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Helsinki, 18 January 2023

Addressee
Registrant of JS_205-287-8 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
15 April 2020

Registered substance subject to this decision ("the Substance")
Substance name: Copper bis(dimethyldithiocarbamate)
EC number: 205-287-8

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 January 2026***.

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. In vivo skin sensitisation (Annex VII, Section 8.3.2; test method: EU B.42./OECD TG 429);

3. In vitro cytogenicity study in mammalian cells (test method: B.10./OECD TG 473) or In vitro micronucleus study (test method: B.49./OECD TG 487) with the Substance (triggered by Annex VII, Section 8.4., column 2);

4. In vivo genetic toxicity study (triggered by Annex VII, Section 8.4., column 2) to be selected according to the following specifications:

   If the results of the *in vitro* cytogenicity study requested under 3. are **negative**:

   Transgenic rodent somatic and germ cell gene mutation assay (test method: OECD TG 488) in transgenic mice or rats, oral route, on the following tissues: liver and glandular stomach; duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.
   OR
   In vivo mammalian alkaline comet assay (test method: OECD TG 489) in rats, or if justified, in other rodent species, oral route, on the following tissues: liver, glandular stomach and duodenum.

   If the results of the *in vitro* cytogenicity study requested under 3. are **positive**:

   In vivo mammalian alkaline comet assay (test method: OECD TG 489) combined

with *in vivo* mammalian erythrocyte micronucleus test (test method: OECD TG 474) in rats, or if justified, in mice, oral route. For the comet assay the following tissues shall be analysed: liver, glandular stomach and duodenum.

5. If the information on water solubility (results of request 1) show a water solubility 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)
   OR
6. If the information on water solubility (results of request 1) show a water solubility 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 aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201).

The reasons for the decision(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

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Reasons related to the information under Annex VII of REACH

1. Water solubility

1 Water solubility is an information requirement under Annex VII, Section 7.7.

1.1. Information provided

2 You have provided the following information:

(i) The estimation of the water solubility range based on the preliminary solubility assessments performed as part of partitioning coefficient and ecotoxicity tests and an indication that the actual water solubility study is in progress.

1.2. Assessment of the information provided

3 We have assessed this information and identified the following issue(s):

4 To fulfil the information requirement for the Substance, a study must comply with the OECD TG 105 or the EU Method A.6 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- The shake-flask method is applicable to test material with the water solubility ≥ 10 mg/L.

5 Your registration dossier provides information showing the following:

- Under IUCLID section 4.8 "Test guideline", you indicate a test method equivalent or similar to OECD TG 105 using a shake flask method (2018);
- However, under IUCLID section 4.8 "Principles of method if other than guideline", you also specify that the water solubility is determined based on "*preliminary solubility assessments performed as part of partition coefficient and ecotoxicity tests*" and you also say that "*Solubility assessed as part of coefficient study, water solubility study in progress*";
- You conclude that the water solubility is in the range of 0 - <0.0123 mg/L.

6 ECHA understands from the information in the dossier that the water solubility value currently reported in your registration dossier is derived from partition coefficient and ecotoxicity tests. Information on actual water solubility study using OECD TG 105 and shake flask method is not available from your dossier. Since only preliminary solubility assessments are available, the reliability of the reported water solubility value is questionable.

7 On the basis of the above, the information requirement is not fulfilled.

1.3. Study design

8 Considering the reported properties of the Substance (solubility < 10 mg/L based on preliminary information), the shake-flask method is not applicable but column elution described in EU A.6/OECD TG 105 is the most appropriate method to fulfil the information requirement for the Substance.

2. Skin sensitisation

9 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, 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).

2.1. Information provided

10 You have provided following in vitro studies conducted with the Substance:

(i) a direct peptide reactivity assay (DPRA; OECD TG 442C; 2018);

(ii) a keratinocyte activation test (OECD TG 442D; 2018);

(iii) a human cell line activation test (OECD TG 442E; 2018).

11 We have assessed this information and identified the following issue(s):

2.2. Assessment of the information provided

2.2.1. Assessment whether the Substance causes skin sensitisation

2.2.1.1. Keratinocyte activation test (ii) and human cell line activation test (iii) are not applicable for the Substance

12 To fulfil the information requirement for the Substance, in vitro/in chemico information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. The in vitro/in chemico information must be applicable for testing the substance and obtaining adequate information to enable concluding on whether the Substance causes skin sensitisation.

13 You have provided information on an in vitro keratinocyte activation test (ii) and on a human cell line activation test (iii) and indicate that these studies are inconclusive due to high cytotoxicity.

14 Based on the reported high cytotoxicity in these studies, ECHA concludes that the in vitro keratinocyte activation test (ii) and human cell line activation test (iii) are inapplicable test methods for the Substance. Therefore, these studies do not allow to conclude on the inflammatory response in keratinocytes and activation of dendritic cells, and do not contribute to the assessment whether the Substance causes skin sensitisation.

2.2.1.2. The provided DPRA study (i) does not meet the specifications of the test guideline(s)

15 Regarding the direct peptide reactivity assay (i), this study would need to comply with the OECD TG 442C, including Appendix I (Article 13(3) of REACH). Therefore, the following specifications would need to be met and reported in the robust study summary:

a) information on preparation of cysteine and/or lysine-containing peptides;
b) information on preparation of the test chemical;
c) information on preparation of and results obtained from reference controls;
d) information on the acceptance criteria;
e) prediction model applied;
f) results of percent of peptide depletion of each replicate and the mean peptide depletion;

g) other effects, if noted, e.g., precipitation.

16 In study (i) described as a Direct Peptide Reactivity Assay (DPRA):

a) no information on preparation of cysteine and/or lysine-containing peptides was provided;
b) no information on preparation of test chemical was provided;
c) no information on preparation of and results obtained from reference controls was provided;
d) no information on whether the acceptance criteria was met was provided;
e) no information on prediction model applied was provided;
f) no information on results on peptide depletion of each replicate and the mean peptide depletion was provided;
g) no information whether precipitation occurred was provided.

17 The information provided does not allow to conclude if the study (i) covers the specification(s) listed above and required by the OECD TG 442C, Appendix I.

18 Therefore, it does not allow to make a conclusion whether the Substance is reactive towards proteins, and does not contribute to the assessment whether the Substance causes skin sensitisation.

2.2.1.3. Conclusion on whether the Substance causes skin sensitisation

19 Based on above, the in vitro studies (i-iii) provided in the dossier do not allow to conclude wether the Substance causes skin sensitisation.

2.2.2. No assessment of potency

20 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).

21 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 2.2.1. above), this condition cannot be assessed.

2.3. Conclusion on skin sensitisation

22 No information is provided to conclude if the Substance causes skin sensitisation or on the assessment of potency. On this basis, the information requirement is not fulfilled.

2.4. Specification of the study design

23 No conclusion on the skin sensitisation potential or skin sensitsation potency can be made for the Substance based on the existing in vitro/in chemico data.

24 As the in vitro keratinocyte activation and human cell line activation test methods as described in the OECD TG 442D and OECD TG 442E are not applicable for the Substance, and the in vitro direct peptide reactivity assay alone would not be sufficient to conclude whether the Substance causes skin sensitisation (OECD TG 442C, paragraph 8), the 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.

3. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study

25 Further mutagenicity studies must be considered under Annex VII to REACH in case of a positive result (Section 8.4., column 2).

3.1. Triggering of the information requirement

26 The Guidance on IRs & CSA, Section R.7.7.6.3, further specifies that "REACH Annex VII substances for which only a bacterial gene mutation test has been conducted and for which the result is positive should be studied further, according to the requirements of Annex VIII." This is for the reason that the in vitro cytogenicity test under Section 8.4.2 will allow to further investigate the mutagenicity of the substance and confirm the selection of an appropriate follow up in vivo mutagenicity study in accordance with the REACH integrated testing strategy (ECHA Guidance r.7.a, section R.7.7.6).

27 Your dossier contains positive results for the in vitro gene mutation study in bacteria (2018).

3.2. Information provided

28 You have not provided any in vitro cytogenicity studies in the dossier.

29 Instead, you have provided a document '[redacted]The document states that "further testing is not recommended at this stage as the conclusions from the other salts can be used". Therefore, ECHA understands that you have intended to adapt this information requirement under the read-across adaptation according to Annex XI, section 1.5.

3.3. Assessment of the information provided

30 We have assessed this information and identified the following issue(s):

31 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.

32 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).

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

34 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 an explanation why the properties of the Substance may be predicted from information on the source substance(s), robust study summaries for the source studies, and supporting information to scientifically justify the explanation for prediction of properties.

35 You have provided a document [redacted]. This document describes in vitro and in vivo genotoxicity study results (name of the study, outcome as positive or negative) from experiments conducted with sodium, potassium and zinc salt of the dimethylthiocarbamate and not the the Substance.

36 However, this document and your dossier do not contain

- an explanation why the properties of the registered substance may be predicted from the other substances,
- robust study summaries (source substance identity, methods, results and conclusions) for each source study used in the adaptation, and
- supporting information to scientifically justify such explanation for prediction of properties.

37 In the absence of such information the read-across documentation is inadequate to support the predictions and the properties of the Substance cannot be reliably predicted from the data on the source substance(s).

38 Therefore, your read-across approach under Annex XI, Section 1.5. is rejected and the information in accordance with the REACH integrated testing strategy is still needed.

3.4. Specification of the study design

39 Either the in vitro cytogenicity study in mammalian cells (test method OECD TG 473) or in vitro micronucleus study (test method OECD TG 487) are considered suitable.

4. In vivo genetic toxicity study

40 Further mutagenicity studies must be considered under Annex VII, Section 8.4., column 2, in case of a positive result.

4.1. Triggering of the information requirement

41 Your dossier contains positive results for the in vitro gene mutation study in bacteria (2018) which raise the concern for gene mutations. Following a positive result in an in vitro mutagenicity test, adequately conducted somatic cell in vivo testing is triggered to ascertain if this potential can be expressed in vivo.

4.2. Information provided

42 You have not provided any in vivo genetic toxicity studies in the dossier.

43 Instead, you have provided a document [redacted]

44 The document states that "further testing is not recommended at this stage as the conclusions from the other salts can be used". Therefore, ECHA understands that you have intended to adapt this information requirement under the read-across adaptation according to Annex XI, section 1.5.

45 We have assessed this information and identified the following issue(s):

4.3. Assessment of read-across approach

46 As described under section 3.2, the read-across documentation is inadequate to support the predictions. Therefore, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

4.4. Test selection

47 According to the Guidance on IRs & CSA, Section R.7.7.6.3 either the in vivo mammalian alkaline comet assay ("comet assay", OECD TG 489) or the transgenic rodent somatic and germ cell gene mutation assay ("TGR assay", OECD TG 488) are suitable to follow up a positive in vitro result on gene mutation.

48 As explained above, under request 3, in the dossier there is no adequate information from an in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study to conclude on the selection of an appropriate follow up in vivo mutagenicity study. Therefore, by this decision, ECHA also requests an In vitro cytogenicity study in mammalian cells or in vitro micronucleus study, which may raise a concern for chromosomal aberration in the case of positive results.

49 If there is also a concern for chromosomal aberration, the comet assay can be combined with an in vivo mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) in a single study (see OECD TG 489 para. 33; OECD TG 474 para. 37c; Guidance on IRs & CSA, Section R.7.7.6.3). While the comet assay can detect primary DNA damage that may lead to gene mutations and/or structural chromosomal aberrations, the MN test can detect both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy). A combined study will thus address both the identified concerns for chromosomal aberration as well as gene mutation.

50 The combined study, together with the results of the in vitro mutagenicity studies, can be used to make definitive conclusions about the mechanism(s) inducing in vivo mutagenicity and lack thereof. Furthermore, the combined study can help reduce the number of tests performed and the number of animals used while addressing (structural and numerical) chromosomal aberrations as well as gene mutations.

51 Therefore, you must wait for the results of the in vitro test requested under request 3 and, depending on these results, to conduct either a) the TGR assay or Comet assay if the test results of request 3 are negative; or b) Comet assay combined with MN test if the test results of request 3 are positive. The deadline set in this decision allows for sequential testing.

4.5. Specification of the study design

*4.5.1. Comet assay (if the test results of request 3 are **negative**)*

52 In case you decide to perform the comet assay, according to the test method OECD TG 489, rats are the preferred species. Other rodent species can be used if scientifically justified (OECD TG 489, paragraph 23).

53 Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

54 In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver, as primary site of xenobiotic metabolism, and from glandular stomach and duodenum, as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

*4.5.2. TGR assay (if the test results of request 3 are **negative**)*

55 In case you decide to perform the TGR assay, according to the test method OECD TG 488, the test must be performed in transgenic mice or rats.

56 Also, according to the test method OECD TG 488, the test substance is usually administered orally.

57 Based on OECD TG 488, you are requested to follow the 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals.

58 According to the test method OECD TG 488, the test must be performed by analysing tissues from liver, as slowly proliferating tissue and primary site of xenobiotic metabolism, and from glandular stomach and duodenum, as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 ºC) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed, only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

*4.5.3. Comet assay combined with MN test (if the test results of request 3 are **positive**)*

59 According to the test method OECD TG 489, rats are the preferred species. Other rodent species can be used if scientifically justified. According to the test method OECD TG 474, the test may be performed in mice or rats. Therefore, the combined study must be performed in rats, or if justified, in mice.

60 Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

61 In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver, as primary site of xenobiotic metabolism, and from glandular stomach and duodenum, as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

62 The combination of OECD TGs 489 and 474 should not impair the validity of and the results from each individual study. Careful consideration should be given to the dosing, and tissue sampling for the comet analysis alongside the requirements of tissue sampling for the mammalian erythrocyte micronucleus test (see OECD TG 489, e.g. Bowen et al. 2011 [1]).

63 [1] Bowen D.E. et al. 2011. Evaluation of a multi-endpoint assay in rats, combining the bone-marrow micronucleus test, the comet assay and the flow-cytometric peripheral blood micronucleus test. Mutation Research 722 7–19.

4.5.4. Germ cells

4.5.4.1. Comet assay or Comet assay combined with MN test

64 In case you perform a comet assay, you may consider collecting the male gonadal cells from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and

protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

4.5.4.2. TGR assay

65 In case you perform a TGR assay, you may consider collecting the male germ cells (from the seminiferous tubules) at the same time as the other tissues, to limit additional animal testing. According to the OECD 488, the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 ºC). This duration is sufficient to allow you or ECHA to decide on the need for assessment of mutation frequency in the collected germ cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

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

66 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

5.1. Information provided

67 You have provided a study on short-term toxicity to aquatic invertebrates (2018) with the Substance (study i).

5.2. Assessment of the information provided

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

68 To fulfil the information requirement, a study must comply with OECD TG 202 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

69 Validity criteria

a) the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls.

70 Technical specifications impacting the sensitivity/reliability of the test

b) at least 20 animals are used at each test concentration and the controls and at least five concentrations are tested;
c) the test concentrations are below the limit of solubility of the test material in the dilution water.

71 Characterisation of exposure

d) 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).

72 Reporting of the methodology and results

e) the methods used to prepare stock and test solutions is reported;
f) 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;
g) 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.

73 In study (i) described as short-term toxicity study on daphnids you provide the following information:

74 Validity criteria

a) the percentage of immobilised daphnids was not reported at the end of the test in the controls.

75 Technical specifications impacting the sensitivity/reliability of the test

b) the number of animals used at each test concentration and the controls and the number of concentrations tested was not reported;
c) while the test concentrations were not reported in your dossier, the observed EC_{50} effect values are reported to be in the range of 1 -10 mg/L and a limit of solubility of the test material in water is reported to be in the range of 0 - <0.0123 mg/L, i.e. the test concentrations may have been above the limit of solubility of the test material in the dilution water.

76 Characterisation of exposure

d) the reported effect values are based on initial measured concentrations. However, measured concentrations of the test material were not reported and it is therefore not demonstrated that they remained within ± 20 % of the nominal or measured initial concentration.

77 Reporting of the methodology and results

e) the methods used to prepare stock and test solutions is not reported;
f) tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported;
g) adequate information on the analytical method, i.e. reported specificity, recovery efficiency, precision and limits of determination is not reported and the results of the analytically determined exposure concentrations are not provided.

78 Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, the stock solution preparation method was not described, the number of replicates and the number of animals per replicate is not known, test concentrations (nominal and measured) and the adequate information on the method used to analyse test concentrations are not reported, and the results of the study (i.e number of immobilised daphnids for each treatment and control) are not reported.

79 Therefore, the requirements of OECD TG 202 are not met and the information requirement is not fulfilled.

5.3. Study design and test specifications

80 The Substance may be difficult to test due to the reported low water solubility (0 – 0.0123 mg/L) and/or adsorptive properties (log kow 4.5). OECD TG 202 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. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. 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. 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.

6. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2): If the results of request 1 showed a water solubility below 1 mg/L

81 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

6.1. Triggering of the information requirement

82 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. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

83 You have provided information which indicates that the saturation concentration of the Substance in water is in the range of 0 - <0.0123 mg/L. However, as mentioned under Section 1 of this Appendix, the reliability of the range of values reported in the dossier is uncertain.

84 Therefore, if the results of the water solubility study requested under Section 1 of this Appendix will show that the water solubility is below 1 mg/L the Substance will be considered as poorly water soluble, and information on long-term toxicity on aquatic invertebrates will need to be be provided.

6.2. Information provided

85 You have provided a short-term toxicity study on aquatic invertebrates, the reliability of which cannot be confirmed by ECHA based on the reported information (see the reasons under point 5.2 above), but no information on long-term toxicity on aquatic invertebrates for the Substance.

6.3. Study design and test specifications

86 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 5.

7. Growth inhibition study aquatic plants

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

7.1. Information provided

88 You have provided a study for algae growth inhibition (2018) with the Substance (study i).

7.2. Assessment of the information provided

89 To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

90 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.

91 Technical specifications impacting the sensitivity/reliability of the test

b) the test concentrations are below the limit of solubility of the test material in the dilution water.

92 Characterisation of exposure

c) 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.

93 Reporting of the methodology and results

d) the test design is reported (*e.g.*, number of replicates, number of test concentrations);
e) the test conditions are reported (*e.g.*, composition of the test medium, biomass density at the beginning of the test);
f) the methods used to prepare stock and test solutions are reported;
g) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
h) 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;
i) 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.

94 In study (i) described as growth inhibition study on algae you provide the following:

95 Key parameter measured

a) the concentration of the test material leading to a 50 % inhibition of growth at the end of the test is estimated but no estimate is provided for the concentration leading to 0% (or 10%) inhibition of growth at the end of the test.

96 Technical specifications impacting the sensitivity/reliability of the test

b) while the test concentrations were not reported in your dossier, the observed EC_{50} effect values are reported to be in the range of 1 -10 mg/L and a limit of solubility of the test material in water is reported to be in the range of 0 -

<0.0123 mg/L, i.e. the test concentrations may have been above the limit of solubility of the test material in the dilution water.

97 Characterisation of exposure

c) you have expressed the effect values based on nominal concentrations. However, measured concentrations of the test material were not reported and it is therefore not demonstrated that they remained within ± 20 % of the nominal or measured initial concentration.

98 Reporting of the methodology and results

d) on the test design, you have not specified the number of replicates and number of test concentrations;
e) on the test conditions, you have not specified composition of the test medium and biomass density at the beginning of the test;
f) on the test procedure, you have not specified the methods used to prepare stock and test solutions;
g) tabulated data on the algal biomass determined daily for each treatment group and control are not reported;
h) microscopic observations to verify a normal and healthy appearance of the inoculum culture are not reported;
i) adequate information on the analytical method, i.e. reported specificity, recovery efficiency, precision and limits of determination is not reported and the results of the analytically determined exposure concentrations are not provided.

99 Based on the above,

- the information provided does not cover all the key parameters required by the OECD TG 201
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, the stock solution preparation method was not described, the number of replicates is not reported, the biomass density at the beginning of the test per replicate is not known, test concentrations (nominal and measured) and the adequate information on the method used to analyse test concentrations are not reported, and the results of the study (i.e algae biomass for each treatment and control) are not reported.

100 Therefore, the requirements of OECD TG 201 are not met and the information requirement is not fulfilled.

7.3. Study design and test specifications

101 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 5.

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 01 February 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 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;

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 and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

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