the strains *S. typhimurium* TA100, TA1535, TA97, TA98 (i.e., the strains *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 are missing);
b) 2-Aminoanthracene was used as the sole indicator of the efficacy of the S9-mix;
c) no information whether the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory since the historical control range of the laboratory was not reported.

37 Based on the above, the information provided does not cover the key parameters required by the OECD TG 471. Therefore, the information requirement is not fulfilled.

1.3. Specification of the study design

38 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

2. Growth inhibition study aquatic plants

39 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

2.1. Information provided

40 You have provided:

(i) an OECD 201 study (1995) with the analogue substance Lanthanum chloride, hydrate, EC No. 640-503-8. For the purpose of hazard assessment, this Substance is considered equivalent to the Substance, the only difference being the degree of hydration.
(ii) an ISO 8692 study (2010) with the Substance
(iii) a non-guideline study type (1965) on *Chlorella vulgaris* with the Substance
(iv) a non-guideline study type (2005) on *Chlorella autotrophica* with the Substance
(v) a non-guideline (2002) on duckweed (*Lemna minor* L.) with the analogue substance Lanthanum chloride, hydrate, EC No. 640-503-8.

2.2. Assessment of the information provided

2.2.1. The provided study (i) does not meet the specifications of the applicable test guideline

41 To fulfil the information requirement, a study must comply with OECD TG 201 Article 13(3) of REACH). Therefore, the following specifications must be met:

42 Characterisation of exposure

a) if the concentration of the test material has not been maintained within ±20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material over the exposure period;

43 Reporting of the methodology and results

b) the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported. Algal biomass is normally determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (*e.g.* flow cytometry, *in vitro* or *in vivo* fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test;
c) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
d) adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

44 Your registration dossier provides an OECD TG 201 study showing the following:

45 Characterisation of exposure

a) the concentrations of the test material were not detectable for the lower two tested concentrations and 7.77, 31.1 and 34.9 mg/l for remained three tested concentrations at the end of the test. Therefore, exposure was not maintained

within ± 20 % of nominal or measured initial concentration throughout the test. It is unclear if the reported values correspond to either the geometric mean of measured concentrations during exposure or a model describing the decline of the concentration of the test material over the exposure period;

46 Reporting of the methodology and results

b) you report that algal biomass was determined using a counting chamber initially and a spectrophotometer at 720 nm thereafter. However, you have not reported evidence of correlation between the measured parameter and dry weight or cell numbers over the range of biomass occurring in the test;
c) tabulated data on the algal biomass determined daily for each treatment group and control are not reported;
d) on the analytical method adequate information, i.e. analytical method and conditions and performance parameters of the method are not reported. The results of the analytically determined exposure concentrations at the beginning and the end of the test are provided.

47 Based on the above, ECHA considers that:

- there is a critical methodological deficiency resulting in the rejection of the study results. More specifically, due to the lack of information on the model describing the decline of the concentration of the test material over the exposure period and on the analytical information, the reliability of the effect value reported cannot be assessed.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not provided measured biomass data. Therefore, it is not possible to verify whether the validity criteria of the OECD TG 201 were met and to verify the interpretation of the results of this study.

48 Therefore, the specifications of OECD TG 201 are not met.

2.2.2. The provided study (ii) does not meet the specifications of the applicable test guideline

49 To fulfil the information requirement, a study must comply with ISO 8692 (Article 13(3) of REACH). Therefore, the following specifications must be met:

50 Characterisation of exposure

a) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided.

51 Reporting of the methodology and results

b) the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);
c) the methods used to prepare stock and test solutions are reported;
d) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

52 Your registration dossier provides an ISO8692 study showing the following:

53 Characterisation of exposure

a) no analytical monitoring of exposure was conducted;

54 Reporting of the methodology and results

b) on the test conditions, you have not specified, test temperature, test pH and total

hardness.
c) on the test procedure, you have not specified the methods used to prepare stock and test solutions;
d) tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

55 Based on the above, ECHA considers that:

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the exposure concentration was not analytically verified and therefore the reliability of the effect value reported cannot be confirmed.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not provided measured biomass data. Therefore, it is not possible to verify whether the validity criteria of the ISO 8692 were met and to verify the interpretation of the results of this study.

56 Therefore, the specifications of ISO 8692 are not met.

2.2.3. The provided studies (iii) and (iv) do not meet the specifications of Guidance on IRs and CSA

57 To fulfil the information requirement, studies should 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 Agency as being appropriate (Article 13(3) of REACH). As specified in Guidance on IRs and CSA, Section R.7.8.4.1, for the evaluation of data from non-standard ecotoxicity tests on growth inhibition on algae the following specifications must be met:

58 Key parameter to be measured

a) the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated;

59 Characterisation of exposure

b) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;

60 Reporting of the methodology and results

c) the test design is reported (*e.g.*, number of replicates, number of test concentrations and geometric progression used);
d) the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);
e) the methods used to prepare stock and test solutions are reported;
f) the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported. Algal biomass is normally determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (*e.g.* flow cytometry, *in vitro* or *in vivo* fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test;
g) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

61 Your registration dossier provides the studies (iii) and (iv) showing the following:

62 Key parameter to be measured

a) for the study (iii) you provide a NOEC value of 4.1 mg/l based on biomass. For study (iv) you report an EC50 (96h)=4.052 mg/l based on biomass.

63 Characterisation of exposure

b) no analytical monitoring of exposure was conducted for any of the studies (iii) and (iv);

64 Reporting of the methodology and results

c) on the test design, you have not specified number of replicates for study (iii);
d) on the test conditions, you have not specified biomass density at the beginning of the test for any of the studies (iii) and (iv);
e) on the test procedure, you have not specified the methods used to prepare stock and test solutions for any of the studies (iii) and (iv);
f) the method used to determine algal biomass is not reported for study (iii). For study (iv) you report that algal biomass was determined using a spectrophotometer. However, you have not reported evidence of correlation between the measured parameter and dry weight or cell numbers over the range of biomass occurring in the test;
g) tabulated data on the algal biomass determined daily for each treatment group and control are not reported;

65 Based on the above,

- the information provided in studies (iii) and (iv) do not cover the key parameter required by non-standard ecotoxicity tests on algae and aquatic plants. More specifically the values reported in both studies are based on biomass only while the required endpoint is growth rate inhibition.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically,
  - the exposure concentrations were not verified analytically and therefore the reliability of the results cannot be assessed.
  - you have not provided adequate information on the method used to determine algal biomass, on the measured biomass data and adequate information on the test design and procedure for any of the studies. Therefore, it is not possible to verify whether the validity criteria of the OECD TG 201 were met and to verify the interpretation of the results of these studies.

66 Therefore, the specifications set out in Guidance on IRs and CSA, Section R.7.8.4.1, for the evaluation of data from non-standard ecotoxicity tests on algae are not met.

2.2.4. The provided study (v) does not meet the specifications of Guidance on IRs and CSA

67 To fulfil the information requirement, studies should 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 Agency as being appropriate (Article 13(3) of REACH). As specified in Guidance on IRs and CSA, Section R.7.8.4.1, for the evaluation of data from non-standard ecotoxicity tests on aquatic plants the following specifications must be met:

68 Key parameter to be measured

a) the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated.

69 Characterisation of exposure

b) the preparation of test solutions must ensure exposure to the test material.

70 Reporting of the methodology and results

c) tabulated data on the biomass determined at appropriate frequency for each treatment group and control are not reported.

71 Your registration dossier provides a non-guideline study on Lemna sp. (study iii) showing the following:

72 Key parameter to be measured

a) you report an unbound value for NOEC (196h) ≥ 2.45µg/l based growth rate.

73 Characterisation of exposure

b) for the test solutions the study reports that the Lanthanum is mainly associated with EDTA. Specifically, it is reported that "*Speciation calculations showed all La to be in solution up to pH 5.6 (initial pH 5.05) and for more than 99.9% associated with EDTA*". Therefore, the presence of a chelating agent in the test medium led to reducing significantly the exposure to the test material.

74 Reporting of the methodology and results

c) no tabulated data on the biomass is provided.

75 Based on the above,

- the information provided does not cover the key parameter required by non-standard ecotoxicity tests on aquatic plants. While the value is reported as being based on growth rate, you do not define on which measurement the growth rate is calculated on (i.e. front measurement, total frond area, dry weight or fresh weight).
- there is a critical methodological deficiency resulting in the rejection of the study results. More specifically, as shown from the information on the test solution the exposure of the organism to the substance was minimal and thus no conclusion on possible effects can be drawn from the study.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not provided adequate reporting of biomass measurement.

76 Therefore, the specifications set out in Guidance on IRs and CSA, Section R.7.8.4.1, for the evaluation of data from non-standard ecotoxicity tests on aquatic plants are not met.

77 On this basis, the information requirement is not fulfilled.

Reasons related to the information under Annex VIII of REACH

3. In vitro gene mutation study in mammalian cells

78 An in vitro gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

3.1. Triggering of the information requirement

79 Your dossier contains (1) a negative result for in vivo micronucleus study, and (2) no data or inadequate data for in vitro gene mutation study in bacteria.

80 The in vitro gene mutation study in bacteria provided in the dossier is rejected for the reasons provided in Request 1.

81 The result of the Request 1 will determine whether the present requirement for an in vitro mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

82 Consequently, you are required to provide information for this information requirement, if the in vitro gene mutation study in bacteria provides a negative result.

3.2. Information provided to fulfil the information requirement

83 You have adapted this information requirement by using a Grouping of substances and read-across approach based on experimental data from the following substances:

(i) an OECD 476 (2005) with the analogue Lanthanum carbonate, CAS Number 587-26-8

84 Your registration dossier also contains the following *in vivo* study:

(ii) an OECD 486 (2005) with the Substance

85 ECHA understands that this information is provided as an attempt to adapt this information requirement under Annex VIII, Section 8.4.3., Column 2.

86 We have assessed this information and identified the following issues:

3.2.1. The read-across adaptation relating to study (i) is rrejected

87 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

88 Therefore the provided study cannot be considered a reliable source of information.

3.2.2. The provided adaptation relating to study (ii) does not meet the criteria of Annex VIII, Section 8.4.3., Column 2

89 Under Annex VIII, Section 8.4.3., Column 2, the study may be omitted if adequate data from a reliable in vivo mammalian gene mutation test are available. The Guidance on IRs and CSA, Section R.7.7.6.3. clarifies that the in vivo study must be a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (TGR), performed according to the OECD TG 488. This test investigates gene mutations using reporter genes.

90 The study (ii) is described as a UDS test. This is an indicator test that detects some DNA repair mechanisms (measured as unscheduled DNA synthesis in liver cells). However, it does not provide direct evidence of mutation as the TGR. According to the Guidance on IRs and CSA, Section R.7.7.6.3. (page 571-572), a negative result in a UDS assay alone is not a proof that a substance does not induce gene mutations. Moreover, the Guidance also clarifies that while a positive result in the UDS assay can indicate exposure of the liver DNA and induction of DNA damage by the substance under investigation, it is not sufficient information to conclude on the induction of gene mutation by the substance.

91 The study (ii) is not a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay.

92 Therefore, the requirements of Annex VIII, Section 8.4.3., Column 2 are not met and your adaptation is rejected.

93 The study is not adequate for the information requirement and is therefore rejected.

3.3. Specification of the study design

94 To fulfil the information requirement for the Substance, either the in vitro mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

4. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested in a parallel decision for this jointly submitted dossier (Annex VIII, Section 8.6.1.).

95 Annex VIII, Section 8.6.1., Column 2 provides that an experimental study for this information requirement is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

96 A parellel decision requests the other registrants relying on this jointly submitted dossier to generate and submit a reliable sub-chronic toxicity study (90 days) (draft decision issued on 22 April 2022). According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not therefore need to be conducted.

97 Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

5. Screening for reproductive/developmental toxicity

98 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

5.1. Information provided

99 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2. In that respect, you have submitted the following sources of information:

(i) a 3-generation study (1975) with the Lanthanum oxide
(ii) a one-generation study (2000) with the Substance

5.2. Assessment of the information provided

100 As explained in Section 0.2., it would be sufficient to reject your weight of evidence adaptation based on the fact that you have not submitted any justification for your adaptation.

101 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.7.1. includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422 with a design as specified in this decision. OECD TG 421/422 require the study to investigate the following key elements:

1) sexual function and fertility,
2) toxicity to offspring, and
3) systemic toxicity.

5.2.1. Sexual function and fertility

102 Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

103 None of the studies provide information on gestational length, maintenance of pregnancy (abortions, total resorptions), parturition, organ weights and histopathology of reproductive organs and tissues, oestrus cyclicity, sperm count and analysis, hormone levels and nursing performance. However, the source of information (i) may provide relevant information on mating, fertility, lactation and litter size.

104 In any case, the reliability of these sources of information is significantly affected by the following deficiency:

5.2.1.1. The provided studies do not meet the specifications of the applicable test guidelines

105 To inform on the screening for reproductive/developmental toxicity, a 3-generation study (source of information i) a one-generation study (source of information ii) must normally follow the specifications of EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, the following specifications must be met:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose;
b) at least 10 male and 12-13 female animals are included for each dose and control group;
c) the exposure duration is at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;
d) food consumption is measured at least weekly;
e) thyroid hormone levels are measured;
f) Examination of parameters for sexual function and fertility such as /those for mating and fertility/duration of gestation, parturition, lactation and weight and histopathology of reproductive organs and tissues

g) Monitoring of oestrus cycles
h) Examination of offspring parameters such as /number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/number of nipples/areolae in male pups
i) Functional observations such as sensory reactivity to stimuli/assessment of grip strength/assessment of motor activity
j) Haematological examinations and clinical biochemistry
k) histopathology of reproductive organs and tissues is performed, and the presence or absence, incidence and severity of abnormalities is evaluated.

106 However, these sources of information show the following:

a) The highest dose level in the studies (i) and (ii) did not induce any systemic toxicity and you have not shown that the aim was to induce toxicity. Therefore, the dose level selection was too low, and the studies do not fulfil the criterion set in OECD TG 421/422 and ECHA Guidance R7a.
b) The study (i) was conducted with 16 pregnant females but 8 males for each test group. Study (ii) was conducted with 10, 7 and 12 pregnant females for control, low and mid-dose and high dose respectively and no dosed males. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of at least 10 male (both studies) and 12-13 female animals for each test group (study (ii)).
c) In the study (i) you have provided, it is not clear if the P0 males were dosed before mating or the exposure started after mating. In the study (ii) the males were not dosed. Therefore it does not fulfil the criteria set in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.
d) In both studies, monitoring of food consumption was not performed.
e) In both studies, the thyroid hormone assessment (P0 and F1) was not performed.
f) In the study (ii) you have provided, the functional fertility has not been examined. In both studies essential information such as duration of gestation, parturition, and weight and histopathology of reproductive organs and tissues is missing.
g) In both studies, oestrus cyclicity has not been analysed.
h) In the studies you have provided, offspring parameters such as number and sex of pups, stillbirths and live births, pup body weight, litter weight, anogenital distance, number of nipples, areolae in male pups missing.
i) The study (i) does did not include functional observations.
j) In the study (ii) you have provided, investigations for clinical chemistry and haematology has not been performed, and it is limited only to few parameters in the study (i) (erythrocyte and leukocyte count, hemoglobin concentration, packed cell volume, serum protein, albumin, alpha-globulin, beta-globulin, gamma-globulin).
k) In both studies the histopathology of the reproductive organs and tissues has not been performed.

107 Based on the above, the studies (i) and (ii) do not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 422.

5.2.1.2. Rejected read-across

108 The source of information (i) concerns data produced with an analogue substance. As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

109 Therefore the provided study cannot be considered a reliable source of information that could contribute to the conclusion on this key parameter investigated by the required study.

110 The deficiencies affecting the reliability of these sources of information are so significant that these sources of information could not contribute to the conclusion on the key parameter investigated by the study normally required.

111 In your comments on the draft decision, you indicate your intention to provide an improved read-across justification and a study on lanthanum acetate in a future update of your registration dossier. However, you do not provide specific information addressing the issues identified above.

5.2.2. Toxicity to offspring

112 Information on toxicity to offspring must include information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

113 The sources of information (i) and (ii) provide information on litter sizes, on peri- and postnatal toxicity up to postnatal day 13 (survival, clinical signs and body weights of pups). The source of information (i) provides information on the external malformations and the source (ii) provides information on the neurotoxicity toxicity to offspring. None of studies provide information on postimplantation loss (resorptions and dead foetuses) and stillborns.

114 Furthermore, as indicated above under sexual function and fertility, the deficiencies affecting the reliability of sources (i) and (ii) are so significant that these sources of information could not contribute to the conclusion on the key parameter investigated by the study normally required.

5.2.3. Systemic toxicity

115 Information on systemic toxicity include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

116 The sources of information (i and ii) provide some information on systemic toxicity such as clinical signs, survival, body weights. Study (i) provides information on hematology, clinical chemistry and study (ii) on brain weight.

117 However, information on the following aspects are missing: food consumption, organ weights (except for brain weight provided in study (ii)) and histopathology of non-reproductive organs.

118 Furthermore, as indicated above under sexual function and fertility, the deficiencies affecting the reliability of sources (i) and (ii) are so significant that these sources of information could not contribute to the conclusion on the key parameter investigated by the study normally required.

5.2.4. Conclusion on the weight-of-evidence adaptation

119 In summary, the sources of information (i) to (ii) provide limited relevant information on sexual function and fertility, toxicity to offspring and systemic toxicity. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for screening for reproductive/developmental toxicity endpoint.

In the comments to the draft decision, you do not comment on ECHA's findings described above. Nevertheless, you state generally that the sources of information "*do address the essential elements of those tests, as is required for WoE adaptation".*

120 In your comments, you also indicate your intention to refer to an OECD 422 study on Lanthanum acetate and two 28-day oral uptake studies performed on Lanthanum chloride and Lanthanum carbonate to consolidate your adaptation.

121 ECHA takes note of your intention to submit further sources of information for this information requirement. As indicated in your comments, this strategy relies essentially on data which is yet to be submitted, therefore no conclusion on the compliance can currently be made.

122 Regarding the adequacy of the weight of evidence approach, as already explained in this issue of the draft decision, the relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.7.1. should be similar to the information that is produced by the OECD TG 421 or OECD TG 422 with a design as specified in this decision. Nevertheless, as explained under 4.2.1.1., the deficiencies affecting the reliability of sources (i) and (ii) are so significant that these sources of information could not contribute to the conclusion on the key parameter investigated by the study normally required.

123 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for screening for reproductive/developmental toxicity. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

5.3. Specification of the study design

124 A study according to the test method EU B.64/OECD TG 422 must be performed in rats.

125 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

126 Therefore, the study must be conducted in rats with oral administration of the Substance.

6. Short-term toxicity testing on fish

127 Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

6.1. Information provided

128 You have adapted this information requirement by using Column 2 of Annex VII, Section 9.1.3. To support the adaptation, you have provided following justification: "*Data on chronic toxicity to fish are available for Lanthanum trichloride hydrate, thus in accordance with column 2 of REACH Annex VIII no testing on short-term toxicity to fish is required*".

6.2. Assessment of the information provided

6.2.1. The provided adaptation does not meet the criteria of Annex VIII, Section 9.1.3., Column 2

129 Under Section 9.1.3., Column 2, second indent, Annex VIII to REACH, the study may be omitted if a long-term aquatic toxicity study on fish is available.

130 Your registration dossier provides:

(i) an OECD 204 (1995) study with the analogue substance Lanthanum chloride, hydrate (EC 640-503-8)

6.2.1.1. The OECD TG 204 is not a valid test guideline to meet the information requirement for long-term toxicity on fish

131 To fulfil the information requirement for long-term toxicity on fish, a study must be a long-term fish test. Guidance on IRs and CSA, Section R.7.8.4.1. specifies that only studies in which sensitive life-stages (juveniles, eggs and larvae) are exposed can be regarded as long-term fish tests.

132 Your registration dossier provides an OECD TG 204 study in which only adults were exposed to the test material.

133 This study does not provide information on the toxicity of the test material to relevant sensitive life-stages (i.e. juveniles, eggs and larvae). OECD TG 204 only provides information on prolonged acute toxicity in adults and, based on the above, it does not qualify as a long-term fish test.

134 On this basis, your adaptation under Section 9.1.3., Column 2, second indent, Annex VIII to REACH is rejected and the information requirement is not fulfilled.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not yet addressed for this Substance. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the parallel compliance check decision on the same Substance is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS.

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

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

The compliance check was initiated on 21 February 2023.

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

ECHA did not receive any comments within the commenting period.

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 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII to REACH, for registration at 1-10 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;

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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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 summaries[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. 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.

[2] https://echa.europa.eu/practical-guides

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 dossiers[3].

[3] https://echa.europa.eu/manuals