~~Confidential~~

Helsinki, 31 October 2022

Addressees
Registrant(s) of JS 701-400-4 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
21/09/2021

Registered substance subject to this decision ("the Substance")
Substance name: copper sulfate;N'-[2-[2-(2-aminoethylamino)ethylamino]ethyl]ethane-1,2-diamine
EC/List number: 701-400-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***7 November 2024***.

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

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

1. In vitro cytogenicity study in mammalian cells (test method: OECD TG 473) or In vitro micronucleus study (test method: OECD TG 487)

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

3. 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 addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You

must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

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

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

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

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, 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.

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

0.1.1. Scope of the grouping of substances (category)

5 You provide a read-across justification document in IUCLID, section Linked categories.

6 For the purpose of this decision, the following abbreviations are used for the category members:

- CuTETA, Reaction product of copper sulfate ($CuSO_4$) and N'-[2-(2-aminoethylamino)ethyl]ethane-1,2-diamine (TETA), EC No. 701-399-0
- CuTEPA, Reaction product of copper sulfate ($CuSO_4$) and N'-[2-[2-(2-aminoethylamino)ethylamino]ethyl]ethane-1,2-diamine (TEPA), EC No. 701-400-4
- CuDETA, Reaction product of copper sulfate ($CuSO_4$) and N-(2-aminoethyl)ethane-1,2-diamine (DETA), EC No. 701-411-4

7 You justify the grouping of the substances as: "*The copper chelates considered in this category consist of two main functional groups:* [redacted]".

8 You define the applicability domain as follow: "Any copper chelate with polyamines where the chelating agents has stability constants similar or higher than CuDETA can thus be a category member for the ecotoxicity. […] Any metal chelate with DETA, TETA or TEPA can be considered a member of the category if the toxicity of the metal ion is lower or similar to copper".

9 ECHA understands that this is the applicability domain of the grouping and your predictions are assessed on this basis.

0.1.2. Predictions for Aquatic toxicity

10 You provide a read-across justification document in IUCLID Section Linked categories.

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

- CuDETA, Reaction product of copper sulfate ($CuSO_4$) and N-(2-aminoethyl)ethane-1,2-diamine (DETA), EC No. 701-411-4.

12 You provide the following reasoning for the prediction of aquatic toxicity: "For each (eco)toxicity endpoint, the copper chelate that could be regarded as a worst-case based on available information (e.g. literature, classification) for that endpoint was tested and used as for the read-across to other category members, as a worst-case (RAAF Scenario 3)."

13 ECHA understands that your read-across hypothesis is based on the formation of common (bio)transformation products. You predict the properties of your Substance based on a worst-case approach.

14 We have identified the following issue with the predictions of aquatic toxicity:

0.1.2.1. Missing supportive information

15 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information 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.).

16 As indicated above, your read-across hypothesis is based on the (bio)transformation of the category members to a common compound(s). In this context, information characterising the rate and extent of the (bio)transformation of the category members is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds.

17 Furthermore, your read-across hypothesis is based on the assumption that the source substance (CuDETA) constitutes a worst-case for the prediction of the property under consideration of the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the category members is necessary to confirm a conservative prediction of the properties of the Substance from the data on other category members. Such information can be obtained, for example, from bridging studies of comparable design and duration for the category members.

18 For the source substance (CuDETA), you provide the studies specified in sections 2 and 3 of this decision used in the prediction in the registration dossier. Apart from those studies, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of bridging studies, studies on (bio)transformation of category members to common compound(s) or other supportive data for the Substance and source substance that would confirm a conservative prediction of the properties of the Substance.

19 In the absence of such information, you have not established that the source substance (CuDETA) constitutes a worst-case for the prediction of the properties under consideration of the Substance. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

0.1.2.2. Adequacy and reliability of source studies

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

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

21 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement in sections 2 and 3.

0.1.3. Conclusion on the read-across approach

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

Reasons related to the information under Annex VII of REACH

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

23 Further mutagenicity studies must be considered under Annex VII to REACH in case of a positive result in an in vitro gene mutation study in bacteria (Section 8.4., Column 2).

1.1. Triggering of the information requirement

24 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 in accordance with the REACH integrated testing strategy. The obtained in vitro data will inform on the genotoxic concern(s) associated with the Substance and help identify the most adequate follow-up in vivo study (requested in a parallel testing proposal decision for your dossier).

25 Your dossier contains positive results for the in vitro gene mutation study in bacteria (OECD TG 471, 2017) which raise the concern for gene mutation.

26 ECHA therefore considers that an appropriate in vitro cytogenicity or micronucleus study is necessary to further investigate the mutagenicity of the Substance.

1.2. Information provided to meet the requirement

27 No information from an *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study on the Substance is available in the dossier.

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

1.3. Specification of the study design

29 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.

2. Short-term toxicity testing on aquatic invertebrates

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

2.1. Information provided

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

(i) A study on short-term toxicity to Daphnia (2017) with the category member CuDETA, EC 701-411-4.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

32 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

2.2.2. Adequacy and reliability of study on the source substance

33 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed / cover an exposure duration comparable to or longer than the one specified in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 202. Therefore, the following specifications must be met:

34 Characterisation of exposure

a) 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;

35 Reporting of the methodology and results

b) the test procedure is reported (e.g. composition of the test medium, age of daphnids);
c) the dissolved oxygen and pH measured at least at the beginning and end of the test is reported.

36 Your registration dossier provides an OECD TG 202 study showing the following:

37 Characterisation of exposure

a) the concentration of the test material was determined in the medium with a method that measures only Cu concentration. However, the concentration of the whole Substance (CuDETA) or its organic part, i.e. DETA, are not measured and it is not shown that the Cu concentration could be used as a surrogate measurement of the Substance or DETA concentration in the test medium.

38 Reporting of the methodology and results

b) on the test procedure, you have not specified age of daphnids. Also, the test medium characteristics, particularly hardness is not reported;
c) the dissolved oxygen and pH measured at least at the beginning and end of the test is not reported. You have reported only the range (pH 7.7-8.0 and dissolved oxygen 8.7-8.9 mg/L) in both cases without specifying the time points of the measurements.

39 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the applied analytical method measures only concentration of the Cu part of the substance in the test medium and the concentration of the Substance (CuDETA) or its organic part (DETA) is not measured. Therefore, the concentration of the Substance or DETA in the test medium during the test is not known.
  In your comments to the draft decision, you state that "[d]*ue to the high water solubility of the test item itself (more than 1000 g/L) and the high water solubility of the parent components (copper sulfate and 2,2'-iminodi(ethylamine)) the measurement of copper is believed to be representative for the availability and presence of the substance in the test medium*". You provided a method validation

report for the analytical method (*i.e.*, ICP/OES) used in study (i). You state that "[s]*ince no deviations were reported (i.e. precipitations or other phenomena which should indicate that the test substance as such would not be available in the test medium) the analysis of the copper content was considered to be representative for the test Substance*".
However, stability of measured copper concentrations over the study period does not demonstrate that the organometallic complex remained stable. Also, in case the organic moiety (DETA) and the copper ion dissociates, stable concentrations stability of measured copper concentrations does not demonstrate stable exposure to the organic moiety. Therefore, while this report provides supporting information that the method to measure copper was adequate, it does not address the issue identified above.

- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. You have not reported the age of the test animals. As a result, it is not possible to conclude that the age of the test animals have an adequate and reliable coverage of the requirements of the test guideline, i.e. the animals were aged less than 24 h at the start of the test. Also, you have not reported the test medium characteristics in full detail, and the characteristics of the test water cannot be confirmed to have an adequate and reliable coverage of the test guideline requirements, particularly water hardness is not reported to be within the required range between 140 and 250 mg/L (as CaCO3). In addition, the measurement of dissolved oxygen and pH were not reported to have taken place at the beginning and at the end of the test and it is not possible assess if the dissolved oxygen concentration and pH remained within acceptable range throughout the experiment.
  In your comments to the draft decision, you have attached the full study report for the study. The report includes the missing information listed above. This information supports that the study was conducted under test conditions that are mostly consistent with the OECD TG 202 (with the exception of water hardness which was 270 mg/L (as CaCO3) hence above the maximum value specified in the test guideline). However, as the information is currently not available in your registration dossier, you should submit this information in an updated registration dossier by the deadline set in the decision.

40 Therefore, as you have not provided adequate information to demonstrate tha exposure was satisfactorily maintained in this test, the study submitted in your adaptation does not provide an adequate and reliable coverage of the key parameter(s) of the test guideline for the corresponding study that shall normally be performed for this information requirement.

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

42 In your comments to the draft decision, you agree to perform the requested study.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

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

(i) a growth inhibition test on freshwater algae (2018) with the category member CuDETA, EC 701-411-4.

3.2. Assessment of the information provided

3.2.1. Read-across adaptation rejected

45 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

3.2.2. Adequacy and reliability of study on the source substance

46 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed / cover an exposure duration comparable to or longer than the one specified in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 201. Therefore, the following specifications must be met:

47 Characterisation of exposure

a) analytical monitoring must be conducted.

48 Reporting of the methodology and results

b) the test conditions are reported (e.g., composition of the test medium);
c) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

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

50 Characterisation of exposure

a) analytical monitoring of the Substance was not conducted and only Cu concentration was measured in the medium. However, the concentration of the whole Substance (CuDETA) or its organic part, i.e. DETA, are not measured and it is not shown that the Cu concentration could be used as a surrogate measurement of the Substance or DETA concentration in the test medium.

51 Reporting of the methodology and results

b) on the test conditions, you have not specified composition of the test medium;
c) tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

52 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the applied analytical method measures only concentration of the Cu part of the substance in the test medium and the concentration of the Substance (CuDETA) or its organic part (DETA) is not measured. Therefore, the concentration of the Substance or DETA in the test medium during the test is not known.
  In your comments to the draft decision, you provided similar comments as those detailed under Request 2. You also provided a method validation report for the analytical method (*i.e.*, ICP/OES) used in study (i). ECHA's reply to your comment provided under Request 2 equally apply to this endpoint.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, composition of the test medium is not provided and it is not possible to assess the suitability of the applied test medium for the

test. In addition, tabulated data on the algal biomass determined daily for each treatment group and control are not reported and therefore, it is not possible to conduct an independent assessment of whether the validity criteria of the test guideline were met and of the interpretation of the study results.

In your comments to the draft decision, you have attached the full study report for the study. The report includes the missing information listed above. This information supports that the study was conducted under test conditions that are consistent with the OECD TG 201. However, as the information is currently not available in your registration dossier, you should submit this information in an updated registration dossier by the deadline set in the decision.

53 Therefore, as you have not provided adequate information to demonstrate tha exposure was satisfactorily maintained in this test, the study submitted in your adaptation does not provide an adequate and reliable coverage of the key parameter(s) of the test guideline for the corresponding study that shall normally be performed for this information requirement.

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

55 In your comments to the draft decision, you agree to perform the requested study.

References

The following documents may have been cited in the decision.

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

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

Guidance on data-sharing; ECHA (2017).

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

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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 16 December 2021.

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

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

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

Appendix 3: Addressees of this decision and their corresponding information requirements

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

- the information specified in 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 identify all the constituents as far as possible as well as their concentration (OECD GLP (ENV/MC/CHEM(98)16) and EU Tests Methods Regulation (EU) 440/2008 (Note, Annex). Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods

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