~~Confidential~~

Helsinki, 16 November 2022

Addressees
Registrant(s) of JS_25322-68-3_[redacted] as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
05 December 2018

Registered substance subject to this decision ("the Substance")
Substance name: Poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxy- Ethane-1,2-diol, ethoxylated
EC number: 500-038-2

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 ***21 February 2025***.

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

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

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

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);

4. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4 C/D/E/F/OECD TG 301 B/C/D/F or EU C.29./OECD TG 310).

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

5. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487);

6. If negative results are obtained in test performed for the information requirement of Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490);

7. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below;

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

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

The reasons for the decision(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. Inadequate characterisation of the test material

1 You have provided for several information requirements the following studies claimed to be conducted on the Substance:

- A study on short-term toxicity on aquatic invertebrates (2018;)
- Under biodegradation in water:
  - An OECD 301 D study (Ready Biodegradability: Closed Bottle Test), 2018;
  - A non-guideline study on "Biodegradation of test chemical in water", authoritative database, 2018;
  - A non-guideline study on "Biodegradation of test chemical in water", according to Birch R.R et al., 1989;
- a short-term toxicity to fish study (2013);
- an *in vitro* gene mutation study in bacteria (1986).

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

3 To comply with the information requirements, the test material in a study must be representative for the Substance; Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1). The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents". Such information includes EC and/or CAS numbers and composition of the test material.

4 In Section 1.1 of your registration dossier you indicate that the Substance is a UVCB substance. In Section 1.2 you report that the Substance contains 6 constituents with molecular weights ranging from 44.0526 to 168.

5 You indicate that all the studies indicated above have been conducted with a test material with the same name as the UVCB Substance "*Poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxy-Ethane-1,2-diol,ethoxylated*", however you do not provide information on the composition of the test material, i.e. identity and quantitative occurrence of the consitutents. In addition, you claim that the molecular weight of the test material is 44.0526 or >200 <5000.

6 In the absence of detailed information on the composition of the test material, you have not demonstrated that the test material is representative for the UVCB Substance that you registered.

7 Additionally, the provided information on the molecular weight of the test material is not consistent with the information provided in IUCLID section 1.2 since the Substance contains also constituents with molecular weight higher than 44.0526 or lower than 200. Thus, information on the molecular weight suggests that the test material is not representative for the Substance.

8 Consequently, as it is not demonstrated that the test material is representative for the registered Substance, it cannot be determined whether and how the information from these studies can reliably be used to fulfil the information requirements under consideration.

0.2. Assessment of the read-across approach

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

10 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 appendices.

11 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.

12 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).

0.2.1. *Predictions for (eco)toxicological properties*

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

- Poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxy- Ethane-1,2-diol, ethoxylated 200 (PEG 200), EC No. 500-038-2; CAS No. 25322-68-3 to predict *in vitro* cytogenicity and gene mutation properties of the Substance in mammalian cells;
- Poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxy- Ethane-1,2-diol, ethoxylated 1000 (PEG 1000), EC No. 500-038-2; CAS No. 25322-68-3 to predict ready biodegradability properties of the Substance.

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

0.2.1.1. Absence of read-across documentation

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 must include an explanation why the properties of the Substance may be predicted from information on the source substance(s).

16 You have provided robust study summary for studies conducted with other substances than the Substance in order to comply with the REACH information requirements listed above. However, you have not provided documentation as to why this information is relevant for the Substance and thus why the properties of the Substance may be predicted from information on the source substance(s).

17 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance(s).

0.2.1.2. Adequacy and reliability of source studies

18 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement.

19 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections 4, 5, 6. Therefore, no reliable predictions can be made for these information requirements.

0.2.2. *Conclusions on the read-across approach*

20 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

0.3. Assessment of weight of evidence adaptations

21 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation(s) under Annex XI, section 1.2:

- Short-term repeated dose toxicity study (28 day), oral route (Annex VIII, Section 8.6.1);
- Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.).

22 Your weight of evidence adaptations are based on information obtained from analogue substances structurally similar to the Substance.

23 Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

24 According to Guidance on IRs and CSA Chapter 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 that the Substance has or has not the (dangerous) property investigated by the required study.

25 Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

26 However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

27 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation. Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here,

while the specific ones are set out under the information requirement concerned in the Appendices below.

28 These issues identified below are essential for all the information requirements in which you invoked a weight of evidence.

0.3.1. *Reliability of the contribution of the information on analogue substances to the weight of evidence adaptations*

29 ECHA understands that you use data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to reliably contribute to the weight of evidence approaches, it would have to meet the requirements for Grouping of substances and read-across approaches.

30 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).

31 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA [2] and related documents[3, 4].

32 You provide information from some analogue substances that you include in your weight of evidence approaches. The details of the identity of the analogue substances provided for each of the information requirements listed above are provided in the endpoint-specific sections of this document.

33 Section 0.2.1.1 of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

0.3.2. *Reliability of the contribution to the weight of evidence adaptations of the information from studies with inadequate characterisation/identification of the test material*

34 Section 0.1 of the present Appendix identifies deficiencies of the characterisation of the test material used to generate some of the information included in your dossier. These findings apply equally to some of sources of information submitted as part of your weight of evidence adaptations.The details of the studies affected by this deficiency are provided in the appropriate endpoint-specific sections of this document.

35 Additional issues related to weight of evidence are addressed under the corresponding endpoints.

[2] Guidance on IRs and CSA, Chapter R.6
[3] Read-Across Assessment Framework (RAAF)
[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

36 An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

1.1. Information provided

37 You have provided an *in vitro* gene mutation study in bacteria conducted with the Substance (1986).

1.2. Assessment of the information provided

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

1.2.1. *Inadequate characterisation of the test material*

39 As explained in Section 0.1., you have not demonstrated that the test material is representative for the registered Substance. Therefore, it cannot be determined whether and how the information from this study can reliably be used to fulfil the current information requirement.

1.2.2. *Study not adequate for the information requirement*

40 To fulfil the information requirement, the study must meet the requirements of OECD TG 471 (2020). Therefore, the following specifications must be:

a) The test must be 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)

41 The study (i.) is described as in vitro gene mutation study in bacteria. However, the following specifications are not according to the requirements of OECD TG 471 (2020):

a) results for the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) are missing.

42 The information provided does not cover one of the key parameters required by OECD TG 471.

1.2.3. *Conclusion*

43 For all the reasons presented above, the information requirement is not fulfilled.

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

1.2.4. *Specification of the study design*

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

2. Short-term toxicity testing on aquatic invertebrates

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

2.1. Information provided

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

2.2. Assessment of the information provided

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

2.2.1. *Inadequate characterisation of the test material*

49 As explained in Section 0.1., you have not demonstrated that the test material is representative for the registered Substance. Therefore, it cannot be determined whether and how the information from this study can reliably be used to fulfil the current information requirement.

2.2.2. *Study not conducted according to GLP*

50 (Eco)toxicological studies must comply with GLP or another recognised international standard; Art. 13(4) of REACH.

51 You have indicated that study (i) is "not GLP-compliant", without further explanation.

52 The test does not comply with GLP or another recognised international standard and is therefore rejected.

2.2.3. *The provided study does not meet the information requirement*

53 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:

54 Technical specifications impacting the sensitivity/reliability of the test

a) at least 20 animals are used at each test concentration and for the controls;

55 Additional requirements applicable to difficult to test substances:

b) if the test material is forming dispersion or emulsions (*e.g.* certain surfactants, aliphatic amines), the dispersibility limit or the critical micelle concentration of the test material in the specific test solution under the test conditions is determined.
c) surface-active test chemicals are tested at concentrations below their critical micelle concentration (CMC) in the test medium.

56 Characterisation of exposure

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

57 Reporting of the methodology and results

f) the age of daphnids is reported.

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

59 Technical specifications impacting the sensitivity/reliability of the test

a) 10 animals were used at each test concentration and for the controls;

60 Additional requirements applicable to difficult to test substances:

b) the test material is a surfactant (surface tension 44.5 mN/m) and you do not report the critical micelle concentration;

c) the test is performed at a nominal concentration of 100 mg/L;

61 Characterisation of exposure

d) no analytical monitoring of exposure was conducted
e) the reported effect values are based on nominal concentrations;

62 Reporting of the methodology and results

f) the age of the daphnids was not specified.

63 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically the number of daphnids is lower than required by OECD TG 201 (10 instead of 20 daphnids). Therefore, the statistical power of study (i) is decreased and cannot be considered to have equivalent reliability to OECD TG 201. Furthermore, the Substance is difficult to test since it is a surfactant and you have not determined the critical micelle concentration (CMC) of the Substance in test solution. Therefore, you have not demonstrated that the exposure concentration of 100 mg/L was below the CMC and that the test organisms were exposed to the freely dissolved chemical species and not the micelle form, which is considered to be biologically unavailable. Finally, no analytical monitoring was conducted. Since the substance is difficult to test difficulties in achieving and maintaining stable test concentrations can be expected. You have based effect levels on nominal values but in the absence of analytical monitoring you have not provided confirmation that exposures were within ± 20 % of the nominal concentration. The results based on nominal values are therefore considered unreliable.

64 Furthermore the reporting of the study (i) is not sufficient to conduct an independent assessment of its reliability. In the absence of information on the age of the daphnids, it is not possible to verify if they were aged less than 24h at the test start as required by OECD TG 201.

65 Therefore, the requirements of OECD TG 202 are not met.

2.2.4. *Conclusion*

66 For all the reasons above, the information requirement is not fulfilled.

2.3. Study design and test specifications

67 The Substance is difficult to test due to the due to being a surfactant (surface tension 44.5 mN/m). 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.

68 In the comments to the draft decision, you agree that the study provided does not meet the current standards of an OECD TG 202 study. In your comments you indicate your intention - instead of performing a new OECD TG 202 study - to fulfil the information requirement with a long-term toxicity to aquatic invertebrates study (OECD TG 211) for which you provided a certain information in a target study report as an attachement to your comments to the draft decision. In addition, you indicated your intention to update your dossier with the respective information.

69 Annex VII, section 9.1.1, column 2 of the REACH Regulation specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on invertebrates is available.

70 However, Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries (RSS) are "required of all key data used in the hazard assessment". You have not provided with your comments any RSS.

71 Furthermore, you have not demonstrated that the study referred to in your comments is compliant with OECD TG 211 and OECD GD 23 (as the Substance is difficult to test), and that the study was conducted according to GLP.

72 Moreover, the Substance is a UVCB and you did not provide the required details on the test material applied in the OECD TG 211.

73 In the absence of this information, we cannot assess relevance and reliability of the study.

74 You remain responsible for complying with this decision by the set deadline.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

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

77 In support of your adaptation, you have provided the following study records with the analogue substance (EC No. 500-038-2):

(i) Toxicity to aquatic algae and cyanobacteria, 96-hour study (according to OECD 201, Chemosphere, Vol. 36, No. 7, pp. 1585-1613, 1998)

(ii) Toxicity to aquatic algae and cyanobacteria, 8-day study (according to OECD 201, Chemosphere, Vol. 36, No. 7, pp. 1585-1613, 1998)

3.2. Assessment of the information provided

78 We have assessed this information and identified the following issues.

79 As explained under Section 0.3 the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

80 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VII, Section 9.1.2. includes similar information that is produced by the OECD TG 201. OECD TG 201 requires the study to investigate the following key element:

1. the concentrations of the test material leading to a [redacted] % and [redacted]% (or [redacted]%) inhibition of growth at the end of the test are estimated.

81 The sources of information (i) and (ii) provide relevant information on this key investigation (1).

82 However, the reliability of these sources of information is significantly affected by the following deficiencies:

3.2.1. *Reliability of the contribution of the information on the analogue substance (studies (i) and (ii))*

83 For the reasons explained in the section 0.3, you have not established that the information on the analogue substance used in the studies (i and ii) can reliably contribute to your weight of evidence adaptation.

3.2.2. *Methodological deficiencies of experimental studies*

84 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed. The sources of information (i), and (ii) were conducted following the OECD TG 201. This test guideline requires that:

85 Technical specifications impacting the sensitivity/reliability of the test

a) the test duration is 72 hours; if exposure is longer than 96h, data on biomass must be provided to demonstrate monotone exponential growth of the controls during the whole exposure period (Guidance on IRs and CSA, Section R.7.8.4.1).

86 Characterisation of exposure

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

87 Reporting of the methodology and results

d) the test design is reported (*e.g.*, number of replicates, controls applied, number of test concentrations and geometric progression used);
e) the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);

88 Your registration dossier provides two OECD TG 201 studies (i and ii) with an analogue substance showing the following:

89 Technical specifications impacting the sensitivity/reliability of the test

a) the test duration was 8 d for source study (ii) and you have not reported the data on biomass;

90 Characterisation of exposure for studies (i) and (ii)

b) no analytical monitoring of exposure was conducted;

c) you have expressed the effect values based on nominal concentrations;

91 Reporting of the methodology and results for studies (i) and (ii)

d) on the test design, you have not specified number of replicates, the applied controls, number of test concentrations;
e) on the test conditions, you have not specified composition of the test medium, test temperature, pH, dissolved oxygen, biomass density at the beginning of the test.

92 Based on the above, there are critical methodological deficiencies affecting the reliability of studies (i) and (ii). More specifically, for studies (i) and (ii) you have based effect levels on nominal values but in the absence of analytical monitoring you have not provided confirmation that exposures were within ± 20 % of the nominal concentration. The results of studies (i) and (ii) based on nominal values are therefore considered unreliable. In addition, for study (ii) the 8 d exposure is longer than recommended by OECD TG 201 and you have not provided data on biomass to demonstrate monotone exponential growth of the controls during the whole exposure period. Thus, the results of study (ii) are not considered reliable.

93 Therefore, the reliability of the contribution of the results obtained from the studies (i) and (ii) to the weight of evidence is limited.

3.2.3. *Conclusion*

94 Taken together, the sources of information as indicated above, provide relevant information on the toxicity to algae.

95 However, the reliability of the contribution of the information is impacted by the use of information on analogue substance and by methodological deficiencies in the study design and/or in reporting listed above.

96 It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in a study conducted according to the OECD TG 201. Therefore, your adaptation is rejected.

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

3.3. Study design and test specifications

98 The OECD TG 201 specifies that, for difficult to test substances, the 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 2.

99 In the comments to the draft decision, you agree that the study provided does not meet the current standards of an OECD TG 201 study. In your comments you indicate your intention to fulfil the information requirement with a new OECD TG 201 study, for which you provided certain information in a target study report as an attachement to your comments to the draft decision. In addition, you indicated your intention to update your dossier with the respective information.

100 However, Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries (RSS) are "required of all key data used in the hazard assessment". You have not provided with your comments any RSS.

101 Furthermore, you have not demonstrated that the study referred to in your comments is compliant with OECD TG 201 and OECD GD 23 (as the Substance is difficult to test), and that the study is conducted according to GLP.

102 Moreover, the Substance is a UVCB and you did not provide the required details on the test material applied in the OECD TG 201.

103 In the absence of this information, we cannot assess relevance and reliability of the study.

You remain responsible for complying with this decision by the set deadline.

4. Ready biodegradability

104 Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

4.1. Information provided

105 You have provided the following information with the Substance:

i. An OECD 301 D study (Ready Biodegradability: Closed Bottle Test), 2018

ii. A non-guideline study on "Biodegradation of test chemical in water", authoritative database, 2018

iii. A non-guideline study on "Biodegradation of test chemical in water", according to Birch R.R et al., 1989

106 In addition, you have provided the following experimental data on another substance. While you have not claimed that this information is obtained from another substance than the Substance, the information on the test material identity provided in your dossier indicates that the test material used is different than the Substance. Therefore, the study conducted with this substance is evaluated as a read-across adaptation under Annex XI, Section 1.5 of REACH:

(iv) A non-guideline study on "Biodegradation of test chemical in water", according to Larson et al., 1996, conducted on PEG 1000, EC No. 500-038-2.

4.2. Assessment of information provided

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

4.2.1. *Inadequate characterisation of the test material (studies (i), (ii) and (iii))*

108 As explained in Section 0.1., you have not demonstrated that the test material is representative for the registered Substance. Therefore, it cannot be determined whether and how the information from this study can reliably be used to fulfil the current information requirement.

4.2.2. *Study not conducted according to GLP (study (i))*

109 (Eco)toxicological studies must comply with GLP or another recognised international standard; Art. 13(4) of REACH.

110 You have indicated that study (i) is "not GLP-compliant", without further explanation.

111 The test does not comply with GLP or another recognised international standard and is therefore rejected.

4.2.3. *Read-across adaptation rejected (study (iv))*

112 For study (iv), the study is conducted with PEG 1000. As explained in Section 0.2, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

113 Furthermore, as indicated in Section 0.2, if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

114 For the reasons explained under section 4.2.4. below, for study (iv) the reporting is not sufficient to conduct an independent assessment of its reliability. Therefore, the provided study is not adequate for classification and labelling and/or risk assessment purposes.

4.2.4. *The provided studies (i)-(iv) do not meet the information requirement*

115 To fulfil the information requirement, a study must comply with the OECD TG 301 or 310 (Article 13(3) of REACH). Therefore, for a study according to OECD TG 301, the following requirements must be met:

116 Key parameter to be measured

a) the ultimate aerobic biodegradation (as measured by parameters such as DOC removal, CO2 production and oxygen uptake) of the test material under low inoculum concentration is measured at sufficiently frequent intervals to allow the identification of the beginning and end of biodegradation;

117 Reporting of the methodology and results

b) the source of the inoculum and any pre-conditioning treatment are reported;
c) the number of replicates is reported;
d) the results of measurements at each sampling point in each replicate is reported in a tabular form.

118 Your registration dossier provides one OECD TG 301 D study (i) and three non-guideline studies (ii, iii, iv) showing the following:

119 Key parameter to be measured for study (iii)

a) the ultimate aerobic biodegradation of the test material was not measured in study (iii) as the provided study is an anaerobic test;

120 Reporting of the methodology and results for studies (i), (ii) and (iv)

b) the source of the inoculum, any pre-conditioning treatment are not reported;
c) the number of replicates is not reported;
d) the results of measurements at each sampling point in each replicate is not reported in a tabular form.

121 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study (iii) results. More specifically, for study (iii) the information provided does not cover the key parameter required by the OECD TG 301.
- the reporting of the studies (i), (ii) and (iv) are not sufficient to conduct an independent assessment of their reliability.

122 Therefore, the requirements of OECD 301 are not met.

4.2.5. *Conclusion*

123 For all the reasons above, the information requirement is not fulfilled.

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

Reasons related to the information under Annex VIII of REACH

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

125 An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micro-nucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

5.1. Information provided

126 While you have not identified this information as a read-across approach, the test material used is different than the Substance. Therefore, the study conducted with this substance is evaluated as a read-across adaptation under Annex XI, Section 1.5 of REACH: *in vitro* cytogenicity / chromosome aberration study in mammalian cells (2002) conducted with PEG 200 (study (i)).

5.2. Assessment of the information provided

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

5.2.1. *Read-across adaptation rejected*

128 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

5.2.2. *Adequacy and reliability of study on the source substance*

129 As explained in the Appendix on Reasons common to several requests (Section 0.2.1.2), the results to be read across must have an adequate and reliable coverage of the key parameters addressed for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 473 or OECD TG 487. Therefore, the following specifications must be met:

a) The maximum concentration tested must induce 55±5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 300 well-spread metaphases must be scored per concentration.

130 The study (i.) is described as an in vitro cytogenicity / chromosome aberration study in mammalian cells. However, the following specifications are not according to the requirements of OECD TG 473:

a) The maximum tested concentration used in the study induced 13.3% cytotoxicity and therefore it failed to induce 55±5% of cytotoxicity compared to the negative control. The maximum tested concentration was set to 8 mM, which is also lower than the default maximum concentration of 10 mM.
b) Only 100-200 metaphases were scored instead of 300.

131 Therefore, the study submitted in your adaptation, does not provide an adequate and reliable coverage of the key parameter(s) specified in the corresponding OECD TG.

5.2.3. *Conclusion*

132 For all the reasons presented above your adaptation is rejected and the information requirement is not fulfilled.

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

5.3. Specification of the study design

134 To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

6. In vitro gene mutation study in mammalian cells

135 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (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.

136 Your dossier contains an adaptation for an *in vitro* gene mutation study in bacteria, and an adaptation for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

137 The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in sections 1 and 5.

138 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.

~~139~~ Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria / the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

6.1. Information provided

140 While you have not identified this information as a read-across approach, the test material used is different than the Substance. Therefore, the study conducted with this substance is evaluated as a read-across adaptation under Annex XI, Section 1.5 of REACH: in vitro gene mutation study in mammalian cells (2015) conducted with PEG 200 (study (i)).

6.2. Assessment of the information provided

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

6.2.1. *Read-across adaptation rejected*

142 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

6.2.1. *Source study and reliability of study on the source substance(s)*

143 As explained in the Appendix on Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 476 or OECD TG 490. Therefore, the following specifications must be met:

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.

144 The study (i.) is described as in vitro gene mutation study in mammalian cells. However, the following specifications are not according to the requirements of OECD TG 476:

a) In the dossier you provide information that no cytotoxicity nor precipitation was observed. The maximum tested concentration was set to 5 mM, which is also lower than the default maximum concentration of 10 mM.
b) The positive control dimethylbenz(a) anthracene in experiments with metabolic activation did not produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control. Therefore the experimental setup and ability of the testing laboratory to detect an effect is not demonstrated.

145 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) specified in the corresponding OECD TG.

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

147 In the comments to the draft decision, you agree to perform the requested study, if the *in vitro* gene mutation study in bacteria / the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

6.3. Specification of the study design

148 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.

7. Short-term repeated dose toxicity (28 days)

149 A Short-term repeated dose toxicity study (28 day) is an information requirement under Annex VIII to REACH (Section 8.7.1.).

7.1. Information provided

150 While you have not provided a specific legal reference for your adaptation of this information requirement, ECHA understands that you have adapted this information requirement by using weight of evidence based on the following experimental data:

151 Oral exposure:

i. a sub-chronic toxicity test in rats (1955), a non-guideline study with Poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxy- Ethane-1,2-diol, ethoxylated 400 (PEG 400; EC No. 500-038-2; CAS No. 25322-68-3) PEG 400 g/mol.

ii. a chronic toxicity test in rats (1995), a non-guideline study with PEG 400 g/mol.

iii. a chronic toxicity test in dogs (1955), a non-guideline study with PEG 400 g/mol.

iv. a chronic toxicity test in rats (1955) a non-guideline study claimed to be conducted with the Substance.

152 Inhalation exposure:

v. a sub-chronic toxicity test in rats (1980), a non-guideline study with PEG 200 g/mol.

vi. a sub-chronic toxicity test in mice (1980), a non-guideline study with PEG 200 g/mol.

7.2. Assessment of the information provided

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

154 As explained under section 0.3, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

155 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.1 at Annex VIII includes similar information that is produced by the OECD TG 407. The following aspects are covered: 1) in-life observations, 2) blood chemistry, and 3) organ and tissue toxicity.

156 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issue(s):

7.2.1. *Aspect 1)In-life observations*

157 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).

158 Sources (i., iii.-vi.) provide relevant information on survival, sources (i.-iii., v., vi) provide relevant information on body weight, sources (i.-iii.) provide relevant information on food and/or water consumption and source (v.) provides relevant information on circulatory system.

159 The sources do not provide information on clinical signs, functional observations and other potential aspects of in life observations on the relevant physiological systems (digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory). Therefore, these sources of information provide limited information on this key element.

160 While some relevant information is provided by the sources (i., iii., v., vi), they are further affected by reliability issues.

7.2.1.1. Reliability of the information on analogue substances (studies i., ii., iii., v., vi.)

For the reasons explained in the section 0.3, you have not established that the information on analogue substances from the studies (i., ii., iii., v., vi.) can reliably contribute to your weight of evidence adaptation.

7.2.1.2. Reliability of the contribution of the information from studies with inadequate characterisation/identification of the test material (study iv.)

You have provided inadequate characterisation/identification of the test material for study iv., in the same way as already described in section 0.1. This deficiency, for the reasons explained in the section 0.1, equally affects the reliability of the contribution of study iv to the weight of evidence adaptation. Consequently, it cannot be determined whether and how the information from this study can reliably be used to fulfil the current information requirement.

7.2.1.3. Methodological deficiencies of experimental studies

161 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed. All sources of information were assessed according to the OECD TG 407. This test guideline requires:

a. testing of at least three dose levels (unless conducted at the limit dose) with concurrent controls;
b. highest dose level should aim to induce toxicity or reach the limit dose.

162 The following specifications are not according to the requirements of OECD TG 407:

a. only one dose level used (source iii.);
b. no justification for the dose setting while the highest dose levels tested was 500 mg/kg/day, which is below the limit dose of the test guideline, and no adverse effect were observed (source iii.).

163 The consequences of these deficiencies are insufficient statistical power and inability to observe sufficient toxicity for hazard assessment.

7.2.1.4. Reliability of the contribution of the information generated after exposure via the inhalation route

164 According to the ECHA Guidance[5], the oral route is the default route of administration for repeated-dose toxicity because it is assumed to maximise systemic availability of most substances. However, on a case-by-case basis, the appropriateness of other routes of administration should also be assessed. Testing by the inhalation route is the default route for gases and the preferred route for liquids of high to very high vapour pressure at ambient temperature (>25 kPa or boiling point below 50°C) for which inhalation is usually the predominant route of human exposure. For liquids of lower vapour pressure and for dusts (including nanomaterials), testing by the inhalation route is appropriate if human inhalation exposure is likely taking into account the possibility of exposure to aerosols, particles or droplets of an inhalable size (aerodynamic diameter below 100 µm).

[5] Guidance on IRs & CSA Chapter R.7.5.6.3.4

165 Furthermore, characterisation of the relative bioavailability of a substance after exposure via the inhalation route compared to the default oral route is essential in order to determine the extent of the systemic exposure to the test item after inhalation exposure and to assess the adequacy of the information generated for the purpose of hazard identification.

166 In your technical dossier, you have provided 2 studies conducted with the analogue substance PEG 200 via the inhalation route (studies v. and vi.). For both studies you indicate that PEG 200 is a liquid. No information is provided on the vapour pressure of PEG 200. No details on the methods used to generate the atmosphere used in these whole body exposure studies are included in the robust study summaries provided for these studies. No information on the analytical verification of the doses or concentrations of the test item is provided.

167 In the absence of information on the physico-chemical properties of the test item, on the test conditions ensuring exposure to inhalable forms of the test item and on the relative bioavailability of a substance after exposure via the inhalation route, the suitability of the data obtained after exposure via the inhalation route for the determination of the hazard cannot be confirmed and the contribution of the information obtained from studies (v.) and (vi.) to the weight of evidence is limited.

7.2.2. *Aspect 2) Blood chemistry*

168 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)

169 Sources (ii., iii., v. and vi.) provide relevant information on some haematological and clinical-chemistry parameters, although no information is provided on total cholesterol and bile acids. Sources (i. and iv.) do not provide any information on blood parameters. None of the sources provide information on other potential aspects related to blood chemistry to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary). Therefore, these sources of information provide limited information on this key element.

170 While some relevant information is provided by the sources (ii., iii., v., vi), they are further affected by reliability issues.

171 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed. All sources of information were assessed according to the OECD TG 407. This test guideline requires:

a. haematological and clinical biochemistry tests as specified in paragraphs 32-39 of the test guideline.

172 The following specifications are not according to the requirements of OECD TG 407:

a. data on haematology and clinical biochemistry findings: incidence and severity with relevant base-line values. For the results section of haematology and clinical biochemistry findings sources (ii., iii., v. and vi.) only provide single sentences claiming no effects. The lack of numerical data precludes an independent assessment of this claim.

173 The methodological issues of source (iii.), described in section 7.1.1.3. (a) and (b), and the route of administration of sources (v. and vi.), described in section 7.1.1.4 above, apply equally to aspect 2.

7.2.3. *Aspect 3) Organ and tissue toxicity*

174 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).

175 Sources (v. and vi.) provide relevant information on organ weights, gross pathology and histopathology. Source (i.) provides organ weights, gross pathology and histopathology information only on kidneys and liver. Source (ii.) provides relevant information on organ weights but gross pathology and histopathology information is provided only on the bladder and kidneys. Source (iii.) provides relevant information on histopathology but organ weights information is provided only on urinary and gall bladder concretions, liver and kidney and gross pathology information is not provided. Source (iv.) provides organ weights information only on liver and kidney.

176 While some relevant information is provided by the sources (i., iii., v., vi), they are further affected by reliability issues.

177 The methodological issues of source (iii.), described in section 7.1.1.3. (a) and (b), and the route of administration of sources (v. and vi.), described in section 7.1.1.4 above, apply equally to aspect 3.

7.2.4. *Conclusion on the WoE adaptation*

178 Taken together, the sources of information provide relevant information only on some elements of the aspects, such as some in-life observations (survival, body weight, on food and/or water consumption, circulatory system), some haematological and clinical-chemistry parameters, although no information is provided on total cholesterol, and bile acids, and some organ and tissue toxicity. They do not cover the entire set of elements on clinical signs, functional observations and other potential aspects of in life observations on the relevant physiological systems (digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory) nor aspects related to blood chemistry to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary) expected to be obtained from the OECD TG 407.

179 Moreover, even the elements that provide some relevant information cannot be considered reliable as discussed under each aspect, due to issues of limited statistical power, insufficient level of toxicity, the route of administration, and methodological deficiencies.

180 Therefore, it is not possible to conclude, based on any of the new sources of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 407.

181 Based on the above, the adaptation is rejected and the information requirement is not fulfilled.

7.3. Specification of the study design

182 When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of

REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

183 For information on the study design see request for OECD TG 422 below.

184 In the comments to the draft decision you agree with the request.

8. Screening for reproductive/developmental toxicity

185 A Screening study (OECD TG 421/422) in one species is an information requirement under Annex VIII to REACH (Section 8.7.1.).

8.1. Information provided

186 While you have not provided a specific legal reference for your adaptation of this information requirement, ECHA understands that you have adapted this information requirement by using weight of evidence based on the following experimental data:

i. a reproduction/developmental toxicity screening test (2006) according to the OECD TG 421 with the consitutent of the substance PEG-4.

ii. three-generation reproductive toxicity in rats (1947), a non-guideline study with the analogue substance PEG 1500 and 4000.

iii. toxicity to reproduction, other: Multigeneration Reproductive Toxicity Study (1997), a non-guideline study with the analogue substance PEG 300 and 400.

187 This adaptation is addressed in subsection 8.2.1. below.

188 In addition, you have provided the following experimental data under the PNDT endpoint as a weight of evidence approach:

iv. developmental toxicity in rats test (1989) equivalent or similar to guideline OECD Guideline 414 with PEG 200.

v. developmental toxicity in mice test (1989) equivalent or similar to guideline OECD Guideline 414 with PEG 200.

vi. developmental toxicity test in rat embryos, in vitro culture (1992), a non-guideline study with PEG 200.

189 While you have not provided a specific legal reference for your adaptation of this information requirement with the use of the PNDT studies, ECHA understands that you have used this information as an Annex VIII (8.7.1.) column 2 adaptation for the information requirement for a screening study. This adaptation is addressed in subsection 8.2.2. below.

8.2. Assessment of the information provided

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

191 As explained under section 0.3, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

192 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.1 at Annex VIII includes similar information that is produced by the OECD TG 421. The following aspects are covered: 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity, and 4) specific investigations for hormonal activity.

193 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issue(s):

8.2.1. *Aspect 1) Sexual function and fertility*

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

195 Source (i.) provides relevant information on fertility and maintenance of pregnancy (resorptions and live embryos), source (ii.) provides relevant information on histopathology of reproductive organs and tissues, source (iii.) provides relevant information on mating.

196 According to the information provided in the dossier, the sources do not provide information on gestation (length), maintenance of pregnancy (abortions), parturition, lactation, organ weights of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility. Therefore, these sources of information provide limited information on this key element.

197 While some relevant information is provided by the sources (i. – iii.), they are further affected by reliability issues.

8.2.1.1. Reliability of the information on analogue substances (studies i. - vi.)

For the reasons explained in the section 0.3, you have not established that the information on analogue substances from the studies (i. - vi.) can reliably contribute to your weight of evidence adaptation.

8.2.1.2. Methodological deficiencies of experimental studies

198 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed. All sources of information were assessed according to the EU B.63/OECD TG 421. This test guideline requires:

a. at least 10 male and 12-13 female animals for each dose and control group;
b. an exposure duration of at least four weeks for males, including a minimum of two weeks prior to mating, and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation.

199 The following specifications are not according to the requirements of EU B.63/OECD TG 421:

a. only 3 males and 3 females in each dose and control group used (source ii.);
b. for source (i.) the following information is provided in the dossier: "*beginning 24 h after the last PEG-4 exposure, the males were mated with two naive (nontreated) virgin females. When those females showed evidence of copulation, they were replaced with two more females, until each male had mated with 10 females*". A further passage says: *"Males were dosed with the test chemical for 5 consecutive days. Female rats were exposed for 10 weeks."* It is therefore conflicting information over whether the female animals received the test

substance and the male animals received the test substance for an insufficient exposure period.

The consequences of these deficiencies are insufficient statistical power (study ii) and inadequate design of the experimental phase with regard to exposure period affecting the conclusions which can be derived from study i.

8.2.2. *Aspect 2) Toxicity to offspring*

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

201 Source (ii.) provides relevant information on postimplantation loss (resorptions and dead foetuses), source (iii.) provides relevant information on litter size, external malformations, survival and postnatal body weights of the pups. Source (i.) does not provide any relevant information on toxicity to offspring parameters. Any other potential aspects related to stillborns, postnatal developmental toxicity reflected by clinical signs of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13 were not reported. Therefore, these sources of information provide limited information on this key element.

202 While some relevant information is provided by the sources (ii. and iii.), they are further affected by reliability issues. The issues of limited statistical power and inadequate design of the experimental phase with regard to exposure period of source (ii.) identified in section 8.2.1.2. (a) above apply equally to aspect 2.

8.2.3. *Aspect 3) Systemic toxicity*

203 Information on systemic toxicity include clinical signs, survival, body weights, food consumption, clinical biochemistry, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

204 Source (ii.) provides relevant information on survival, body weights, food consumption, clinical biochemistry, source (iii.) provides relevant information on body weights and food consumption. Source (i.) does not provide any information on systemic toxicity parameters. Any other potential aspects related to clinical signs, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13 were not reported. Therefore, these sources of information provide limited information on this key element.

205 While some relevant information is provided by the sources (ii. and iii.), they are further affected by reliability issues.

206 The issues of limited statistical power and inadequate design of the experimental phase with regard to exposure period of source (ii.) identified in section 8.2.1.2. (a) above apply equally to aspect 3.

8.2.3.1. Conclusion on the Screening Study WoE adaptation

207 Taken together, the sources of information provide relevant information on some elements of the aspects, such as some sexual function and fertility observations (fertility and maintenance of pregnancy (resorptions and live embryos)), histopathology of reproductive organs and tissues, and mating), some information about the toxicity to offspring (postimplantation loss (resorptions and dead foetuses), litter size, external malformations, survival and postnatal body weights of the pups), and some systemic toxicity observations (survival, body weights, food consumption, clinical biochemistry). According to the

information provided, they do not cover the entire set of elements on gestation (length), maintenance of pregnancy (abortions), parturition, lactation, organ weights of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility, nor aspects related to stillborns, postnatal developmental toxicity reflected by clinical signs of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13, nor other potential aspects related to clinical signs, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13 expected to be obtained from the OECD TG 421.

208 Moreover, even the elements that provide some relevant information cannot be considered reliable as discussed under each aspect, due to limited limited statistical power, inadequate design of the experimental phase with regard to exposure period.

209 Therefore, it is not possible to conclude, based on any of the new sources of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 421.

8.2.4. Adaptation under Annex VIII, Section 8.6.1. Column 2 in conjunction *with Annex XI, section 1.2.*

210 Under Annex VIII, Section 8.6.1. Column 2 the study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) or an extended one-generation reproductive toxicity study (OECD TG 443) or a two-generation study (OECD TG 416) is already available.

8.3. Information provided

211 While you have not provided a specific legal reference for your adaptation of this information requirement, ECHA understands that you have adapted this information requirement by using weight of evidence based on the studies (iv.-vi.) listed in section 8.1.

212 As explained under section 0.3, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

213 Relevant information that can be used in a weight of evidence approach to support an adaptation under Annex VIII, Section 8.6.1. Column 2 includes similar information that is produced by the prenatal developmental toxicity study, conducted in accordance with OECD TG 414. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, 3) maintenance of pregnancy.

214 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issue(s):

215 Aspect 1) Prenatal developmental toxicity

216 Prenatal developmental toxicity includes information after prenatal exposure on embryonic/foetal survival (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

217 Source (iv.) provides relevant information on foetal loss and growth (body weights), source (v.) provides relevant information on foetal loss, growth (body weights) and structural malformations and variations (external, visceral and skeletal). Source (vi.) does not provide any relevant information on prenatal developmental toxicity parameters.

218 The sources do not provide information after prenatal exposure on embryonic/foetal survival (number of live foetuses; number of resorptions and dead foetuses), growth (size) and structural malformations and variations (external and visceral). Therefore, these sources of information provide limited information on this key element.

219 While some relevant information is provided by the sources (iv. and v.), they are further affected by reliability issues.

8.3.1.1. Methodological deficiencies of experimental studies

220 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed. All sources of information were assessed according to the OECD TG 414. This test guideline requires:

a. testing of at least three dose levels (unless conducted at the limit dose) with concurrent controls;
b. at least 20 female animals with implantation sites for each test and control;
c. an exposure duration at least from implantation until one day prior to scheduled caesarean section.

221 The following specifications are not according to the requirements of OECD TG 414:

a. for source (iv.) the following conflicting information is given about dosing in the dossier: 1.5 - 5 mg/ animal /day or 1.5 - 5 ml/ animal /day or 1500 - 5000 mg/kg bw/day. It is therefore unclear what dosages and how many dose levels were used. For source (ii.) only 2 dose levels were used: 0.5, 0.7 mg/animal/day
b. both sources (iv. and v.) do not provide any information on the number of animals tested;
c. for source (iv.) 2 different exposure durations were used, as explained in the dossier: *"Rats were orally dosed on gestation days 6-14 or 11-16".* OECD TG 414 is not intended to examine solely the period of organogenesis, (e.g. days 5-15 in the rodent, and days 6-18 in the rabbit) but also effects from preimplantation, when appropriate. Therefore testing for shorter duration will provide some relevant information, but will only provide information on the toxicity of the test item during the the period of organogenesis and after pre-implantation.

The consequences of these deficiencies are insufficient statistical power, inability to observe sufficient toxicity for hazard assessment and inadequate exposure duration.

8.3.1.2. Aspect 2) Maternal toxicity

222 Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

223 Source (iv.) provides relevant information on maternal survival, source (v.) provides relevant information on maternal survival and body weight. Source (vi.) does not provide any relevant information on maternal toxicity parameters. The sources do not provide information after gestational exposure on maternal clinical signs and other potential aspects of maternal toxicity in dams. Therefore, these sources of information provide limited information on this key element.

224 While some relevant information is provided by the sources (iv. and v.), they are further affected by reliability issues.

225 The reliability issues (a. – d.) of sources (iv. and v.) described in sections 8.2.1.1. and 8.3.1.2. above apply equally to aspect 2.

8.3.1.3. Aspect 3) Maintenance of pregnancy

226 Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

227 None of the sources of information provide relevant information for this aspect.

8.3.1.4. Conclusion on the PNDT WoE adaptation

228 Taken together, the sources of information provide relevant information only on some elements of the aspects 1 and 2, such as some prenatal developmental toxicity observations (foetal loss and growth (body weights), and structural malformations and variations (external, visceral and skeletal), and some maternal toxicity observations (maternal survival and body weight). They do not cover the entire set of elements on after prenatal exposure on embryonic/foetal survival (number of live foetuses; number of resorptions and dead foetuses), growth (size) and structural malformations and variations (external and visceral), information after gestational exposure on maternal clinical signs and other potential aspects of maternal toxicity in dams, expected to be obtained from the OECD TG 414. For aspect 3 no relevant information is provided.

229 Moreover, even the elements that provide some relevant information cannot be considered reliable as discussed under each aspect, due to limited statistical power, insufficient level of toxicity and inadequate exposure duration.

230 Therefore, it is not possible to conclude, based on any of the new sources of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 414.

231 Based on the above, the adaptation under Annex VIII Section 8.6.1. Column 2.is rejected.

8.4. Conclusion

232 Based on the above, the information requirement is not fulfilled.

Specification of the study design

233 A study according to the test method EU B.64/OECD TG 422 must be performed in rats. The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

234 In the comments to the draft decision you agree with the request.

9. Short-term toxicity testing on fish

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

9.1. Information provided

236 You have provided a short-term toxicity to fish study (2013) with the Substance (study i).

9.2. Assessment of the information provided

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

9.2.1. *Inadequate characterisation of the test material*

238 As explained in Section 0.1., you have not demonstrated that the test material is representative for the registered Substance. Therefore, it cannot be determined whether and how the information from this study can reliably be used to fulfil the current information requirement.

9.2.2. *Study not conducted according to GLP*

239 (Eco)toxicological studies must comply with GLP or another recognised international standard; Art. 13(4) of REACH.

240 You have indicated that study (i) is "not GLP-compliant", without further explanation.

241 The test does not comply with GLP or another recognised international standard and is therefore rejected.

9.2.3. *The provided study does not meet the information requirement*

242 To fulfil the information requirement, a study must comply with OECD TG 203 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:

243 Technical specifications impacting the sensitivity/reliability of the test

a) the test is conducted on juveniles of similar age (or size);

244 Additional requirements applicable to difficult to test substances:

b) if the test material is forming dispersion or emulsions (*e.g.* certain surfactants, aliphatic amines), the dispersibility limit or the critical micelle concentration of the test material in the specific test solution under the test conditions is determined.
c) surface-active test chemicals are tested at concentrations below their critical micelle concentration (CMC) in the test medium.

245 Characterisation of exposure

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

246 Your registration dossier provides an OECD TG 203 study showing the following:

247 Technical specifications impacting the sensitivity/reliability of the test

a) the mean size of fish was 2.5-3 cm, which does not correspond to juveniles for *Poecilia reticulata* (1-2 cm, Annex 2 of OECD TG 203);

248 Additional requirements applicable to difficult to test substances:

b) the test material is a surfactant (surface tension 44.5 mN/m) and you do not report the critical micelle concentration;
c) the test is performed at a nominal concentration of 100 mg/L;

249 Characterisation of exposure

d) no analytical monitoring of exposure was conducted;
e) the reported effect values are based on nominal concentrations;

250 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the size of the applied fish does not correspond to juvenile fish for Poecilia reticulata. Using adult fish may impact the sensitivity of the fish to the test substance. Furthermore, the Substance is difficult to test since it is a surfactant and you have not determined the critical micelle concentration (CMC) of the Substance in test solution. Therefore, you have not demonstrated that the exposure concentration of 100 mg/L was below the CMC and that the test organisms were exposed to the freely dissolved chemical species and not the micelle form, which is considered to be biologically unavailable. Finally, no analytical monitoring was conducted. Since the substance is difficult to test difficulties in achieving and maintaining stable test concentrations can be expected. You have based effect levels on nominal values but in the absence of analytical monitoring you have not provided confirmation that exposures were within ± 20 % of the nominal concentration. The results based on nominal values are therefore considered unreliable.

251 Therefore, the requirements of OECD TG 203 are not met.

9.2.4. *Conclusion*

252 For all the reasons above, the information requirement is not fulfilled.

9.3. Study design and test specifications

253 OECD TG 203 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 2.

254 In the comments to the draft decision, you agree that the study provided does not meet the current standards of an OECD TG 203 study. In your comments you indicate your intention to fulfil the information requirement with a new OECD TG 203 study, for which you provided certain information in a taget study report as an attachement to your comments to the draft decision. In addition, you indicated your intention to update your dossier with the respective information.

255 However, Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries (RSS) are "required of all key data used in the hazard assessment". You have not provided with your comments any RSS.

256 Furthermore, you have not demonstrated that the study referred to in your comments is compliant with OECD TG 203 and OECD GD 23 (as the Substance is difficult to test), and that the study is conducted according to GLP.

257 Moreover, the Substance is a UVCB and you did not provide the required details on the test material applied in the OECD TG 203.

258 In the absence of this information, we cannot assess relevance and reliability of the study.

259 You remain responsible for complying with this decision by the set deadline.

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 10 August 2021.

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

ECHA took into account your comments and did not amend the request(s).

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 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;
- 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]

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[6].

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.

Selection of the Test material(s)

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

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) 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.

Information on the Test Material needed in the updated dossier

a) 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.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

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

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

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).