~~Confidential~~

Helsinki, 17 May 2023

Addressee(s)
Registrant(s) of JS_217-100-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
25/07/2019

Registered substance subject to this decision ("the Substance")
Substance name: 1,2,4,5-tetramethyl-1H-imidazole
EC number/List number: 217-100-7

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 ***26 May 2025***.

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

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

1. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105/OECD GD 29)
2. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; test method: EU A.8/OECD TG 107 or EU A.23/OECD TG 123 or EU A.24/OECD TG 117)
3. Skin sensitisation (Annex VII, Section 8.3.)
   (i) in vitro/in chemico skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
   (ii) only if the in vitro/in chemico test methods specified under point i.) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, in vivo skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429);
4. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020)
5. If the study requested under request 1 above shows that the Substance`s solubility is above 1 mg/L: Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)
6. If the study requested under request 1 above shows that the Substance` solubility is below 1 mg/L: Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., Column 2; test method: EU C.20./OECD TG 211)
7. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3/OECD TG 201)

The reasons for the request(s) 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 addressee of the decision and its corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 request(s)
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 request(s)

Contents

Reasons related to the information under Annex VII of REACH

1. Water solubility

1 Water solubility is an information requirement under Annex VII to REACH (Section 7.7).

1.1. Information provided

2 You have provided:

(i) a water solubility study (2017) with the Substance;

1.2. Assessment of the information provided

1.2.1. The provided study does not meet the specifications of the test guideline(s)

3 To fulfil the information requirement, a study must comply with OECD TG 105 Article 13(3) of REACH). Therefore, the following specifications must be met:

Applicability domain

a) the flask method is applicable to substances having a water solubility above 10^{-2} g/L;

4 In study (i):

Applicability domain

a) a water solubility of 0.12 mg/L was determined for the Substance, which is lower than the solubility range at which the flask elution method is applicable;

5 Based on the above,

- the Substance is outside of the applicability domain of OECD TG 105 – flask method

6 On this basis, the specifications of OECD 105 are not met.

7 Therefore, the information requirement is not fulfilled.

2. Partition coefficient n-octanol/water

8 Partition coefficient n-octanol/water is an information requirement under Annex VII to REACH (Section 7.8).

2.1. Information provided

9 You have provided:

(i) a partition coefficient n-octanol/water study (2017) with the Substance;

2.2. Assessment of the information provided

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

10 To fulfil the information requirement, a study must comply with OECD TG 117 Article 13(3) of REACH). Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) duplicate determinations are conducted;

b) the solid phase consists of long hydrocarbon chains (e.g. C8, C18) chemically bound onto silica;

c) the HPLC operation mode is isocratic;

d) the mobile phase consists of HPLC-grade methanol mixed with distilled or de-ionised water with a minimum water content of 25%;

e) at least 6 reference substances are used to determine the capacity factor (k);

f) the reference substances have log K_{ow} values which encompass the log K_{ow} of the test material;

g) the test material and the reference substances are soluble in the mobile phase in sufficient concentration to allow their detection;

h) the test temperature does not vary by over ± 1°C;

i) the regression equation used to determine the log K_{ow} of the test material is determined at least daily;

Reporting of the methodology and results

j) the test material and reference substances used are reported, including their purity, structural formula and CAS number;

k) details on the fitted regression line (log k *versus* log K_{ow}), including the correlation coefficient and the confidence intervals, are reported;

l) details of the calculation of the reported log K_{ow} are provided;

m) the upper and lower limits of log K_{ow}, and the area % of each log K_{ow} peak are reported;

n) the weighted average log K_{ow} (calculated based on single log K_{ow} values and the corresponding are % values for all peaks that contribute to ≥ 5% to the total peak area) is reported;

11 In study (i):

Technical specifications impacting the sensitivity/reliability of the test

No information is provided on:

a) the conduct of duplicate determination;

b) the solid phase;

c) the HPLC operation mode;

d) the mobile phase;

e) the number of reference substances used to determine the capacity factor (k);

f) the log K_{ow} of the reference substances used and whether they encompassed the log K_{ow} of the test material;

g) the solubility of the test material and the reference substances in the mobile phase;

h) test temperature variation during the study;

i) the regression equation used to determine the log K_{ow} of the test material;

Reporting of the methodology and results

j) the reference substances used are not reported, including their purity, structural formula and CAS number;

k) details on the fitted regression line (log k *versus* log K_{ow}), including the correlation coefficient and the confidence intervals, are not reported;

l) details of the calculation of the reported log K_{ow} are not provided;

m) the upper and lower limits of log K_{ow}, and the area % of each log K_{ow} peak are not reported;

n) the weighted average log K_{ow} (calculated based on single log K_{ow} values and the corresponding are % values for all peaks that contribute to ≥ 5% to the total peak area) is not reported;

12 Based on the above:

- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, without the information listed under i) – n) it is not possible to assess whether the technical specifications listed under a)- h) were met, which impact the sensitivity and/or the reliability of the study outcome. Therefore, no conclusion can be made on the reliability of the reported result.

13 On this basis, the specifications of OECD 117 are not met.

14 Therefore, the information requirement is not fulfilled.

2.1. Study design and test specifications

15 To fulfil the information requirement, the test method(s) according to OECD TG 107, 117 or 123 are in general appropriate. You can choose any of these methods, but you must ensure that the Substance is within the applicability domain of the test method chosen.

3. Skin sensitisation

16 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

3.1. Information provided

17 You have provided:

(i) An *in vitro* skin sensitisation study - Direct peptide reactivity assay (2019) with the Substance;

(ii) An *in vitro* skin sensitisation study - ARE-Nrf2 Luciferase test method (2019) with the Substance.

3.2. Assessment of the information provided

3.2.1. Assessment whether the Substance causes skin sensitisation

3.2.1.1. Reliability of the results obtained from study (i)

18 To fulfil the information requirement, a study must comply with the OECD TG 442C, including Appendix I (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) information on preparation of the test chemical;
b) information on preparation of and results obtained from reference controls;
c) information on the acceptance criteria.

19 In study (i):

a) no information on preparation of test chemical was provided: no information is provided on the identity of the solvent used in the assay and of the concentration of the test item solution achieved in the solvent;
b) no information on preparation of and results obtained from reference and positive controls was provided: the OECD TG 442C requires the use of cinnamic aldehyde or other suitable substance as positive control and of reference controls to validate the results of the assay. No information is provided on the identity of the positive control used in the assay, if any, and on the results obtained from this positive control. No information on the response obtained in the assay with the reference controls is provided.
c) no information on whether the acceptance criteria were met was provided. The acceptance criteria listed in the OECD TG 442C include range of values for peptide depletion obtained with the positive control and the reference controls. No information on these parameters has been provided.

20 The information provided does not cover the specification(s) required by the OECD TG 442C, Appendix I and does not allow to make a conclusion whether the Substance is reactive towards proteins. Therefore, it does not contribute to the assessment whether the Substance causes skin sensitisation.

3.2.1.2. Absence of information on activation of dendritic cells

21 Information from in vitro/in chemico test method(s) recognised according to Article 13(3), addressing each of the following three key events of skin sensitisation is a standard information requirement according to Annex VII, Section 8.3.1 column 1 of the REACH Regulation: molecular interaction with proteins (Annex VII, Section 8.3.1(a)), inflammatory response in keratinocytes (Annex VII, Section 8.3.1(b)) and activation of dendritic cells (Annex VII, Section 8.3.1(c)).

22 According to Annex VII, Section 8.3 column 2, if information from test method(s) addressing one or two of the key events in column 1 already allows classification and risk assessment according to point 8.3, studies addressing the other key event(s) need not be conducted.

23 The studies (i) and (ii) inform on molecular interaction with proteins and inflammatory response in keratinocytes, respectively.

24 You have not submitted any information addressing the activation of dendritic cells.

25 For the reasons presented in section 3.2.1.1 above, the information from study (i) provided in your dossier does not allow to make a conclusion whether the Substance is reactive towards proteins.

26 The positive results reported from study (ii) support the identification of the Substance as skin sensitiser but do not allow, on their own to conclude on classification and risk assessment including assessment of potency categorisation (Cat 1A vs 1B), as stated in the OECD TG 442D. Therefore, information from studies addressing the third key event activation of dendritic cells is required to conclude on classification and risk assessment.

27 Since you have not submitted any information addressing the activation of dendritic cells, the information requirement Annex VII, Section 8.3.1(c) is not fulfilled.

3.2.1.3. Conclusion on the assessment of whether the Substance causes skin sensitisation

28 As a result of the deficiencies in the information provided in your technical dossier identified above, it cannot be concluded whether the Substance causes skin sensitisation.

3.2.2. No assessment of potency

29 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

30 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 3.1.1 above), this condition cannot be assessed.

31 Therefore, the information requirement is not fulfilled.

3.3. Specification of the study design

32 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and activation of dendritic cells (OECD TG 442C and OECD TG 442E) must be provided.

33 Furthermore, an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

34 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing in vitro (study ii) data and newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

35 Since some data are already available, you should consider whether the Defined Approaches to Skin Sensitisation can be applied based on the information already available or to be generated (https://echa.europa.eu/support/oecd-eu-test-guidelines).

4. *In vitro* gene mutation study in bacteria

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

4.1. Information provided

37 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on:

(i) Data from structural analogues identified using the OECD QSAR toolbox.

38 ECHA understands that you also seek to adapt the information requirement by applying a (Q)SAR approach in accordance with Annex XI, Section 1.3. based on:

(ii) Results from predictions derived from structural analogues using the consensus method from the Toxrun software.

39 You provide a read-across justification document "[redacted]", an Excel file "[redacted]" and a prediction report "predicted mutagenicity from Consensus method" as attachments to the endpoint study record in IUCLID Section 7.6.1.

4.2. Assessment of the read-across adaptation

4.2.1. Information provided

40 You predict the properties of the Substance from information obtained from the following 5 source substance(s):

- 1,2-Dichloropropane, CAS 78-87-5;
- Pure Molybdenum oxide, CAS 1313-27-5;
- 2,2-Dichloro-1,1,1-trifluoroethane, CAS 306-83-2;
- 1,1-dichloroethene, CAS 75-35-4;
- cyclohexylethylcarbamoyl chloride, CAS 62899-75-6.

41 These 5 substances are considered to be the 5 nearest neighbours from the Substance when the substances are ordered based on their partition coefficients.

42 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to the highest mode value from the 5 nearest neighbour substances.

4.2.2. Read-across adaptation rejected

43 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, toxicological and ecotoxicological 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.

44 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).

45 We have identified the following issue(s) with the prediction of toxicological properties:

4.2.2.1. Missing supporting information to compare properties of the substances(s)

46 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.).

47 Supporting information must include supporting information/bridging studies to compare properties of the source substances and the Substance.

48 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

49 Your read-across justification document "[redacted]" and the Excel file "[redacted]" attached to the endpoint study record under section 7.6.1 of the IUCLID dossier do not include any information on the property under consideration for the Substance or the source substances that would confirm that the substances cause the same type of effects.

50 Based on the information provided in the Excel file "data matrix", the chemical structures of the source substances are significantly different from the structure of the Substance. Some key structural elements of the Substance such as the imidazole aromatic heterocycle are not present in the structure of any of the source substances. Conversely, 4 out of 5 source substances are halogenated and one is purely inorganic with a Molybdenum moiety.

51 You have not provided your considerations on the impact of these significant structural differences on the prediction of the properties of the Substance.

52 You have also not provided any supporting information to compare properties of the source substances and the Substance.

53 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

4.2.2.2. Missing source studies

54 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 include a robust study summary for each source study used in the adaptation.

55 You have not provided in your dossier any robust study summary for the source studies .

56 You indicate on page 6/8 of your read-across justification document "[redacted]" that "[redacted] *is reported in a separate Excel file*". You have attached an Excel spreadsheet to the endpoint study record under section 7.6.1 in IUCLID. However this Excel spreadsheet is empty and does not report any hazard information on the source substances.

57 You have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the studies. Therefore, you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.5.

4.2.3. Conclusion of the read-across assessment

58 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. On this basis, your read-across approach under Annex XI, Section 1.5. is rejected and the information requirement is not fulfilled.

4.3. Assessment of the QSAR adaptation

4.3.1. Information provided

59 You seek to adapt the information requirement of Annex VII, 8.4.1 by applying a (Q)SAR approach in accordance with Annex XI, Section 1.3 based on results from predictions derived from structural analogues using the consensus method from the Toxrun software.

60 ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

4.3.2. QSAR prediction rejected

61 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

(1) the prediction needs to be derived from a scientifically valid model,
(1) the substance must fall within the applicability domain of the model,
(2) results need to be adequate for the purpose of risk assessment or classification and labelling, and
(3) adequate and reliable documentation of the method must be provided.

62 With regard to these conditions, we have identified the following issue(s):

4.3.2.1. Inadequate documentation of the model (QMRF)

63 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and Guidance on IRs and CSA R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

64 You have not provided information about the model.

65 In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

4.3.2.2. Inadequate documentation of the prediction (QPRF)

66 Guidance on IRs and CSA R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

67 The prediction report ”predicted mutagenicity from Consensus method” included in your dossier provides information on the structures and CAS numbers of the substances

considered in the prediction from the external test set and from the training set of the model. It also lists similarity coefficients established by comparison with the structure of the Substance alongside experimental values and predicted values.

68 The information you provided about the prediction lacks the following elements:

- Adequate documentation of the model prediction, including the endpoint
- Adequate documentation of the relationship between the modelled substance and the defined applicability domain;
- Adequate documentation of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

69 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

4.3.2.3. The prediction is not adequate due to low reliability

70 Under Guidance on IRs and CSA R.6.1.3.4. a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. Guidance on IRs and CSA R.6.1.5.3. specifies that, among others, the following conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used.

71 The prediction report ”predicted mutagenicity from Consensus method” included in your dossier provides information on the structures and CAS numbers of the substances considered in the prediction from the external test set and from the training set of the model. It also lists similarity coefficients established by comparison with the structure of the Substance alongside experimental values and predicted values.

72 The prediction(s) for the Substance used as input is not reliable for the following reasons:

- No substances that are similar to the substance of interest are reported in training set or such substances are not well predicted by the model;
- No information on the input parameters used for the prediction is provided.

73 Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

4.3.3. Conclusion of the QSAR assessment

74 Based on the above, as the conditions of Annex XI, section 1.3. are not met, your adaptation is rejected and the information requirement is not fulfilled.

4.4. Specification of the study design

75 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471, 2020) should be performed using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

5. Short-term toxicity testing on aquatic invertebrates (if the results of request 1 showed a water solubility above 1 mg/L)

76 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

5.1. Information provided

77 You have provided:

(i) a short-term toxicity study on *Daphnia magna* (2019) with the Substance;

5.2. Assessment of the information provided

5.2.1. The provided study does not meet the specifications of the test guideline(s)

78 To fulfil the information requirement, a study must comply with OECD TG 202 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria

a) the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls (including the solvent control, if applicable);

b) the dissolved oxygen concentration is ≥ 3 mg/L in all test vessels at the end of the test;

Technical specifications impacting the sensitivity/reliability of the test

c) young daphnids, aged less than 24 hours at the start of the test, are used;

Characterisation of exposure

d) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;

e) the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;

f) the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also Guidance on IRs and CSA, Section R.7.8.4.1);

Reporting of the methodology and results

g) the test design is reported (e.g. static or semi-static test, number of replicates);

h) the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;

i) the dissolved oxygen and pH measured at least at the beginning and end of the test is reported;

j) 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;

79 In study (i):

Validity criteria

No information is provided on:

a) the percentage of immobilised daphnids at the end of the test in the controls;

b) the dissolved oxygen concentration in controls and test vessels at the end of the test;

Technical specifications impacting the sensitivity/reliability of the test

No information is provided on:

c) the age of the test animals, i.e. if animals were aged less than 24 h at the start of the test;

Characterisation of exposure

No information is provided on:

d) the analytical method for the quantification of the test material in the test solutions (i.e. specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range;

e) measuring interval of the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;

f) the reported effect values are based on nominal concentrations. However, no information on measured concentrations of the test material is provided to confirm test material stability within ± 20 % of the nominal or measured initial concentration;

Reporting of the methodology and results

g) on the test design, you have not specified the exposure regime;

h) tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported;

i) the dissolved oxygen and pH measured at least at the beginning and end of the test is not reported;

j) on the analytical method adequate information, i.e. specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification] is not reported and the results of the analytically determined exposure concentrations are not provided;

80 Based on the above,

- it cannot be confirmed that the validity criteria a) to b) of OECD TG 202 are met
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, in the lack of information listed under c) to j) it is not possible to assess whether the test material was stable during the test and thus if reported effect concentrations are reliable. Consequently, the hazard can be underestimated.

81 On this basis, the specifications of OECD TG 202 are not met.

82 Therefore, the information requirement is not fulfilled.

6. Long-term toxicity testing on aquatic invertebrates (if the results of request 1 showed a water solubility below 1 mg/L)

83 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

6.1. Triggering of the information requirement

84 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required.

85 As explained under request 1, the information currently provided on the saturation concentration of the Substance in water is not reliable.

86 Therefore, if the study requested under request 1 shows that the Substance is poorly water soluble, information on long-term toxicity on aquatic invertebrates must be provided.

87 You have provided a short-term toxicity study on aquatic invertebrates but no information on long-term toxicity on aquatic invertebrates for the Substance.

88 In the absence of information on long-term toxicity on aquatic invertebrates, this information requirement would not be fulfilled if the Substance is poorly water soluble.

6.2. Study design and test specifications

89 If the study requested under request 1 above shows that the Substance` solubility is below 1 mg/L, the Substance would be difficult to test due to the low water solubility. OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations.

90 Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results.

91 If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202.

92 In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

7. Growth inhibition study aquatic plants

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

7.1. Information provided

94 You have provided:

(i) a growth inhibition study on aquatic algae (2019) with the Substance;

7.2. Assessment of the information provided

7.2.1. The provided study does not meet the specifications of the test guideline(s)

95 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:

Validity criteria

k) exponential growth in the control cultures is observed over the entire duration of the test;

l) at least 16-fold increase in biomass is observed in the control cultures by the end of the test;

m) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;

n) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with *Pseudokirchneriella subcapitata*.

Technical specifications impacting the sensitivity/reliability of the test

o) three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;

p) for *Pseudokirchneriella subcapitata* the initial cell density is 5 x 10^3-10^4 cells/mL;

Characterisation of exposure

q) the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within ±20 % of the nominal or measured initial concentration throughout the test;

Reporting of the methodology and results

r) the test design is reported (*e.g.*, number of replicates, number of test concentrations and geometric progression used);

s) the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);

t) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;

u) microscopic observation performed to verify a normal and healthy appearance of the inoculum culture are reported. Any abnormal appearance of the algae at the end of the test is reported;

v) 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;

96 In study (i):

Validity criteria

No information is provided on:

w) exponential growth in the control cultures over the entire duration of the test;

x) the biomass at the start and end of the test, respectively;

y) the mean coefficient of variation for section-by-section specific growth in the control;

z) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures;

Technical specifications impacting the sensitivity/reliability of the test

No information is provided on:

aa) the number of replicates in each test concentration and the controls;

bb) the initial cell density applied with *Pseudokirchneriella subcapitata*;

Characterisation of exposure

cc) You have expressed the effect values based on nominal concentrations. However, no information on the measured concentrations of the test material is provided and you did not demonstrate that those were within ± 20 % of nominal or measured initial concentration throughout the test;

Reporting of the methodology and results

dd) on the test design, you have not specified number of replicates used per test concentration;

ee) on the test conditions, you have not specified composition of the test medium, test temperature, biomass density at the beginning of the test;

ff) tabulated data on the algal biomass determined daily for each treatment group and control are not reported;

gg) microscopic observations to verify a normal and healthy appearance of the inoculum culture are not reported;

hh) on the analytical method adequate information, i.e. performance parameters of the method is not reported and the results of the analytically determined exposure concentrations are not provided;

97 Based on the above,

- it cannot be confirmed that the validity criteria a) to d) of OECD TG 201 are met
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, in the lack of information on h) to l) it cannot be concluded whether the technical specifications e) – g) were met and hence the study is valid and its results are reliable. Consequently, the hazard can be underestimated

98 On this basis, the specifications of OECD TG 201 are not met.

99 Therefore, the information requirement is not fulfilled.

7.3. Study design and test specifications

100 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, if the study requested under request 1 above shows that the Substance` solubility is below 1 mg/L the Substance is difficult to test. Therefore, in that case you must fulfil the requirements described in "Study design and test specifications" under request 6.

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).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are 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

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 02 May 2022.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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: Addressee(s) 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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 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

(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 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.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).

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