~~Confidential~~

Helsinki, 20 February 2024

Addressees
Registrants of Joint subm. Perkacit TBzTD as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
17/02/2020

Registered substance subject to this decision ("the Substance")
Substance name: Tetrakis(phenylmethyl)thioperoxydi(carbothioamide)
EC number/List number: 404-310-0

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 requests 1, 2, 3, 4, 5, 10, 11, 12 listed below ***by 28 May 2026***.

The information listed under requests 6, 7, 8, 9 below has already been requested in decision TPE-D-2114599157-34-01/F. The same test on the same substance must not be duplicated. Therefore, the deadline applicable to the submission of this information must be the deadline already imposed for this same information under decision TPE-D-2114599157-34-01/F. Consequently, the information listed must be submitted **by 25 September 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. Skin sensitisation (Annex VII, Section 8.3.)
    a) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
    b) only if the *in vitro/in chemico* test methods specified under point a) 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)
2. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020))
3. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3/OECD TG 201)

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

4. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei

5. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490)
6. Long-term toxicity testing on fish, also requested below (triggered by Annex VIII, Section 9.1.3., Column 2)

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

7. Sub-chronic toxicity study (90 days), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats
8. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)
9. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)
10. Long-term toxicity testing on terrestrial invertebrates (triggered by Annex IX, Section 9.4.1., column 2; test method: EU C.33/OECD TG 222 or EU C.32/OECD TG 220 or EU C.35/OECD TG 232)
11. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: EU C.21./OECD TG 216)
12. Long-term toxicity on terrestrial plants (triggered by Annex IX, Section 9.4.3., column 2; test method: EU C.31./OECD TG 208 with at least six species or ISO 22030)

The reasons for the requests 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.

~~Confidential~~

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. Skin sensitisation

1 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).

1.1. Information provided

2 You have provided a Guinea Pig Maximisation Test (1988) with the Substance;

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

3 To fulfil the information requirement, and to enable concluding whether the Substance causes skin sensitisation, a study must comply with the EU Method B.6/OECD TG 406 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) a positive control is included to establish the sensitivity and reliability of the experimental technique;

b) the exposure conditions are described.

4 In the provided study:

a) no information on positive control group was provided;

b) the exposure duration steps and the procedures performed are not clear (e.g. duration of induction period is not reported but should be 10-14 days)

5 The information provided does not cover the specification(s) required by the EU Method B.6/OECD TG 406.

6 On this basis, it cannot be concluded whether the Substance causes skin sensitisation.

1.2.2. No assessment of potency

7 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).

8 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

9 Therefore, the information requirement is not fulfilled.

1.3. Specification of the study design

10 To fulfil the information requirement for the Substance, 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. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

11 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the newly generated in vitro 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.

1.4. Information regarding data sharing

12 Other registrants' registration for the Substance contains an adequate robust study summary for the same study you included in your registration dossier. In accordance with Title III of the REACH Regulation, you may request the information missing in your registration dossier from the other registrants and then make every effort to reach an agreement on the sharing of data and costs (Guidance on data-sharing).

2. In vitro gene mutation study in bacteria

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

2.1. Information provided

14 You have provided an *in vitro* gene mutation study in bacteria (1987) 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

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

a) the test is performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101);

b) at least 5 doses are evaluated, in each test condition;

c) triplicate plating is used at each dose level;

d) the mean number of revertant colonies per plate is reported for the treated doses and the controls;

e) negative results are confirmed in a repeat experiment with modification of study parameters to extend the range of conditions assessed, or a justification why confirmation of negative results is not considered necessary is provided.

16 In the provided study:

a) the test was performed with the strains *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 (i.e., the strain *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)is missing);

b) you have not specified the number of doses evaluated in each test condition and you only reported the concentration ranges were reported;

c) triplicate plating was not used at each dose level;

d) the mean number of revertant colonies per plate for the treated doses and the controls is not reported;

e) no repeat experiment was performed to confirm the negative results and no justification was provided.

17 The information provided does not cover the specification(s) required by the OECD TG 471.

18 Therefore, the information requirement is not fulfilled.

19 In your comments to the draft decision, you do not agree with the request but you have not provided any key arguments in the attachment.

2.3. Specification of the study design

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

2.4. Information regarding data sharing

21 Other registrants' registration for the Substance contains a robust study summary for the same study you included in your registration dossier which includes the missing information listed under Section 2.2.1. points b) to e). In accordance with Title III of the REACH Regulation, you may request the information missing in your registration dossier from the other registrants and then make every effort to reach an agreement on the sharing of data and costs (Guidance on data-sharing).

3. Growth inhibition study aquatic plants

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

3.1. Information provided

23 You have provided a growth inhibition study on aquatic plants/algae according to OECD TG 201 (2018) with the Substance.

3.2. Assessment of the information provided

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

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

Additional requirements applicable to difficult to test substances

a) if the test material is tested at the saturation concentration, evidence must be provided that all reasonable efforts have been taken to achieve a saturation concentration, which include:

- an analytical method validation report demonstrating that the analytical method is appropriate, and
- information on the saturation concentrations of the test material in water and in the test solution, and
- the results of a preliminary experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test

material in solution;

b) the efficacy of the separation method is assessed (*e.g.* by checking for the Tyndall effect or by any other appropriate means);

Reporting of the methodology and results

c) the test conditions are reported (*e.g.*, composition of the test medium);

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

e) 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.

25 In the provided study:

Additional requirements applicable to difficult to test substances

a) you claim that the test material was tested at the saturation concentration. However, insufficient evidence is provided to support that saturation was achieve. More specifically:

- the analytical method is not sufficiently described as no information on the limit of detection (LoD) and limit of quantification (LoQ) is provided.
- information on the saturation concentrations of the test material in the test solution is not provided.
- the results of a preliminary experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test material in solution is not provided;

b) no information on the efficacy of the separation method is provided;

Reporting of the methodology and results

c) on the test conditions, you have not specified the nature and composition of the test medium (including its TOC/DOC content);

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

e) the results of the analytically determined exposure concentrations are not provided.

26 Based on the above,

- the Substance is difficult to test due to its low solubility and high adsorption properties and there are critical methodological deficiencies resulting in the rejection of the study results. More specifically,
  - insufficient information is provided to demonstrate that test organisms were adequately exposed to the test material. First, you have not provided the results of a preliminary solubility study conducted with the corresponding test solution. In addition, you have not provided the results of a preliminary experiment to demonstrate that the method used to prepare the test solutions allowed to reach saturation and that the separation method had adequate efficiency to remove undissolved test material. Therefore, it remains uncertain whether the test material was tested up to its saturation concentration (as claimed in the study) and whether measured exposure concentrations reflect truly dissolved concentrations of the test material.

- on the determination of exposure concentrations, you have not demonstrated that the analytical method was appropriate in studies. Therefore, the reported values are deemed of low reliability.

- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not provided adequate reporting the analytically determined exposure concentrations and therefore ECHA cannot assess to what extent the reported value reflect exposure throughout the exposure phase. Furthermore, in the absence of tabulated data on the algal biomass, ECHA cannot conduct an independent assessment as to whether the validity criteria of the test guideline were met and assess the interpretation of the results of the provided study.

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

28 Therefore, the information requirement is not fulfilled.

29 In your comments on the draft decision, you have provided additional information that address the study deficiencies identified above. However, as the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set in the decision.

3.3. Study design and test specifications

30 The Substance is difficult to test as it is strongly adsorbing (log K_{oc} > 5.6 based on OECD TG 121) and it has low solubility in water (reported as < 10 µg/L based on OECD TG 105). OECD TG 201 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 201. 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.

Reasons related to the information under Annex VIII of REACH

4. *In vitro* micronucleus study

31 An in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

4.1. Information provided

32 You have provided:

(i) an *in vitro* cytogenicity study in mammalian cells, key study (1988, report number: [redacted]) with the Substance;

(ii) an *in vitro* cytogenicity study in mammalian cells, supporting study (1989) with the Substance;

(iii) an *in vitro* cytogenicity study in mammalian cells, supporting study (1988, report number: [redacted]) with the Substance;

(iv) an *in vivo* micronucleus test (1988) with the Substance.

4.2. Assessment of the information provided

4.2.1. The provided studies do not meet the specifications of the test guideline(s)

33 To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) at least 300 well-spread metaphases are scored per concentration;

b) the positive controls induce responses compatible with those generated in the historical positive control database;

c) the positive controls produce statistically significant increase compared with the negative control;

d) the negative control data is ideally within the 95% control limits of the distribution of the laboratory's historical negative control database;

e) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures is reported;

34 In studies (i), (ii) and (iii):

a) no data on the number of metaphases scored per concentration were provided;

b) no data demonstrating that the positive control data is compatible with those generated in the historical positive control database were provided;

c) no data demonstrating that the positive control produced a statistically significant increase in the induced response when compared with the concurrent negative control were provided;

d) no data demonstrating that the negative control showed a response within the historical control range of the laboratory were provided;

e) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures were not reported.

35 The information provided does not cover the specifications(s) required by the OECD TG 473.

4.2.2. The provided study (iv) does not correspond to the test required and is not supported by any valid adaptation

36 This information requirement must be fulfilled by an *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study, or by a valid adaptation according to Annex XI or column 2 of Annex VIII, Section 8.4.2.

37 However, study (ii) does not correspond to the studies required. In addition, you have not submitted any justification as to why study (ii) could be used in an adaptation and it is not possible for ECHA to identify any legal basis for a possible adaptation.

38 Therefore, the information requirement is not fulfilled.

4.3. Specification of the study design

39 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

4.3.1. Assessment of aneugenicity potential

40 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

41 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

4.4. Information regarding data sharing

42 Other registrants' registration for the Substance contains an adequate robust study summary for the study (i) you included in your registration dossier. In accordance with Title III of the REACH Regulation, you may request the information missing in your registration dossier from the other registrants and then make every effort to reach an agreement on the sharing of data and costs (Guidance on data-sharing).

5. *In vitro* gene mutation study in mammalian cells

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

5.1. Triggering of the information requirement

44 Your dossier contains data for an in vitro gene mutation study in bacteria, and data for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study.

45 The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells or in vitro micronucleus study provided in the dossier are rejected for the reasons provided in requests 2 and 4.

46 The result of the requests for an in vitro gene mutation study in bacteria and for an in vitro cytogenicity study in mammalian cells will determine whether the present requirement for an in vitro mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3. is triggered.

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

5.2. Information provided

48 You have not submitted any information for this requirement.

49 Therefore, the information requirement is not fulfilled.

5.3. Specification of the study design

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

5.4. Information regarding data sharing

51 Other registrants' registration for the Substance contains an in vitro gene mutation study in mammalian cells (2021) which is adequate for this information requirement. In accordance with Title III of the REACH Regulation, you may request it from the other registrants and then make every effort to reach an agreement on the sharing of data and costs (Guidance on data-sharing).

6. Long-term toxicity testing on fish

52 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

6.1. Triggering of the information requirement

53 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.

54 In the provided OECD TG 105 (1989), the saturation concentration of the Substance in water was determined to be below the limit of detection of the analytical method (*i.e.*, 10 µg/L).

55 Therefore, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

6.2. Information requirement not fulfilled

56 The information provided, its assessment and the specifications of the study design are addressed under request 9.

Reasons related to the information under Annex IX of REACH

7. Sub-chronic toxicity study (90 days)

57 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

7.1. Information provided

58 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) One-generation reproductive toxicity study (OECD TG 415) with the Substance;

(ii) 28-days repeated dose toxicity study (OECD TG 407) with the Substance.

7.2. Assessment of the information provided

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

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

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

7.2.1. Lack of documentation justifying the weight of evidence adaptation

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

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

64 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

65 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.6.2 includes similar information that is produced by the OECD TG 408 with a design as specified in this decision. OECD TG 408 requires the study to investigate the following key elements:

(1) In-life observations

(2) Blood chemistry

(3) Organ and tissue toxicity

7.2.2. Relevance of the provided information

In-life observations

66 In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

67 Both sources of information (i - ii) provide relevant information on survival, body weight development, clinical signs, food/water consumption. However, they do not inform on functional observations. Any other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, musculoskeletal, nervous, renal/urinary, and respiratory) was not reported. Therefore, these sources of information provides limited information on this key element.

Blood chemistry

68 Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary)

69 Study (i) does not include the performance of haematology and clinical biochemistry tests. Study (ii) provides relevant information on some haematological and clinical-chemistry parameters. However, the full list of heamatological and clinical chemistry investigations performed is missing. Therefore, these sources of information provides limited information on this key element.

Organ and tissue toxicity

70 Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

71 Study (i) investigates histopathology of reproductive organs and gross lesions, compared to complete histopathology in the sub-chronic study. Therefore, these sources of information provides limited information on this key element.

7.2.3. Reliability of the provided information

72 Additionally, the reliability of the sources of information (i) and (ii) for this endpoint are also affected by the following issue:

73 The conditions of OECD TG 408 include:

- At least 10 female and 10 male animals should be used at each dose level (including control group)
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study.

74 Study (ii) you have provided was conducted with less than 10 animals per sex per test dose group.

75 Studies (i) and (ii) you have provided do not have the required exposure duration of 90 days.

7.2.4. Conclusion on the weight of evidence adaptation

76 In summary, the sources of information (i) and (ii) provide limited relevant information on in-life observations, blood chemistry, and organ and tissue toxicity. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for sub-chronic toxicity.

77 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for sub-chronic toxicity.

78 Based on the above, your adaptation is rejected.

79 Therefore, the information requirement is not fulfilled.

7.3. Specification of the study design

80 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance.

81 According to the OECD TG 408, the rat is the preferred species.

82 Therefore, the study must be performed in rats according to the OECD TG 408 with oral administration of the Substance.

8. Pre-natal developmental toxicity study in one species

83 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

8.1. Information provided

84 You refer in your dossier to an adaptation according to Annex XI, Section 1.2. (weight of evidence). However, a weight of evidence adaptation requires several sources of information, we understand that you rather intend to adapt the information requirement based on the presence in your dossier of only one source of information which is the following:

(i) a one generation toxicity study (2010) with the Substance.

8.2. Assessment of the information provided

8.2.1. Your justification to omit the study has no legal basis

85 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex X, Section 8.7., Column 2.

86 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI or Annex X, Section 8.7, Column 2. You state that "*In the one-generation reproduction toxicity study, in utero death is investigated as a decrease in the number of pups per litter, growth retardation is investigated as a decrease in pup weight, and structural malformations are investigated through thorough examination of the pups. A reason to perform a prenatal developmental toxicity study is the potential confounding*

effect of maternal cannibalism. However, a decreased litter size indicates when severely malformed offspring are cannabilized. Therefore, the performance of pre-natal developmental toxicity study is not scientifically justified and will only result in the unnecessary use of animals."

87 ECHA understands you are claiming that when a one generation study is available, a PNDT study is not necessary. ECHA is unable to identify any legal basis that would support your intended adaptation.

88 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

8.3. Specification of the study design

89 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

90 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

91 Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

9. Long-term toxicity testing on fish

92 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

9.1. Information provided

93 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information: "*Adequate short-term (all trophic levels) and long-term aquatic toxicity data (daphnia and algae) are available and the corresponding assessment factors for derivation of PNECs (10 and 100 for freshwater and marine species, respectively) are considered to be sufficiently conservative to derive reliable PNECs for the aquatic compartments*".

9.2. Assessment of the information provided

9.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

94 Annex IX, Section 9.1., Column 2 is not basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6.

95 Your adaptation is therefore rejected.

96 Therefore, the information requirement is not fulfilled.

9.3. Study design and test specifications

97 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

98 OECD TG 210 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 3.

10. Long-term toxicity on terrestrial invertebrates

99 Short-term toxicity to invertebrates is an information requirement under Annex IX to REACH (Section 9.4.1). Long-term toxicity testing must be considered (Section 9.4., column 2) if the substance has a high potential to adsorb to soil or is very persistent.

10.1. Triggering of the information requirement

100 Under Annex IX, Section 9.4., column 2, for substances that have a high potential to adsorb to soil or that are very persistent, long-term toxicity testing must be considered instead of short-term. Guidance on IRs and CSA, Section R.7.11.5.3. clarifies that a substance is considered to be very persistent in soil if it has a half-life >180 days. In the absence of specific soil data, high persistence is assumed unless the substance is readily biodegradable.

101 Based on the information from your registration dossier:

- the Substance is considered to be highly adsorptive to soil as you report a log K_{oc} > 5.6 based on OECD TG 121;
- the Substance is considered to be potentially highly persistent in soil as it is not readily biodegradable (2% degradation after 28 days based on EU Method C.5).

102 Therefore, the Substance has a high potential to adsorb to soil and is potentially very persistent. On this basis information on long-term toxicity on terrestrial invertebrates must be provided.

10.2. Information provided

103 You have adapted this information requirement under Annex IX, Section 9.4, column 2. To support your adaptation, you provided the following justification:

- "*In the current chemical safety assessment, the PNEC for the soil compartment is derived from the available acute terrestrial toxicity data in earthworms and plants. This PNEC is however considered to be sufficiently conservative for chemical safety assessment*";
- "*although no L(E)C50 value could be determined from the available data (as no 50%-effect level was reached), still the standard assessment factor of 1000 (for short-term effects) was applied which may be considered as a worst case approach*";
- "*no risk for the soil compartment is identified (i.e. risk characterisation ratios for all uses are all well below 1) no further investigation on the effects of the substance on soil organisms is considered necessary*".

10.3. Assessment of the information provided

104 Under Annex IX, Section 9.4., column 2, in the absence of toxicity data to soil organisms, the equilibrium partitioning method (EPM) may be applied to assess the hazard to soil organisms. In this context, the Guidance on IRs and CSA, Section R.7.11.5.3. and R.7.11.6. describe an integrated testing strategy (ITS) to adapt the information requirements on

Effects on Terrestrial Organisms. The Guidance on IRs and CSA, Section R.7.11.5.3. states that "where the data available are sufficient to derive a PNEC for aquatic organisms, this PNEC can be used in a screening assessment for soil risks through the use of the EPM approach" while Table R.7.11-2 from Section R.7.11.6. describes the confirmatory test that must be conducted depending on the Hazard category assigned to the Substance and the outcome of the screening assessment. Therefore, as a precondition for using the equilibrium partitioning method (EPM) to adapt the information requirement on Effects on Terrestrial Organisms, adequate information on aquatic toxicity must be available.

105 For the reasons explained under Requests 3, the information requirement for Growth inhibition study on aquatic plants and Long-term toxicity on fish are not fulfilled. In addition, for the reasons explained under Request 9, the information requirement for long-term toxicity to plants is not fulfilled.

106 Therefore, your registration dossier currently does not include adequate information to derive a PNEC for aquatic organisms. Furthermore, the long-term toxicity test on plants currently in your dossier does not meet the information requirement and cannot therefore be used a confirmatory test in the context of the ITS. As a result, the conditions to use the EPM to adapt the information requirement on Effects on Terrestrial Organisms are not met and you adaptation is rejected and the information requirement is not fulfilled.

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

10.4. Study design and test specifications

108 ECHA Guidance on IRs and CSA, Section R.7.11.3.1. specifies that the earthworm reproduction test (OECD TG 222), the Enchytraeid reproduction test (OECD TG 220), and the Collembolan reproduction test (OECD TG 232) are appropriate to cover the information requirement for long-term toxicity testing on terrestrial invertebrates.

11. Effects on soil micro-organisms

Effects on soil microorganisms is an information requirement under Annex IX to REACH (Section 9.4.2).

11.1. Information provided

109 You have adapted this information requirement under Annex IX, Section 9.4, column 2. To support your adaptation, you provided the following justification:

(i) the same justification as already detailed under Request 10;

(ii) "a reliable study investigating the toxicity of the test substance to microorganisms (activated sludge respiration inhibition test). In this study, the test substance had no significant inhibitory effect (<15%) on the respiration rate of activated sludge after the incubation period of three hours at the limit test concentration of 1000 mg/L".

11.2. Assessment of the information provided

11.2.1. Your column2 adaptation is rejected

110 For the reasons already explained under Section 10.3., you adaptation under Annex IX, Section 9.4, column 2 is rejected.

11.2.2. Your justification to omit the study under point (ii) has no legal basis

111 A registrant may only adapt this information requirement based on the specific rules set out under Annex IX, Section 9.4, column 2 or the general rules set out in Annex XI.

112 Your justification that limited effects were observed in an activated sludge respiration inhibition test as a basis to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

113 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

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

11.3. Study design and test specifications

115 The Soil Microorganisms: Nitrogen Transformation Test (EU C.21/OECD TG 216) is appropriate to cover the information requirement on effects on soil microorganisms (Guidance on IRs and CSA, Section R.7.11.3.1.).

12. Long-term toxicity on terrestrial plants

116 Short-term toxicity to invertebrates is an information requirement under Annex IX to REACH (Section 9.4.1). Long-term toxicity testing must be considered (Section 9.4., column 2) if the substance has a high potential to adsorb to soil or is very persistent.

12.1. Triggering of the information requirement

117 For the reasons explained under Request 10.1., the Substance is potentially very persistent. On this basis information on long-term toxicity on terrestrial plants must be provided.

12.2. Information provided

118 You have provided:

(i) a toxicity study on plants according to OECD TG 208 with 6 species (two monocotyledonous species and four dicotyledonous species) with the Substance (2009)

119 You have also adapted this information requirement under Annex IX, Section 9.4, column 2. To support your adaptation, you provided the same justification as already detailed under Request 10.2.

12.3. Assessment of the information provided

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

120 To fulfil the information requirement, a study must comply with OECD TG 208 with 6 species (two monocotyledonous species and four dicotyledonous species) (Article 13(3) of REACH). Therefore, the following specifications must be met:

121 Reporting of the methodology and results

a) soil characteristics are reported (texture or type of soil: soil particle distribution and classification, physical and chemical properties including % organic matter, % organic carbon and pH)

b) table of all endpoints for each replicate, test concentration/rate and species are reported.

122 In the provided study:

123 Reporting of the methodology and results

a) You specified that the study was conducted with LUFA 2.3 (USDA: sandy loam). However, you did not specify any of the soil characteristics specified above.

b) You have provided a summary of the results obtained in the study but no detailed reporting of the results.

124 Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. On this basis, the specifications of OECD TG 208 are not met.

12.3.2. Your column2 adaptation is rejected

125 For the reasons already explained under Section 10.3., you adaptation is rejected and the information requirement is not fulfilled.

126 In your comments to the draft decision, you refer to an ongoing OECD TG 210 requested from another registrant of the Substance under testing proposal evaluation. You explain that once the results of this study becomes available, you intend to assess whether this information requirement may be adapted under Annex IX, Section 9.4., column 2. If you conclude this is not possible, you agree to conduct the requested study.

127 As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

12.4. Test selection and study specifications

128 The Terrestrial Plant Test (EU C.31./OECD TG 208, with at least six species) is appropriate to cover the information requirement for long-term toxicity on terrestrial plants.

129 The OECD TG 208 (EU C.31.) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. Testing must be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD TG 208.

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 14 June 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 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: 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

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

1.2. Test material

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

(1) Selection of the Test material(s)

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

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.

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

- 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 and whether it is suitable for use by all members of the joint submission.

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